OBJECTIVE: Previous studies indicate that positive trials are more likely to be published in a timely manner. We sought to investigate whether this trend is ongoing and to evaluate other variables in the publication of positive and negative clinical trials. RESEARCH DESIGN AND METHODS: A set of phase III Pharma-sponsored trials with 1500 patients in the cardiovascular therapy area compared between Jul 2008 and Jun 2009 was obtained from www.ClinicalTrials.gov. PubMed and Google Scholar were used to determine if results were published. Abstracts were retrieved with and without prepublication data. The primary endpoint was met in 85% (29/44) and 72% (21/29) of trials that did not meet their primary endpoint (Fisher’s exact test, P = 0.32). While 68% of published negative trials appeared in journals with an impact factor (IF) greater than the median (13.4), there was no significant association between IF and results (P = 0.41). Only 18% (4/22) of trials with a median IF of 10 (6 positive, 3 negative) were published within 1 year of completion. All had enrolment greater than the median (1049 patients).

CONCLUSION: No significant difference in publication rates existed for positive and negative studies. Although publication within the median window could be improved, these findings suggest that other factors, including broad clinical applicability, drive the timely publication of clinical data.

Positive and negative trial data: Are there publication differences?

Background

• Clinical trials are designed to demonstrate safety and efficacy of a drug for its proposed indication and any intervention in gaining approval from agencies such as the Food and Drug Administration (FDA).
• In order for the FDA to accurately assess a drug, it is essential that all data are submitted, however, public disclosure is often selective.
• The principal route for public disclosure is through peer-reviewed literature.
• Laws in the USA mandate that all trials are registered at inception and basic results publicly posted by the National Institute of Health.
• Corporate Integrity Agreements and industry organizations both provide guidance regarding the timely publication of clinical trial data.

As an example, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has approved a “Joint Industry Position on the Publication of Clinical Trial Results in the Scientific Literature” — Members committed to publishing the results of all phase III clinical trials for publication in a peer-reviewed journal, regardless of whether the outcome was positive or negative — For marketed products, submission should occur within 12 months (and not exceeding 18 months) of study completion

• As part of a recent legal settlement regarding the delayed publication of data on Vetence, Merck is reported to report annually to its board any clinical trials that haven’t been announced within 12 months of completion.

• Previous reports have highlighted the problem of publication bias, including the incomplete reporting of trials. Furthermore, positive trials were more likely to be published in a timely manner.1

• We investigated whether this trend is ongoing and possible differences in the publication of positive and negative trials.

Methods

• The www.ClinicalTrials.gov site was accessed to identify Pharma-sponsored phase III cardiovascular therapy single center trials with ≥500 patients completed between July 2008 and Jun 2009.

• Publication status was determined using PubMed and Google Scholar.

• Both abstracts obtained from PubMed and TrialTrove (www.clinicaltrials.info) were interrogated to confirm whether primary endpoints were met.

• Statistical analyses (Fisher’s exact test and Chi-square with continuity correction) were used to assess differences between publication parameters and positive versus negative trial results.

Results

• In total, 44 clinical trials were included in the analysis. 29 of 44 (65.9%) were published before completion, while no publication was identified for 15 of 44 (34.1%) as of January 20, 2012.

• Publication Status of Positive and Negative Trials

• Of the 29 trials that had been published, 21 met the primary endpoint (positive) compared with 8 that failed to meet the primary endpoint (negative) (74.2% and 25.8%, respectively) (Figure 1).

• Of 11 (31.3%) trials for which no publication was identified met the primary endpoint whereas 7 of 11 (63.6%) either failed to meet the primary endpoint, or the results were indeterminate or no results were identified (Figure 1).

• While a higher percentage of positive trials have been published, this difference did not reach statistical significance by Fisher’s exact test (P = 0.32) (Figure 1).

• 8 trials (5 positive and 3 negative) were published in the NEJM, the journal with the highest impact factor included in this analysis and the top 10 ranking trials by enrollment (2776 to 18,000).

• Our analyses show that there was no significant difference in the publication rate for positive or negative trials, although there is a trend toward positive trials being more likely to be published.

• A notable difference was seen in the impact factor of the journal publishing the trial, but there was a trend that positive trials were reported in a higher impact factor journal than negative ones. Furthermore, NEJM, a very high impact factor journal, published the trials with the largest number of patients.

• It is evident that the time to publication for both positive and negative trials should be improved since the majority were published within 1 year.

• This suggests that other factors, including clinical applicability, may influence the timely publication of clinical data.

• This topic should be further investigated by analyzing a greater number of trials across multiple therapeutic areas to establish the rate of publication within 1 year, and provide further insight into the real-world factors that influence publication rates.

• In addition, the analyses performed here can be repeated with a sample of publications published after the most recent IFPMA Position (June 2010) to determine the results of such guidance of publication practices.

References

1. IFPMA. EFPIA, JFMA & PAREXEL Joint Industry Position on the Publication of Clinical Trial Results in the scientific literature, 10 June 2010.


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Figure 1: Publication status of positive and negative trials

Figure 2: Time before trials published

Figure 3: Time before trials published (months)

Figure 4: Publication in below- or above-average impact factor journal (mean impact factor in this sample = 12)

Table 1: The relationship between the impact factor of the publishing journal and positive or negative trials

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<thead>
<tr>
<th>Impact Factor</th>
<th>Trials</th>
<th>Positive Trials (n)</th>
<th>Negative Trials (n)</th>
<th>Total (n)</th>
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<td>10</td>
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CONCLUSIONS

• In total, 8 of 44 (18.2%) of the trials (5 positive and 3 negative) were published within 1 year of completion, meeting current industry best practices, and an additional 6 trials (5 positive and 1 negative) were published within 18 months (Figure 2).

• There was little difference between the number of months from trial end to publication for positive and negative trials (Figure 3).

• All 8 trials that were published promptly enrolled a greater number of patients than the median (1049) for all trials.

• 8 trials (5 positive and 3 negative) were published in the NEJM, the journal with the highest impact factor included in this analysis and the top 10 ranking trials by enrollment (2776 to 18,000).

• Our analyses show that there was no significant difference in the publication rate for positive or negative trials, although there is a trend toward positive trials being more likely to be published.

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