Cancer Trials 2006 - 2012: From Research to Publication at The Ohio State University

Authors: Cheek, Fern, A.M.L.S[1]; Bohrer, Angela[2]; Wei, Lei, Ph.D. [3]

Abstract

Clinical research is important to facilitate more accurate diagnoses, discover cures for diseases and provide novel treatments to help patients recover and/or prolong life. After the results from the research have been concluded, the next step should be to share and publish the information. Sharing those results enables physicians and other health care providers to disperse knowledge, efficiently and effectively diagnose diseases and treat patients with the latest drugs, devices and interventions. Studies have shown that it can take from 3-5 years for research results to be published.

This study is a case report of cancer clinical trials conducted at the Ohio State University (OSU). The OSU Clinical Scientific Review Committee reviews proposed cancer protocols for scientific validity. Once the proposals are approved, they are submitted to the OSU Cancer Institutional Review Board. We sought to determine how many of these approved proposals resulted in clinical trials that were completed and subsequently published.

Methods

Data for this research was collected from the ClinicalTrials.Gov registry, the National Library of Medicine's PubMed database, and an internally maintained database of published articles of the members of the OSU Comprehensive Cancer Center. Time from trial completion to publication was tracked and a statistical analysis was done to determine the length of time. 775 proposed trials were examined for the years 2006 – 2012. The analysis was done to determine if there was a noticeable change in publication time for these trials.

Results

Among the total number of trials (775) opened at OSU between 2006 to 2012, 42% had published results. The time analyzed occurs from the opening date of the trial until the completion (status determined by the Ohio State University Clinical Trials Office) ranged from 8-132 months. The average time the from trial opening to publication is 55 months.

Conclusion

Published research should include both negative and positive results, to prevent bias towards

the research. Funding agencies are requiring that results be published within a certain period of time, and this may accelerate the dissemination of the trial results. Publishing results from trials expeditiously can also prevent duplication of research efforts. It would allow future researchers to learn from, expand, examine, and delve further into research based on results from prior trials.

Introduction

Clinical trials are the cornerstone in improving global health by finding cures for disease states. To foster advancements in science and research, clinical trials must be proposed and conducted. Clinical trials are good indicators that the information and conclusions derived from the studies are both dependable and reputable. (1)

Results of research should be shared and reported for a number of reasons. Academic misconduct and erosion of the public's confidence are just a few of those reasons. As such, scientists and researchers are tasked with the responsibility to provide reliable evidence from research. (2) In section # 36 of the World Medical Association's Declaration of Helsinki regarding research ethics, it states "Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports." (3) Tumbler states, "Without publication, knowledge gained from the research is effectively lost." (4) The published results can then be translated from the laboratory to the clinical realm and the advancement of research towards cures and treatments.

As early as Hippocrates, results from experiments/trials were published. However, they probably would not pass the rigors of editors and journal standards today. (1) The manner in which the information has been distributed has evolved over the years. From the researcher to the journal publishers and the steps in between, the process has lengthened considerably.

Several steps are involved in the process of publishing the results and it takes a collaborative effort to succeed. The researcher conducts the research, the journal editor determines if the manuscript is appropriate for the journal, reviewers evaluate the validity and finally the consumer is able to access the information provided in the published article. (1)

The publication of the research can be complicated for a number of reasons. The hypothesis may not pan out; the results may be negative, thus discouraging publication; and numerous time factors are among only a few of the obstacles for publication. (5) Any of these circumstances may prevent the results from being disseminated.

According to the Center for Disease Control (CDC), Cancer is the 2nd highest cause of death after heart disease. (6) Cancer research is one of the top areas, for which, cures and treatments are of the utmost priority. (7) In their 2019 annual report of progress of cancer, the American Society for Clinical Oncology, indicates that considerable progress has been made in the fight against cancer. Clinical research has been the catalyst behind the progress. (8) Therefore, dissemination of results and reported outcomes of cancer clinical trials is imperative. In 2005, Camacho et. al., explored oncology clinical trials presented to scientific conferences to ascertain how many were subsequently published and results of this study show that "67% of the studies submitted were published at a rate of 7.5 years." (9) Ideally, sharing the results should be done efficiently and exhibit the highest quality. With the demands of the promotion and tenure process for researcher faculty, many investigators may be so focused on getting published that this may lead to rushing to publish the results. (5, 10) Hastiness in getting the results to publication can result in misinformation and perhaps misconduct. (2) As Binns and Low enumerate, "poor writing, multiple analyses of the same data, plagiarism and fraud" are some of the issues facing many journal editors. (1)

Several articles have been published that discuss the lack of reporting results from clinical trials. (11-14) This is an inadequate way to fulfill the promise of research that may have been federally funded. Solicited participants, who may or may not have benefited from the research, agreed to participate in a process that might well benefit others in the future. Not reporting results, could lead to a bias of the future research. (15)

Chen et. al did a study of 51 academic medical centers, including the Ohio State University Medical Center. The study included the trials within ClinicalTrials.gov and presented the reporting of results and the time of publication from trial completion date. (16) The focus of this study is to review oncology trials opened at a single institution between 2006-2012, and the publication rates and time to publication

Review of the Literature

In the past, as early as 1998, many studies on clinical trials both by specialty and in general have originated to examine the length of time for results and publications to come to fruition. These studies examined the lack of results and summaries submitted to trial registries, such as the clinicaltrials.gov. Many of the studies focus on the lack of publications connected to the clinical trials. Some of the summaries posted in clinical trials were more complete that those in the published manuscripts. (17)

Many possibilities have been offered to explain the lack of published results. More routine reasons include uninteresting results, time factors, and authors' relocations ex. leaving the institution where the research was done. Primary investigators may not decide to publish

results due to circumstances such as not attaining accrual or results that are not significantly relevant. These aspects may ultimately contribute to no publication and outcome biases. There are several types of bias (18) that may prevent the dissemination of important knowledge derived from scientific research. In this review of the literature, outcome and publication bias will be the focal points.

Outcome bias

Cochrane Reporting Bias defines outcome reporting bias as "The selective reporting of some outcomes but not others, depending on the nature and direction of the results." (12) Outcome bias includes research results that are not shared because the outcome is not necessarily positive or the trial's statistics are not compelling. (16, 17)

Industry sponsored funding of trials often plays a significant role influencing several areas. These include parts of the trial protocol such as design, methods, etc. as well as the submission of manuscripts. This influence is especially noticeable when the trial produces positive outcomes and as a result the manuscripts are published more quickly. (19)

To overcome the outcome bias, researchers have increasingly been required to register their clinical trials. "For the purposes 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. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials." (20) The World Health Organization (WHO) defines trial registration as "the publication of an internationally agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly - accessible website managed by a registry conforming to WHO standards." (20) Recommendations have been made to ensure that the content of the published article meshes with the trial's intent, by having editors compare the trial information with registered trials. Dal-Re and Caplan's study revealed that 1/3 of trials in the study changed their initial outcomes. (21)

Publication bias

Publication bias is defined by Cochrane as "The publication or non-publication of research findings, depending on the nature and direction of the results." (18) The World Health Organization recommended clinical trial registration. (22) As a way to provide openness and clarity in the research world, "In 2005, the International Committee of Medical Journal Editors, (ICMJE) required clinical trial investigators to enroll in an accepted trial registry." (22) In 2007,

as an amendment to the Food and Drug (FDA) Modernization Act of 1997, the FDA "required registration of all applicable trials and with required basic results reporting." (23)

In addition, as a way to combat publication bias, some journals have required registration of clinical trials as a condition of publication of manuscripts. (24) However, this is not always enforced, due to the fact that smaller journals are in competition with other journals and may overlook the registration requirement. Despite these recommendations and requirements, the lag in publishing and sharing of results remains.

Methods

This is a retrospective study conducted at The Ohio State University after appropriate approval of the Chairman of the Clinical Scientific Review Committee. Since this is not human subjects research it was exempt of review from the OSU institutional review board.……The clinical trials for this retrospective study were acquired from protocols submitted for review by the Ohio State University Clinical Scientific Review Committee (CSRC). This committee reviews protocols for clinical trials for their scientific soundness. Once approved they continue through the process to be reviewed by the Ohio State University Cancer Institutional Review Board.

The work began in 2016 and searching for publications ended in 2018. All of the oncology trials opened during 2006-2012 were utilized. The process entailed setting up an Excel table with the OSU protocol #, title of the protocol, primary investigator, status of the trial, Clinicaltrials.gov (CTG) link if located and finally the reference to the published work.

Three databases were used to locate the articles, Clinical Trial.Gov, the OSU Comprehensive Cancer Center database and PubMed/Medline. On occasion, the author used Google to search for the title to determine if there was a publication related to the research title. This was the most difficult part of the process because the title of the trial was not always the title used for the published work.

The status of the trial was noted in the table, from the beginning to completion. Additional statuses included abandoned (which could include anything from lack of accrual to the primary investigator leaving the institution) to still accruing, or not completed.

Results

The total number of reviewed original clinical trials from 2006 -2012 was 775. 408 (52.6%) were not published, see **Table 1**. Of that number, 190 (24%) were trials that were abandoned, which could be attributed to a number of reasons. Some of the reasons could be connected to things such as the trial was never started, a lack of funding and a lack of accrual to name a few. Some

of the trials were suspended, terminated/withdrawn, not completed or no longer in the Ohio State University Clinical Trials Office system. Other trials are either still active and/or still recruiting 28 (5.8%). There were 149 (19.2%) completed trials for which no publications could be located.

Table 1

Trials opened between 2006-2012	**# Of clinical trials**	**%**
Total trials	775	
Number of abandoned trials	190	24.5%
Number of trials suspended	2	0.3%
Number of trials terminated/withdrawn	32	4.1%
Number of trials that have no record in Oncore or CTO sheet	6	0.8%
Number of trials still active	17	2.2%
Number of trials still recruiting	11	1.4%
Number of trials not completed	1	0.1%
Number of trials for which no publication can be located	149	19.2%
Total number of all the above	408	52.6%

Table 2 shows 323 (42%) of the 775 clinical trials with publications. Among those 323 trials with publications, 258 clinical trials have both publication date/year and open to accrual date available. For those 258 clinical trials, the average time from accrual to publication is 55 months (Standard deviation is 23 months). The range is 8 – 132 months (11 years).

Table 2

Trials open between 2006-2012	**# Of clinical trials (%)**	**%**
Trials with publications:	323	41.7%
Trials with missing open to accrual date	65	8.4%
*Trials with publication year and /or open to accrual date available	10	1.3%
Trials with both publication date and open to accrual date available	258	32.0%
Total trials	775	

*The middle of the year (June) was used to calculate the time to publication

Among those 258 clinical trials, there were 154 trials opened between 2006 and 2009 (see Table 3) and 104 trials opened between 2010 and 2012

Table 3

Year to open the trial	# Of trials	Percent	Cumulative Frequency
2006	15	5.81	15
2007	37	14.34	52
2008	45	17.44	97
2009	57	22.09	154
2010	40	15.50	194
2011	31	12.02	225
2012	33	12.79	258

Later trials (2010-2012) were published significantly faster (average of 13 months faster (standard deviation of 22, 95% CI is 8-19 months)) than those in the earlier years (2006-2009) ($p<0.0001$).

Figure 1:

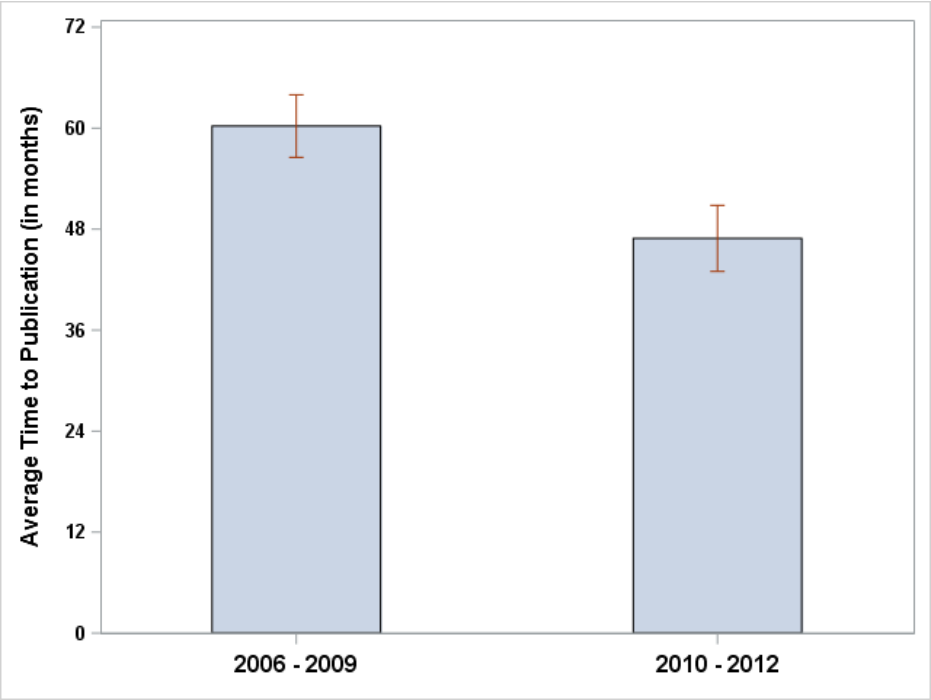

Table 4

year	N	Mean (month)	Std Dev	95% Confidence interval		p-value
2010-2012	104	47	20	43	51	<0.0001
2006-2009	154	60	23	57	64	
Diff		13	22	8	19	

Discussion

As mentioned previously, requirements by the FDA were designed to get researchers to comply by posting their trial results and subsequent dissemination to the greater scientific community. In the study by Gopal et al, it is apparent when looking at the ClinicalTrials.Gov database that completion of trials has increased and publications are more timely, as an outcome of the mandates. (23) Results from this study have shown that from 2010 – 2012, articles were published much faster than during the earlier years. A reasonable explanation for this could be attributed to the mandates, which includes the NIH mandate of 2008. It requires that researchers with NIH funding deposit their accepted publications, within a year, into the open access repository, PubMed Central. (25)

The study by Chen et.al in 2016, looked at academic institutions across the US, to discover how many were publishing their research within 2 years from trial completion. (16) While the methods of the study examined trials in the Ohio State University's Clinical Trials Office database, it did not focus specifically on cancer trials as this study examines. Within that study, OSU ranked 12 out of the 51 institutions in terms of trial to results and/or publication time. The average time was 18.7 months for primary completion date to publication. The overall rate of reporting results for publication was 40 (63.5%). 25 (39.7%) were published in less than 2 years. It is interesting to note that these statistics align somewhat with this cancer trials study. See Table 3 and Figure 1

In the future, distinction between industry and institution/investigator initiated clinical trials may be an area to investigate. (26, 27). Industries have a vested interest getting the results shared as quickly as possible. In addition, the possibility that some results may take longer to publish if consideration is given to the time it may take for trial follow-up. (28) The actual stopping of the trial and then the time taken for follow-up of results can be months or years.

Cancer researchers do want to get results out to the health community in a timely manner and are continuing to find ways in which to accomplish this goal. This study provides evidence that the time from trial to publication is reduced by various factors. These include things such as registry requirements and government funding mandates that have been put in place to accelerate the process.

This study was concluded with the year 2012 to allow time for publication and final searching which ended in 2018.

Searching for publications was primarily done in CTG, PubMed and OSU's CCC. Perhaps with a shorter period of years, further searching of additional databases could have been accomplished, though there is no real indication that the results would have been any more successful.

Conclusion

With funding agencies requiring that results be published within a certain period of time, this may accelerate the dissemination of the trial results. Published research should include both negative and positive results, to prevent bias towards the research. Solutions to expedite the published results could include the following:

1. Have a member of the research team serve as the point person to work on the review of the literature, write the introduction and methodology during the trial (29)
2. A team member could also identify journals to which the manuscript could be submitted
3. Journal editors and/or funding agencies need to consider consistencies in the reporting and publishing requirements; for example, no funding or manuscripts would not be published without registration of trials and report of results.
4. Communicating results to as many scientists, researchers, and health care professionals as quickly possible would provide the best option to maximize the research impact.

In general, as technology increases, online or e-publishing will be the most expedient way to achieve this goal. As early as 2000, this was a suggestion made as a quick fix to "fast track" results by utilizing electronic preprints, with limitations included as a caveat. (5) In 2020, many journals have electronic preprints, which means that the article is available electronically,

perhaps before the print. Open access, which is defined “as the free, immediate, online availability of research articles coupled with the rights to use these articles fully in the digital environment. Open Access ensures that anyone can access and use these results—to turn ideas into industries and breakthroughs into better lives.” (30) There are pros and cons to open access. However, in the future, the publishing model should adapt and change to support research, especially clinical research.

Future researchers would benefit in many ways and could learn from, expand, examine, and delve further into research based on results from prior trials. Additional research should be continuously examined and explored to get the results out quickly to the health care community. Publishing results from trials shared expeditiously can also prevent duplication of research efforts. The optimal benefit would be to get the research results quickly from the bench to the bedside to allow patients to receive treatment and therapies.

References

1. Binns, Colin W.|Low, Wah Yun. Publications from clinical trials: Process, conflict of interest and the evidence base. Preventive Medicine. 2013;57: S3-4.

2. Wallach JD, Krumholz HM. Not Reporting Results of a Clinical Trial Is Academic Misconduct. Ann Intern Med. 2019;171(4):293.

3. WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. [cited Mar 5, 2020]. Available from: https://www-wma-net.proxy.lib.ohio-state.edu/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

4. Tumber MB, Dickersin K. Publication of clinical trials: accountability and accessibility. Journal of Internal Medicine. 2004 Oct;256(4):271-83.

5. The Lancet Oncology. Publishing clinical trial data-a long and winding road. Lancet Oncology. 2000;1(3):129.

6. FastStats [Internet].; 2019 [updated -10-29T06:46:02Z; cited Dec 30, 2019]. Available from: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm.

7. Jaffee EM, Dang CV, Agus DB, Alexander BM, Anderson KC, Ashworth A, et al. Future cancer research priorities in the USA: a Lancet Oncology Commission. Lancet Oncol. 2017 Nov;18(11): e653-706.

8. Pal SK, Miller MJ, Agarwal N, Chang SM, Chavez-MacGregor M, Cohen E, et al. Clinical Cancer Advances 2019: Annual Report on Progress Against Cancer from the American Society of Clinical Oncology. J Clin Oncol. 2019 Apr 1;37(10):834-49.

9. Camacho LH, Bacik J, Cheung A, Spriggs DR. Presentation, and subsequent publication rates of phase I oncology clinical trials. Cancer. 2005 Oct 1;104(7):1497-504.

10. Siemens DR, Saad F. Addressing concerns around the veracity of scientific research and publication. Cuaj-Canadian Urological Association Journal. 2016;10(5-6):151.

11. Anette Blümle, Joerg J Meerpohl, Martin Schumacher, Erik von Elm. Fate of Clinical Research Studies after Ethical Approval – Follow-Up of Study Protocols until Publication. PLoS One. 2014 Feb 1;9(2): e87184.

12. Hoeg RT, Lee JA, Mathiason MA, Rokkones K, Serck SL, Crampton KL, et al. Publication Outcomes of Phase II Oncology Clinical Trials. American journal of clinical oncology. 2009 Jun;32(3):253-7.

13. Archer SW, Carlo WA, Truog WE, Stevenson DK, Van Meurs KP, Sanchez PJ, et al. Improving publication rates in a collaborative clinical trials research network. Semin Perinatol. 2016;40(6):410-7.

14. Chen Y, Liu X, Lv J, Li W, Zhang Y, Guo Y, et al. Publication status of contemporary oncology randomised controlled trials worldwide. Eur J Cancer. 2016; 66:17-25.

15. Chan A, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles. JAMA. 2004 May 26;291(20):2457-65.

16. Chen R, Desai NR, Ross JS, Zhang W, Chau KH, Wayda B, et al. Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers. BMJ. 2016 Feb 17;352: i637.

17. Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, Ravaud P. Timing, and completeness of trial results posted at ClinicalTrials.gov and published in journals. PLoS Med. 2013 Dec;10(12): e1001566; discussion e1001566.

18. Reporting Biases [Internet]. [cited Mar 10, 2020]. Available from: https://methods-cochrane-org.proxy.lib.ohio-state.edu/bias/reporting-biases.

19. Liang F, Zhu J, Mo M, Zhou CM, Jia HX, Xie L, et al. Role of industry funders in oncology RCTs published in high-impact journals and its association with trial conclusions and time to publication. Ann Oncol. 2018 Oct 1;29(10):2129-34.

20. International Clincal Trials Registry Platform (ICTRP) [Internet].: World Health Organization [cited Jun 16, 2020]. Available from: https://www.who.int/ictrp/en/.

21. Dal-Ré R, Caplan A. Time to ensure that clinical trial appropriate results are actually published. Eur J Clin Pharmacol. 2014 Apr;70(4):491-3.

22. Bonita RE, Adams S, Whellan DJ. Reporting of Clinical Trials: Publication, Authorship, and Trial Registration
2011;7(4):561-7.

23. Gopal, Ravi K.|Yamashita, Traci E.|Prochazka, Allan V. Research without results: Inadequate public reporting of clinical trial results. Contemporary Clinical Trials. 2012;33(3):486-91.

24. Wager E, Williams P. “Hardly worth the effort”? Medical journals’ policies and their editors’ and publishers’ views on trial registration and publication bias: quantitative and qualitative study. BMJ: British Medical Journal. 2013 Sep 6;347(sep06 1): f5248.

25. Suber P. An open access mandate for the National Institutes of Health. Open medicine: a peer-reviewed, independent, open-access journal. 2008;2(2): e39-41.

26. Mathias M, LaFlamme KE. Industry-Sponsored Clinical Trials: Time to Publication. Curr Med Res Opin. 2012 APR;28: S12.

27. Liang F, Zhu J, Mo M, Zhou CM, Jia HX, Xie L, et al. Role of industry funders in oncology RCTs published in high-impact journals and its association with trial conclusions and time to publication. Ann Oncol. 2018 Oct 1;29(10):2129-34.

28. Hopewell S, Clarke M, Stewart L, Tierney J. Time to publication for results of clinical trials. The Cochrane database of systematic reviews. 2007 Apr 18, (2):MR000011.

29. 12 Tips for Accelerating Manuscript Publication | AJE [Internet]. [cited Apr 17, 2020]. Available from: https://www.aje.com/arc/12-tips-accelerating-manuscript-publication/.

30. Open Access [Internet]. [cited Apr 17, 2020]. Available from: https://sparcopen.org/open-access/.

Authors: The Ohio State University 1. Associate Professor, Emerita, Health Sciences Library; was Associate Professor/Research Librarian at Health Sciences Library during the research portion of this study 2. 4th Year Student, College of Dentistry; Was Research Student Assistant for the Health Sciences Library during the research collection 3. Research Assistant Professor, College of Medicine, Department of Biomedical Informatics

NOTE: OSU Center for Clinical Translation Science provided funding for the statistical analysis.