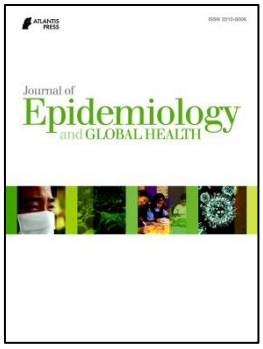

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Availability of results from clinical research: Failing policy efforts

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Abstract *Objectives:* Trial registration has a great potential to increase research transparency and public access to research results. This study examined the availability of results either in journal publications or in the trial registry from all studies registered at ClinicalTrials.gov.

Methods: All 137,612 records from ClinicalTrials.gov in December 2012 were merged with all 19,158 PubMed records containing registration numbers in the indexing field or in the abstracts. A multivariate analysis was conducted to examine the association between the availability of the results with study and participant characteristics available in registration records.

Results: Fewer than 10% of the registered studies and 15% of the registered and completed studies had published results. The highest publication rate of 22.4% was for randomized trials completed between 2005 (starting year for structured indexing in PubMed of study registration) and 2010. For 86% of overall and 78% of completed registered studies, no results were available in ClinicalTrials.gov or in journal publications. Studies funded by industry vs. other funding sources and drug studies vs. all studies of other interventions were published less often after adjustment for study type, subject characteristics, or posting of results in ClinicalTrials.gov.

Conclusion: Existing policy does not ensure availability of results from clinical research. International policy revisions should charge principal investigators with ensuring that the approved protocols and posted data elements are aligned and that results are available from all conducted studies.

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1. Introduction

Clinical research aims to inform clinical and policy decision-making by providing valid evidence for treatment benefits and harms [1—4]. However, when conclusions about treatment benefits and harms are based on incomplete evidence, biased decisions and ineffective health care can result [5]. Bias in the publication of studies that show impressive results can exaggerate the benefits of examined treatments [6—10].

Several policy initiatives have tried to improve transparency and ensure wider availability of results from clinical research. The Food and Drug Administration Modernization Act of 1997 required that the NIH create a trial registry — ClinicalTrials.gov — for drug efficacy studies approved with Investigational New Drug applications. In 2000, the National Library of Medicine at the National Institutes of Health launched ClinicalTrials.gov and opened it to the public via the Internet, and Congress mandated the registration of all clinical trials of pharmacological treatments for serious or life-threatening diseases at the ClinicalTrials.gov online database [11—14]. Then in 2005, the International Committee of Medical Journal Editors (ICMJE) and the World Association of Medical Editors made registration a condition of publication for all clinical studies [15]. Finally, the International Clinical Trials Registry Platform (ICTRP) was developed to include 13 primary registries which met the requirements of the ICMJE in providing 20 items with ''the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered'' (see Supplementary Appendix 1, also available at http://www.who.int/ictrp/network/trds/en/index.html).

Ensuring the public access to the results from clinical studies, the Food and Drug Administration Amendments Act (FDAAA) of 2007 mandated posting of the results from applicable clinical trials (e.g., interventional, non-phase I trials of drugs and devices subject to FDA regulation) on ClinicalTrials.gov within 1 or 2 years of study completion [16].

Nonetheless, publication of the results in journal articles remains voluntary. Less than half of the NIH-funded registered trials are published in a peer-reviewed journal within 30 months of trial completion [17]. Only 29% of completed registered studies involving children and 53% of NIH-funded trials have been published [18].

Previous research used time-consuming manual searchers of the publications in various subsets of registered studies (i.e., by source of funding [17], study participants [18], and specific health conditions) [19]. In contrast, this paper examines result availability from all studies registered with ClinicalTrials.gov to answer the question: *Do existing policies in research registration, publication, and indexing guarantee access to the results?* This study defines ''availability of the results'' as publication in the journals indexed on Medline or posting the results with ClinicalTrials.gov

2. Methods

For this study, ClinicalTrials.gov registration records were linked with Medline publication records by a unique registered study identifier (number of clinical trial or NCT). First, all records of the registered studies with no time restriction were downloaded from ClinicalTrials.gov from February 2000 to December 2012 (Appendix 2). All 20 fields required by the ICMJE were downloaded. The frequency of study types, design, funding, participant characteristics, and posting of the results were analyzed relying on information provided by the investigators in registration records [20]. Accuracy of the data in ClinicalTrials.gov can be confirmed only by comparing the posted data elements with those approved by the institutional review boards, which was beyond the scope of this study. For validation purposes, ambiguous data (e.g., enrollment values of more than 99,999 participants or negative publication time intervals when publications occurred before studies started subject recruitment) were excluded from the validated analyses.

In contrast with the previous research focusing on clinical trials only [21], all registered studies were analyzed irrespective of study design, funding, subject characteristics or market status of the examined treatments assuming that all clinical research evidence is important for decision-making (Appendix 2). The study design was categorized: as randomized trial when the study design field mentioned random allocation of participants into the treatment groups; as non-random studies when investigators did not explicitly mention randomization; and as unknown study design when investigators left this field blank. Interventions were categorized as drug, procedure, radiation, biologics, or behavioral according to the categories in ClinicalTrials.gov. Study findings were categorized into two categories: industry funding category included all studies funded by pharmaceutical or device companies exclusively or in combination with individuals, universities, or community-based orga-

nizations; all other funding sources category included studies funded by the National Institutes of Health or other U.S. Federal agencies exclusively or in combination with industry funding, as well as studies funded by individuals, universities, or community-based organizations without any industry involvement. The length of studies was calculated as the time period between start and completion dates. The publication time was estimated as the time period between study completion and journal publication.

Medline publication records have unique study registration numbers in a specifically designated field with secondary study identification ([SI]) (detailed information about indexing of the registered studies is available in PubMed tutorial at http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/020_810.html) [22]. In compliance with ICMJE's recommendations from 2005, all publications should report a trial registration number in the article abstract. Since the specific field for indexing of registered studies (secondary study identification field) was introduced in 2005, Medline was searched for registration numbers in that designated [SI] field, but also in the article abstracts. A subgroup analysis was then conducted among the studies registered before and after 2005.

All retrieved references were imported into the reference manager Endnote and then were exported to an Excel worksheet compatible with the SAS statistical software.

When the article reported the results from more than one registered study, additional reference records were created for each NCT. When a registered study was published in more than one article, the fact of the publication was counted only once using the earliest available publication.

For validation purposes, in order to determine the accuracy of the Medline indexing of the registered studies (since some publications of the registered trials did not report study identification numbers in abstracts but may have mentioned the registration status in the full texts of the articles), this study examined whether the secondary study identification field identified all publications of the registered studies in the core clinical journal (Abridged Index Medicus list of core clinical journals is available in Appendix 3) that published the greatest number of registered RCTs. To carry out this task, trial registration numbers were searched for in all Medline fields and in the full texts of the articles published in that journal. If full text articles did not include study registration numbers, it was concluded that the published study was not registered [15].

The publication records from PubMed were then merged with the registration records from ClinicalTrials.gov by the unique NCT number and the availability of the results and factors associated with publication status were examined. Publication rates were calculated as percentages of the registered studies with linked publication records in PubMed. The percentages of the registered studies were calculated with disposition of the results within the trial registry. Speculative imputations for missing data were avoided. Multivariate odds ratios of publication were calculated by study type (observational vs. interventional), random allocation of participants, recruitment as reported in ClinicalTrials.gov, funding, examined interventions, posting of the results in ClinicalTrials.gov, and age and sex of enrolled participants. It was hypothesized that odds of publications differ by study funding, design, and examined interventions. Subgroup analyses were conducted of the publication odds among registered completed or terminated studies to test the hypothesis that completed studies would have greater odds of publication. Publication odds may depend on the year of study registration, for example, recently published studies would have lower publication odds compared with the studies registered more than 3 years ago. To address this issue survival analysis was also conducted to examine publication of the completed studies by study design and funding [23]. The detailed analysis of the factors associated with posting the results in ClinicalTrials.gov was beyond the scope of this study [24]. All hypotheses testing at 95% CL were performed using SAS 9.3.

3. Results

A total of 137,612 registered studies were identified in ClinicalTrials.gov and 19,158 publications of registered studies in PubMed in December 2012 (Fig. 1). After deleting duplicates and merging the data from the trial registry with publication records from PubMed, 137,607 records of the registered studies and 12,938 publications of the registered studies were included in the analyses (analytical data file is available at https://netfiles.umn.edu/xythoswfs/webui/_xy-23709234_1-t_xCJavcvC).

The studies were published in 1332 journals; 55% of the studies were published in 32 journals. Each of these 32 journals published more than 100 registered studies. The completed ''Secondary Source ID'' field identified 97.3% of the publications of the registered studies and 2.7% of the articles