Rates of Publication/Non-publication of Trials Funded by the Stanley Medical Research Institute

Mark Weiser MD
Associate Director for Treatment Trials
The Stanley Medical Research Institute
Chairman, Dept. of Psychiatry, Tel Aviv University
Chief Psychiatrist, Sheba Medical Center
Collaborators

Jana Bowcut
Michael Knable
Linda Levi
Michael Davidson
John Davis
"The death of Ted Stanley on January 4 deprives the psychiatric research field of a philanthropic giant. The Stanley Medical Research Institute (SMRI) was founded in 1989 and had a major impact on schizophrenia and bipolar research. $600 million were donated to SMRI. Funds were also used to set up the Stanley Brain Collection and the Stanley Laboratory of Developmental Neurovirology at Johns Hopkins. In 2014 Mr. Stanley donated $650 million to the Broad Institute. Altogether the Stanleys donated more than $1.2 billion to research".

E. Fuller Torrey, MD, Associate Director, SMRI
INTRODUCTION

- Progress in developing drugs in medicine in general and in psychiatry in particular is plagued by non-publication and improper publication of the results of research studies.
- We examined publications of 253 studies funded by the Stanley Medical Research Institute (SMRI) between the years 2000 and 2009.
• 54.6% were published
• Mean time to publication from completion of study was 2.06±0.83 years.
61 studies published with positive findings

- compared the original protocols with the published papers
- Primary outcome measures
- Enrollment goals (±10% of protocol)

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<th>N=61</th>
<th>Same Protocol vs. Paper</th>
<th>Different Protocol vs. Paper</th>
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<tr>
<td><strong>Primary Outcome Measures</strong></td>
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<td>N=53 (87%)</td>
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<td>N=8 (13%)</td>
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<td><strong>Enrollment (±10%)</strong></td>
<td>N=42 (69%)</td>
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<td>N=19 (31%)</td>
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The NCSS-2000 PC program (Hintze, 1998) will be used for all analyses. Statistical comparisons of all studied parameters will be done between repeated measures using analysis of variance (ANOVA) with Bonferroni multiple comparison tests. Differences between continuous variables will be evaluated with paired two-tailed t-test (or equivalent non-parametric test), and on categorical variables - using chi-square tests with Yates correction. In addition, we will use ANCOVA models to control for possible effects of any baseline variables on the outcomes.

Statistical Analysis
Scales and laboratory data were analyzed by using the general linear models of analysis of covariance (ANCOVA), with a repeated-measurement factor of time (baseline, weeks 2, 4, and 6) controlling for the baseline values of relevant variables. Post hoc analyses were performed with 3-tailed t-test. The NCSS-2000 PC program was used for all analyses.
Statistical Assessment

(2x2 ANOVA with our primary efficacy variable being PANSS score).

Secondary efficacy variables will be measured by CGI. A Repeated Measures Analysis of Variance will be used to analyze the main hypotheses of this mixed design study. Exploratory analyses will be performed to determine whether response correlates with changes in immunological parameters.

analyses were performed by mixed models with time and treatment group as fixed effects.

With regard to the different statistical methods of analyzing our trial, a beneficial effect measured by the CGI, could be shown. Additionally, a slight effect showing a trend to significance was observed in the PANS negative subscale.
Statistical Considerations

Standard ANOVA correlations will be undertaken. T-tests will be used to compare various demographic data between groups. Variables such as illness duration, age, and illicit substance use can be retrospectively compared and controlled.

Demographic differences between groups were assessed by one way analysis of variance (ANOVA) or Chi square tests. Multilevel modelling was used to assess changes in the outcome measures. There are a number of advantages of using multilevel modelling over repeated measure MANOVA.
We emailed the authors of the 61 studies that were published with positive findings and asked if their studies were replicated, 28 (47%) said yes.
Overall 56% of the studies were published

Of the positive studies only 47% replicated

Only 40% of the negative studies published

Damaging for the field

- compounds which have already been tested but have not been published might be tested again
- unnecessary exposure of patients to study procedures/placebo
- waste of funds
- These are academic data, no industry interference

Significant differences between protocols and papers

- Changes in statistics
- Changes in primary outcome measures
Publication of Trials Funded by the National Heart, Lung, and Blood Institute

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D., Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.

BACKGROUND—Rapid publication of clinical trials is essential in order for the findings to yield maximal benefits for public health and scientific progress. Factors affecting the speed of publication of the main results of government-funded trials have not been well characterized.

METHODS—We analyzed 244 extramural randomized clinical trials of cardiovascular interventions that were supported by the National Heart, Lung, and Blood Institute (NHLBI). We selected trials for which data collection had been completed between January 1, 2000, and December 31, 2011. Our primary outcome measure was the time between completion of the trial and publication of the main results in a peer-reviewed journal.

RESULTS—As of March 31, 2012, the main results of 156 trials (64%) had been published (Kaplan–Meier median time to publication, 25 months, with 57% published within 30 months). Trials that focused on clinical events were published more rapidly than those that focused on surrogate measures (median, 9 months vs. 31 months; P<0.001). The only independent predictors of more rapid publication were a focus on clinical events rather than surrogate end points (adjusted publication rate ratio, 2.11; 95% confidence interval, 1.26 to 3.53; P = 0.004) and higher costs of conducting the trial, up to a threshold of approximately $5 million (P<0.001). The 37 trials that focused on clinical events and cost at least $5 million accounted for 67% of the funds spent on clinical trials but received 82% of the citations. After adjustment of the analysis for a focus on clinical events and for cost, trial results that were classified as positive were published more quickly than those classified as negative.

CONCLUSIONS—Results of less than two thirds of NHLBI-funded randomized clinical trials of cardiovascular interventions were published within 30 months after completion of the trial. Trials that focused on clinical events were published more quickly than those that focused on surrogate end points. (Funded by the National Heart, Lung, and Blood Institute.)
Non-publication and delayed publication of randomized trials on vaccines: survey

Lamberto Manzoli associate professor, Maria Elena Flacco resident physician, Maddalena D’Addario resident physician, Lorenzo Capasso PhD student, Corrado De Vito assistant professor, Carolina Marzuillo assistant professor, Paolo Villari professor, John P A Ioannidis professor.

Abstract

Objective To evaluate the extent of non-publication or delayed publicaton of registered randomized trials on vaccines, and to investigate potential determinants of delay to publication.

Design Survey.

Data sources Trials registry websites, Scopus, PubMed, Google.

Study selection Randomized controlled trials evaluating the safety or the efficacy or immunogenicity of human papillomavirus (HPV), pandemic A/H1N1 2009 influenza, and meningococcal, pneumococcal, and rotavirus vaccines that were registered in ClinicalTrials.gov, Current Controlled Trials, WHO International Clinical Trials Registry Platform, Clinical Study Register, or Indian, Australian-New Zealand, and Chinese trial registries in 2006-12. Electronic databases were searched up to February 2014 to identify published manuscripts containing trial results. These were reviewed and classified as positive, mixed, or negative. We also reviewed the results available in ClinicalTrials.gov.

Main outcome measures Publication status of trial results and time from completion to publication in peer reviewed journals.

Data synthesis Cox proportional hazards regression was used to evaluate predictors of publication delay.

Results We analysed 384 trials (85% sponsored by industry). Of 355 trials (404 758 participants) that were completed, 176 (n=151 379) had been published in peer reviewed journals. Another 42 trials (total sample size 82 768) remained unpublished but reported results in ClinicalTrials.gov. The proportion of trials published 12, 24, 36, and 48 months after completion was 12%, 29%, 53%, and 73%, respectively. Including results posted in ClinicalTrials.gov, 48 months after study completion results were available for 82% of the trials and 90% of the participants. Delay to publication between non-industry and industry sponsored trials did not differ, but non-industry sponsored trials were 4.42-fold (P=0.008) more likely to report negative or mixed findings. Negative results were reported by only 2% of the published trials.

Conclusions Most vaccine trials are published eventually or the results posted in ClinicalTrials.gov, but delays to publication of several years are common. Actions should focus on the timely dissemination of data from vaccine trials to the public.

Introduction

Randomized controlled trials are crucial in providing reliable and timely information about the effectiveness and safety of all healthcare interventions.1 In the case of emerging pandemics with modifying or even new infectious agents, such as the pandemic A/H1N1 2009 influenza virus, the availability of information on potential vaccines becomes even more time sensitive.3 While a time-lag in the dissemination of results may have adverse consequences for the practice of evidence based medicine and on public health for any disease, for epidemic diseases a delay in publication of relevant randomized controlled trials may distort the available evidence that is used for recommendations, allocation of resources, stockpiling of drugs and vaccines, and other public action.4 Even if trials do eventually get published years later, it may be too late, and the results may have less relevance because of the rapid changes in

Published: 49%
Published: 68%
Research: increasing value, reducing waste*

- only $\frac{1}{2}$ of the health-related studies funded by the EU published
- Positive results more likely to be published
- “Although widely suspected, no empirical evidence is available that journals preferentially publish positive results”
- Investigators report that little time or low priority or importance of results are reasons for not publishing

Lancet January 2014
POTENTIAL REMEDIES

• Withholding final payment until study is published

• SMRI utilizes the NIMH data sharing system:
  • NIMH holds data repositories to which SMRI-funded investigators are asked to send data every 6 months as the study progresses.
  • 2 years after the end of the study data is made public.

• Advantages:
  • SMRI holds investigators’ data → if the investigator does not publish the data, then someone else can.
  • Individual patient meta analyses
  • tighter control on data analyses regarding outliers, type of analyses, etc.
We are obliged to improve our research efforts and methodology to justify the efforts made by Mr. Stanley and others who fund our research.