Review Article

Publication of clinical trial results: Time to wake-up

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Abstract

Scientific publications are important by-product of clinical trials and play a key role in the advancement of medical practice and research. Besides disseminating the efficacy and safety information for new drugs and indications, publications also bring forward the newer trends and techniques, and the drawbacks and limitations of clinical trials. This knowledge is indispensable and contributes to focused growth of clinical research. Importantly, the published data form the base of medical practice and decisions and hence important for physicians, patients, and healthcare payers. Nonetheless, it is a tribute to patients who participated in the trial so that several other patients like them can avail the benefit of the treatment if a drug is safe and efficacious. However, if the data from clinical trials are not adequately published, it thus prohibits the physicians, patients, and researchers from getting the desired benefit. Even the published data are incomplete and biased at times when compared to the study protocols, especially when results are unfavorable or negative. Despite the mandates from regulatory authorities, recommendations, and guidelines, the adherence to publication of clinical trial data remains partial and biased. Thus, this review describes the need for publishing clinical trial data, the challenges, and solutions in light of recommendations and threats.

Key words: Bias, challenges, clinical trial results, disclosures, ethics, publications

Received: 24th October, 2014; ***Revised:*** 20th November, 2014; ***Accepted:*** 28th November, 2014

INTRODUCTION

The main aim of publication of clinical trials results hovers around evidence-based clinical medicine as it potentially impacts clinical practice and research, patient awareness, and implications for future research, thereby minimizing futility and duplication. The unbiased results from clinical trials are of utmost importance for decision-making with respect to new treatments or procedures, treatment guidelines, and policies. A lack of publication or a biased publication seriously affects all these aspects and may jeopardize the knowledge and development in medical research and patient care. Nonetheless, it is also unethical to the participants of a trial as the information is not being used for benefit of other patients, and remains concealed from public and medical fraternity, a key reason that justifies the clinical research including human subjects.[1]

Access this article online	
Quick Response Code:	Website: www.ijcep.org
	DOI: 10.4103/2348-8093.149749

It has been now more than two decades since the importance of publishing the results from clinical trials, and the reasons for nonpublishing were first highlighted.[2,3] Despite this there is a dearth of publications from clinical trials, especially those with unfavorable outcomes or negative findings. Methodological research has shown that for approximately 40–50% of all studies approved and registered, results or reasons for their failure are never published.[4,5] The dilemma is that it is nearly impossible to search the results for several clinical trials, either with positive or negative results, unless obligated by the health authorities. The results from clinical trials are generally available as publications in peer-reviewed journals, and besides this some unpublished data may be available such as abstracts, conference proceedings, press releases, webcasts, newsletters and online sources, drug labels, and package inserts. However, some of these data may not be validated, thereby constraining the reproduction of data, reconstruction of the study, understanding limitations or strengths of the study, and interpretation of the study results. Therefore, it is important to make the data from clinical trials available in the public domain,

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and the best way to do this is publishing the results of a clinical trial. The following sections in this article will discuss the need to publish, the challenges, and a way out in light of various guidelines and recommendations.

SUBSTANTIATING THE NEED TO PUBLISH

The main aim of publishing the results of a clinical trial in today's scenario is the increased need for transparency. In the current competitive world, where there are plethora of drugs and devices with an increasing flutter for market share, it is important to seek and maintain the trust of the consumer by being transparent. Nonetheless, the published data from clinical trials serve multiple objectives: Forms basis for further research and prevent duplicate research, enables informed treatment-related decisions by health-care providers, documents/data review by ethics committees and funding agencies, policy and guidelines development, and patient education [Figure 1]. Above all, this is a gratitude towards study participants, whose participation contributed towards enhancing treatment modalities and better health. Underscoring these needs, the current regulations not only mandate the publications from clinical trials, there are guidelines and initiatives in place that make the publication process easy and transparent. The first initiative in this direction was clinical trial registry for clinical trials, followed by publication of clinical trial results in peer-reviewed journals, and at clinical trial registry websites.

WHAT DOES DATA SAY

Several studies have made an effort to identify the gap between clinical trial registrations and publishing their results in the public domain after study completion. These studies indicate that there is a large amount of primary outcome data that is submitted to Food and Drug Administration (FDA), however, about one-fourth of this remained unpublished, more so when the results were unfavorable or when primary endpoint was not met.[6-10] The publication deficit data is presented in Table 1. Such publication bias becomes evident when the publication documents are compared with regulatory documents,[8,11] documents submitted to ethics committees,[12] or funding agencies.[13] It is important to stress here that this practice of nonpublishing is highly variable in industry as well as academia.[14]

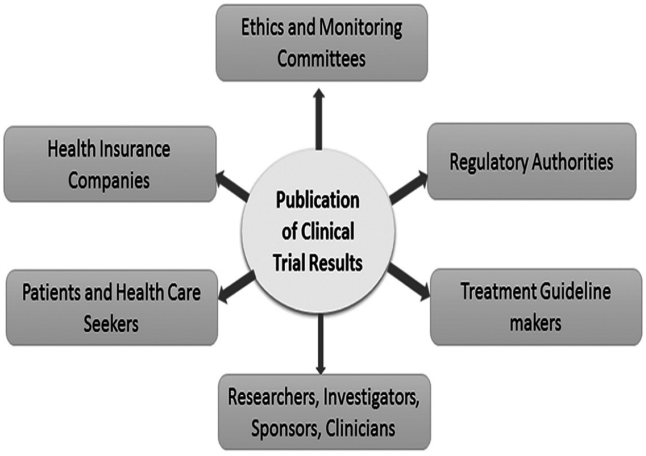

Figure 1: Stakeholders for clinical trial results

A study focusing on the studies conducted by GlaxoSmithKline (GSK) in Spain showed that public availability rate was 80% for all studies and 78% for clinical trials, and the publication rates being 68% and 61%, respectively. Furthermore, the results showed that therapeutic area, sample size, positive trial results, duration of experimental phase, and being a clinical trial did not predict publication or public availability while cancellation of projects was the single factor negatively influencing publication and public availability rates.[15] Further, even large randomized trials are liable to nonpublication or publication bias.[16] Another study demonstrated that 78% of the efficacy trials for approved new drug applications (NDA) were published, while remaining were not published.[8] A multivariate analysis revealed that trials with favorable primary outcomes and active controls were more likely to be published. Further, there was a tendency towards missing primary outcomes from published papers and appearance of additional outcomes that favored the new drug, while statistical significance varied between NDA and corresponding published papers. Several trials were not published even after 5 years of drug approval. Similar results were observed in a recent study that showed that clinical trials with positive outcomes have significantly higher rates and shorter times to publication versus those with negative results.[17]

Contrary to this, clinical trials with extremely good results on an interim analysis and early termination based on these results are published on priority. This is plausible and ethically acceptable as health benefits cannot be denied to those who need it. However, this is not the case with trials with unfavorable or negative results. Due to adverse safety events or in case of lack of efficacy, the trial may be prematurely discontinued, and same may be updated on trial registry site, but publication of the same is either quite delayed or many times remains unpublished. Estimated time to publication of trials with favorable results was 4–5 years versus 6–8 years for trials with unfavorable results.[18] Two plausible reasons for nonpublication for unfavorable results could be a decreased interest of investigators or sponsors, and reduced rate of acceptance in scientific journals. However, only decreased interest of investigators and sponsors appeared as a factor associated with nonpublication.[19]

Table 1: Clinical trial publications from registered trials

References	Number of trials/subjects	Type of trials	Percentage published/not published	Percentage published subset	Factors favoring publication and other notable findings
Dickersin K *et al.* JAMA 1992;267:374-8	737 trials	Approved by two ethics committees	81% and 66% from each of the two ethics committees were published	NA	Significant results, external funding, and multiple data collection sites favored publication
Stern and Simes. BMJ 1997;315:640-5	Not specified	Studies submitted to ethics committee for 9 years	NA	NA	Positive results were published more, and sooner
Melander H *et al.* BMJ 2003;326:1171-3	42 studies	Studies specific to a molecule submitted to swiss regulatory authority	57% were published	NA	Significant or positive results favored publication Two publications from each of 21 studies 5 publications from other 3 studies
Krzyzanowska MK *et al.* JAMA 2003;290:495-501	510 abstracts	Presented at ASCO meetings (1989-1998) Large, phase iii, randomized controlled trials	26% were not published even after 5 years after presentation	NA	Studies with significant or positive results (81%), and studies with higher impact and pharmaceutical sponsorship published sooner
Chan AW *et al.* CMAJ 2004; 171:735-40	48 trials	Approved for funding by the canadian institutes of health research	44% were published	NA	Statistically significant efficacy outcomes favored publication 31% of efficacy outcomes and 59% harm outcomes per trial were incompletely reported Primary outcomes differed between protocols and publications for 40% of the trials
Lee *et al.* PLoS Med 2008;5:e191	909 trials	90 approved NDAs	43% published	76% of pivotal trials	Statistically significant results, larger sample size, and pivotal studies favored publication
Turner EH *et al.* N Engl J Med 2008;358:252-60	12,564 subjects	Studies of 12 antidepressants	31% not published	NA	Positive results favored publication Published results showed 94% with positive outcomes while FDA showed 51% with positive outcomes
Rising K *et al.* PLoS Med 2008;5:e217; discussion e217	164 trials	All efficacy trials from 2001 to 2002	78% published	NA	Favorable outcome, active-controlled trials favored publication Forty-one primary outcomes from the NDAs were omitted from the papers 47% unfavorable outcomes not included in publications Statistical outcome changed for 22% of outcomes and 9% conclusions changed between published paper and NDA
Chan AW *et al.* BMJ 2008;337:a2299	70 studies approved by scientific-ethics committees for copenhagen and frederiksberg, denmark	NA	NA	NA	Discrepancies between protocols and publications were found for sample size calculations, methods of handling protocol deviations, missing data, primary outcome analyses, subgroup analyses, and adjusted analyses Interim analyses were described in 13 protocols but mentioned in only five corresponding publications
Crockett SD *et al.* Am J Gastroenterol 2009;104:1097-105	396 trials	Awarded by american college of gastroenterology to 341 recipients in the 25 years between 1983 and 2008	90% of the funded projects were published, 69% of these were published in peer-reviewed journals		Higher award value was associated with publication

Contd..

Table 1: Contd....

References	Number of trials/subjects	Type of trials	Percentage published/not published	Percentage published subset	Factors favoring publication and other notable findings
Vawdrey and Hripcsak. J Biomed Inform 2013;46:139-41	Clinical trials.gov	NA	76% published	NA	Positive results favored publication Of published, 74% were positive, 21% were neutral, and 4% were negative Of unpublished studies for which the investigator responded, 43% were positive, 57% were neutral, and none were negative
Dal-Ré R *et al.* Eur J Clin Pharmacol 2010;66:1081-9	143 studies	94 clinical trials of these 87 were included in international products clinical development plans	80% were published	Publication rates were 78% for clinical trials	Therapy area, sample size, positive trial results, duration of the experimental phase, and being a clinical trial did not predict the publication or public availability
Bourgeois FT *et al.* Ann Intern Med 2010;153:158-66	546 trials	Safety and efficacy trials various drug classes between 2000 and 2006	66.3% were published	NA	Industry-funded trials reported positive outcomes in 85.4% of publications, compared with 50.0% for government-funded trials and 71.9% for nonprofit or nonfederal organization-funded trials Positive trials more frequently published
Ross JS *et al.* BMJ 2012;344:d7292	632 trials	Funded by NIH and registered within clinicaltrials.Gov	46% were published within 3 years, and 68% were published by 4th year	NA	Median time to publication was 23-month
Jones CW *et al.* BMJ 2013;347:f6104	Not specified	Trials with at least 500 participants prospectively registered with clinical trials.Gov and completed prior to january 2009	29% unpublished	NA	Industry-sponsored trials remained more frequently unpublished Of the 171 unpublished trials, 133 (78%) had no results available in clinical trials.gov
Sune P *et al.*, PLoS One 2013;8:e54583	Not specified	All drug-evaluating clinical trials submitted to and approved by a general hospital ethics committee between 1997 and 2004	48.4% were published	NA	Study results were identified for 68.9% of completed trials Publication rate was 84.9% for positive studies and 68.9% for negative studies Time to publication was 2.09 years for positive studies and 3.21 years for negative studies
Nguyen TA *et al.* J Clin Oncol 2013;31:2998-3003	646 trials	Phase II to IV cancer trials registered at clinical trials.gov between december 2007 and may 2010	At 1-year after completion of the trials 9% at clinical trials.gov 12% in journals 20% in either of these two At 3 years: 31% at clinicaltrials.gov 35% in journals 55% in either of these two	At 1-year 12% at clinical trials.gov 5% in journals 17% in either of these two At 3 years 38% at clinicaltrials.gov 32% in journals 56% in either of these two	Results for nearly half the trials of cancer drugs in the united States were not publicly available 3 years after completion of the trials

NDAs: New drug applications, NIH: National Institutes of Health, FDA: Food and Drug Administration

A recent study done post Food and Drug Administration Amendment Act (FDAAA) for oncology trials showed that the cumulative percentages of all trials with results posted at ClinicalTrials.gov, published in journals, and available either at ClinicalTrials.gov or in journals were 9%, 12%, and 20%, respectively, and for randomized clinical trials (RCT), the percentages were 12%, 5%, and 17%, respectively. At 3 years, these percentages were 31%, 35%, and 55%, respectively, and for RCTs, they were 38%, 32%, and 56%, respectively. Public availability of Phase III trials was 15% at 1-year, 39% at 2 years, and 64% at 3 years. This clearly indicates that the results for nearly half the trials of cancer drugs in the United States were not publicly available even after 3 years of completion of the trials despite the recommendation from FDAAA.[20]

It is important to understand if such bias and nonpublication of studies is industry driven or is prevalent in academics as well. Studies have shown that the research funded by drug companies was less likely to be published than research funded by other sources, and studies funded by pharmaceutical companies were more likely to have outcomes favoring the sponsor than were studies with other sponsors.[21] In a follow-up study of multicenter clinical trials at a large academic medical center, it was observed that about half of the trials were published in the peer-reviewed journals, while 44% trials remained unpublished, and 26% of trial results were not disseminated in any form. Of these Phase III trials, low-risk trials, and investigational trials had highest publication rates. Further, the trend of nonpublishing in academic setup was similar to that observed in the industry.[22]

Overall, we firmly believe that publishing unfavorable or negative results is taken as an act of high ethical standards, and positions the investigators, the sponsors and/or drug company strongly in the market due to a transparent action. Therefore, not publishing the clinical trials with unfavorable or negative results is self-detrimental rather than a savior.

PUBLICATION BLUES: BIAS IS THE DARKEST SHADE

The available data clearly indicates that bias is the key issue in the publication of clinical trial data. The bias encompasses suppression of unfavorable data, selective reporting and showcasing the favorable results, misinterpretation or manipulation of results by changing the definitions of primary outcome measures, and employing additional or different statistical methods for data analyses for publication without notifying or clarifying the same in the publication.

At times, bias may creep-in under pressure to publish when investigator(s) want to publish the data for academic/professional reasons while pharma companies may want to publish under regulatory mandate or market strategies. The bias may be more pronounced when a subgroup or exploratory analyses is more favorable than the primary results. This may take a predilection over the not-so-favorable primary endpoints while publishing the study data. Commercially, the aim of such publications is to make the presence felt in the market, and increase sales by more prescription.[23] The implications of this "known" bias are a wrongful treatment decision, a decreased trust for both patient and the physician, misguidance to clinical research personnel, violation of ethical responsibilities of researchers and sponsors, and cost implications for a noneffective treatment. Therefore, it is important to bring forth the key results of the study even if these are negative or unfavorable along with the publications of subgroup analyses or exploratory analyses, which may suggest that treatment may be better for a specific subgroup of patients, and/or also provide guidance for further studies. Factors contributing to publication bias are presented in Figure 2.

GUIDELINES, RECOMENDATIONS, AND INITIATIVES: ARE THESE TOO RESTRICTIVE?

Food and Drug Administration Amendment Act, 2007

The FDAAA specified that enrollment and data outcomes from all trials of drugs, biologics, and devices, except that of Phase I trials, must be submitted to the open repository associated with the trial's registration in about a year of the trial completion, whether or not these results have been published. Failing to comply with this, a fine up to USD 10,000/day may be imposed upon the defaulter. The aim of this initiative was to account for the clinical trials registered, and allow an access to stakeholders and beneficiaries to

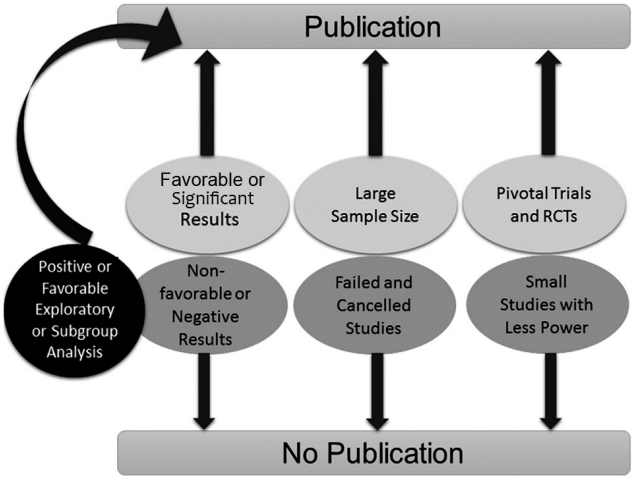

Figure 2: Bias associated with nonpublication

the key data from these trials such as demographic and baseline characteristics of the study population, data for primary and secondary outcome variables, and the safety data. Similar publication mandate has been recently released by British Medical Association.[24]

However, mandate of publishing trial data online invites a fear for the investigators and sponsors, mainly due to two reasons. First, from publication guidelines by journals that specify that the "data has not been published previously in any form, part or full." However, FDA clearly specifies that the data submitted to this repository would not be taken as publication, and hence would not deter the publication in peer-reviewed journals.[25] Second, the investigators and sponsors are concerned toward confidentiality and misuse of data such as the use of proprietary information for commercial benefits, and plagiarism, which is a valid concern. World Health Organization's registry platform working group on the reporting of findings of clinical trials comes with a more investigator and sponsor friendly recommendation that states "the findings of all clinical trials must be made publicly available," but also specified that "Although some journal editors have acknowledged the changing climate around results registration and reporting … they may have a conflict of interest in that they will probably want the key (and potentially most exciting) messages from a trial to appear first, and perhaps exclusively, in their publication."[26] This clearly indicates that though there is a large need for transparency in clinical research, and at the same time, there is a dire need to protect data plagiarism and its misuse as discussed later in this article.

International dialog on the public reporting of clinical trial outcome and results – PROCTOR Meeting, 2008

In another notable meeting presided by Canadian Institutes of Health Research in 2008, the public reporting of clinical trial results was discussed. The discussion was based on the Ottawa Statements, World Health Organization International Standards of Trial Registration, CONSORT statement, the International Committee of Medical Journal Editors, the International Conference on Harmonization, and the recommendations from FDAAA. The options and challenges with publication of clinical trial data were discussed in details, and there was a consensus that there should be an international dialog toward global standards on results reporting, and should include opening communication channel with agencies listed above.

Overcome failure to publish negative findings (OPEN) project, 2011

The Overcome failure to Publish nEgative fiNdings project was a very good initiative that catered to the concerns with publishing the negative findings. This project was a 24-month project (November 1, 2011 to October 31, 2013) co-funded by the European Commission under the Seventh Framework Program. The project followed a series of steps to identify the lacunae, the current practices, and develop recommendations to avoid nonpublication of studies and publication bias. In lieu of this, the project has initiated a systemic review of unpublished and grey literature, which is much awaited.

The European federation of pharmaceutical industries and associations and the pharmaceutical research and manufacturers of America

In July 2013, The European Federation of Pharmaceutical Industries and Associations and the Pharmaceutical Research and Manufacturers of America put forwards "Principles for responsible clinical trial data sharing: Our commitment to patients and researchers." The aim was to ensure that the clinical trial data is shared with qualified scientific and medical researchers request, provided patient privacy and confidential commercial information is masked. Pharmaceutical companies were encouraged to share a factual summary of clinical trial results to participants/patients. Furthermore, it was suggested that synopsis of the clinical study reports (CSR) be made public once the new medicine or new indication were approved. A step in this regards was taken by GSK and Roche in early 2013, when they declared that they would publish all the CSR once a drug has been approved or discontinued from development and the results have been published.

Drug repurposing

The data transparency initiative has moved a step forward by data sharing initiative wherein pharma companies have mutually agreed upon to pooling the drug data, especially negative results to analyze and assess the failures and assess if any compound can be taken further with modifications in compound design, trial design or patient population or indication. In-line, a landmark initiative for repurposing the drug molecules was initiated by National Institutes of Health and National Center for Advancing Translational Sciences in May 2012 (http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html). It was aimed at exploring approved, failed, abandoned or upcoming molecules to new disease areas, and would include 58 drug candidates. This would allow sharing of data, and hence reduce and share the cost of further development. Though it is at nascent stage but if any promising drug candidates could evolve out of these, it may immensely benefit the industry, academia, and patients.

WHO SHOULD TAKE THE RESPONSIBILITY

Who should take the responsibility for publishing the results of a clinical trial, whether the investigator

or sponsor, still remains a hot topic of debate. This becomes more pertinent when results are negative or not-so-favorable. Considering the ethics and role-involvement, the investigator remains the most important person to disseminate the study results. Next the responsibility lies with the sponsor or funding agency as they have not only invested in the development of drug and/or conduct of the trial, they also own the data. The responsibility share of the sponsor equals to that of the investigators or maybe even more if the research is industry driven.

While publishing, authors are justified to bring forward positive findings from a research even if the gross or primary outcome was not so favorable, and this can be ethically done by not hiding the negative or not so favorable results. This will allow bringing forth various aspects in a clinical trial and evaluate each aspect with an unbiased approach so as to improve the current research, open new avenues for existing treatment or diagnostic modalities. Though unfavorable results in any case would not allow the approval of a drug/device but disseminating the results will ensure that the learnings from the study are not wasted.

ENSURING DATA SAFETY

While being committed to publishing the clinical trial results, especially on clinical trial registries, it is important to ensure the data safety. There are two key aspects of data safety, first patient confidentiality, and second data security. The patient data should be redacted during publication to ensure that patient confidentiality is maintained. This is important as an unrestricted public access to data may allow patients to identify their own data and use of these data for their personal context. It is equally important to mask the commercially sensitive information to safeguard the interest of the sponsor company. Furthermore, the data should be secured so as to prevent its misuse and theft. Following implementation of various key group initiatives and regulatory guidelines, huge volumes of clinical trial data will be uploaded to public domains. One way to ensure the safety of these data is secured access controls that would avoid data export from the system. Another possible solution is to grant organizational/institutional access only. For additional/new analysis sought for decision-making, in-built data analyzing tools can come handy. An electronic audit trail should be set in place to further ensure the data safety. An independent board that reviews, requests to access the data is also a good option, this is being practiced by GSK for published trials while for ongoing trials, the feasibility and practicality of data sharing is evaluated, and responded accordingly. On similar lines, Roche implemented a signed data-sharing agreement that obligates requestor agreement to share their results with Roche and also with regulatory authorities prior to publication. Taken together, the extent and mode of data access and sharing needs to stream-lined, and a centralized procedure should be adopted to ensure data safety and security.

A WORD OF CAUTION

In this whole gamut of expectations, issues, concerns, and dilemmas, it is important to, not to lose the focus. The aim is to interpret and understand the results from a clinical trial while taking into consideration three key areas: Study design and participants, safety and efficacy of the intervention (s), and the limitations so as to improve future studies. Besides considering the full publication and key primary and secondary outcomes, sub-group analyses and interim analyses also provide key insights into the study design, choice of participants, and/or outcomes. These should be interpreted with caution, as many times the study is not powered to detect a meaningful difference for study subgroups, and/or inappropriate statistical methods have been used. Nonetheless, subgroup analyses allow identifying a patient population that will benefit more with the intervention being tested, being it drug, device or a procedure. This is a double-edged sword that may favor significant subgroup analyses creating a publication bias toward exaggeration of treatment efficacy, but at the same time also suggests the characteristics of the group that would benefit more from the treatment. Furthermore, the inbuilt limitations of the study due to faulty or inadequate study designs and other operational limitations should be considered while interpreting the results so as to arrive at clear and meaningful conclusion. The interim and subgroup analyses should be interpreted with a pinch of salt since the power of the study is compromised while performing such analyses.

WAY AHEAD

Keeping in view these discussions, it is clear that the road to publishing clinical trial results is a tough one, and following the recommendations would make this journey pleasurable, ethical, and safe. The first and landmark initiative in this regards is in place that has mandated the registration of clinical trials allowing the clinical research personnel, investigators, and funding agencies to keep abreast with their research interest portfolio. Importantly, the investigators and funding agencies should take a responsibility to disseminate the trial results on public domain as and when appropriate, especially in situations that warrant an immediate action, e.g. safety, efficacy of an orphan drug or other for other diseases with high socioeconomic burden etc. This implies not only to the

negative or unfavorable findings but also to positive outcomes that would call for an immediate cessation or provision of a treatment, respectively. Having said this, the decision to continue the study for which a similar previous study published negative or unfavorable is a difficult one. Such decision would require a lot of simulation since huge effort, cost, and ethics are at stake. Nevertheless, the decision has to be based on the safety of the participants and research ethics, and an unbiased committee constituted for this decision should be considered in this scenario. Therefore, the clause, "publish or perish" should be taken in a positive and constructive manner, rather than rash publishing by just being smitten with this clause.

CONCLUSION

Clinical trial results are backbone of medical practice and future research, and disseminating the results to the proper audience is, therefore, highly warranted. Responsible sharing of the clinical trial data and publication of the results, whether positive or negative will help to advance the clinical research in a positive direction and reinforce the confidence of consumers in safety and efficacy of medicine. Hiding or nonpublication of results is an unethical behavior towards study participants and is deceiving their trust. Though the reporting of clinical trial results has improved over time, there is still a long way to go.

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How to cite this article: Bhardwaj P, Yadav RK, Pandey R. Publication of clinical trial results: Time to wake-up. Int J Clin Exp Physiol 2014;1:245-52.

Source of Support: Nil, **Conflict of Interest:** Nil.