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Discontinuation of surgical *versus* nonsurgical clinical trials: an analysis of 88,498 trials

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ARTICLE INFO

Article history:
Received 29 November 2017
Received in revised form
4 January 2018
Accepted 15 February 2018
Available online 15 March 2018

Keywords:
Clinical trial
Publication
Discontinuation
Industry funding

ABSTRACT

Background: It has been previously reported that over 20% of surgical trials will be discontinued prematurely raising ethical and financial concerns. Previous studies have been limited in scope owing to the need for manual review of selected trials. To date, there has been no broad analysis comparing surgical and nonsurgical registered clinical trials.

Materials and methods: ClinicalTrials.gov was queried October 7, 2017 for all US trials from 2005 to 2017. Trials were assigned to surgical or nonsurgical groups by automated sorting. The sorting algorithm was validated by comparison with manual assignments made by blinded investigators. Comparisons were made between trial status, funding sources, and trial design. The reasons for discontinuation were examined and tabulated.

Results: The database search yielded 82,719 nonsurgical and 5779 surgical trials after automatic assignment. The algorithm for assignments had an overall accuracy of 87.99% and a positive likelihood ratio of 6.09 and negative likelihood ratio of 0.093. Significant differences existed in trial status (nonsurgical *versus* surgical: completed: 55.51% *versus* 39.49%, $P < 0.001$ and discontinued: 11.07% *versus* 15.97%, $P < 0.001$). Discontinuation due to poor recruitment was more commonly cited by surgical trials (44.65% *versus* 34.74% $P < 0.001$). Industry funding predicted discontinuation for all trials (odds ratio 1.63 $P < 0.001$) and surgical trials independently (OR 1.25 $P = 0.041$). Patient enrollment, reporting results, and NIH funding were all protective against discontinuation.

Conclusions: Surgical trials are more likely to prematurely discontinue than nonsurgical trials. Industry funding independently predicts trial discontinuation. Poor recruitment is a major cause of early trial discontinuation for all trials and is more pronounced in surgical trials.

Introduction

Early discontinuation of clinical trials is a complex issue with serious financial and ethical implications. Unfinished clinical trials are estimated to waste more than $240 billion annually worldwide.[1] Ethical issues include safety issues for participants and the potential denial of benefit to future patients.[1,2] Despite these serious concerns, trial discontinuation and/or failure to report outcomes has not been extensively studied. A 2016 study of academic institutions showed that only 66% of

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https://doi.org/10.1016/j.jss.2018.02.039

all registered trials reported results, and only 35.9% published a research report within 24 mo of study completion.[3] Study discontinuation and failure to report results may be especially prevalent in surgery.[4] However, a direct comparison between surgical and nonsurgical trials has yet to be studied. Estimates on surgical trial discontinuation range from 20% to 43% and 33% to 44% of trials remain unpublished for several years after trial completion.[4,5] This trend has been reported for surgical subspecialties, such as neurosurgery.[6]

Since clinical trial registration became mandatory in 2004, the principal source of data on clinical trials in the United States is the National Library of Medicine database, ClinicalTrials.gov. This archive's information on publicly and privately funded clinical studies was provided by sponsors or principal investigators at trial registration and updated throughout the study. The information reported includes numbers of study participants, status, and outcomes, both intended and unanticipated. Attempts to use this public database to investigate completion and reporting of surgical trials have been complicated as "surgical" is not a defined category.[7] Investigators have been forced to rely on manual review to identify surgical trials.[2-6,8] The narrowing of the query has often resulted in the inability to make comparisons between surgical and nonsurgical trials. One study analyzed 395 surgical trials and found poor recruitment, lack of funding, and negative results as major reasons for discontinuation. Poor recruitment appears to be the largest single factor in discontinuation of surgical trials, but no study has compared surgical and nonsurgical trials. Although industry funding did not predict discontinuation among surgical trials in one study, it was predictive of discontinuation among neurosurgical trials. Industry funding was also predictive of nonpublication.[5,6] As these studies were underpowered to detect the small effect size, the total impact of funding source on discontinuation and nonpublication has not yet been completely evaluated.

These findings lay the foundation for understanding early trial discontinuation, but much more work is needed to identify and quantify the factors involved. Characterizing this process and identifying the factors that influence trial completion will aid investigators in trial design and may influence how resources are allocated. We compared surgical and nonsurgical clinical trials to identify and compare factors influencing trial discontinuation and completion. We hypothesized that surgical trials are more likely to be discontinued early than nonsurgical trials and that enrollment is a larger barrier for surgical trials than that for nonsurgical trials.

Methods

Data collection

The public use database at clinicaltrials.gov was accessed October 7, 2017. Institutional review board approval was not needed for this study as all records were publicly available and contained no patient identifiable data. All clinical trials registered from the United States between 2005 and 2015 were identified and classified by trial status. Trials with status of "withdrawn" or "terminated" were classified as "discontinued". Trials with a status of "completed" were given their own category. All remaining trails were classified as "ongoing". Trials recorded in the database with "suspended" status were excluded from this analysis as they could not reliably be assigned to any of the three study groups. Suspended trials comprised only 0.39% of all available trials. Relevant data on each eligible trial for our study were downloaded as comma-separated values files and compiled into a single spreadsheet for analysis. All available database fields were included in the query. The intervention type is a coded variable defined by the clinicaltrials.gov database. Tabulated results represent all included study arms within any given trial. A single trial may have been funded by more than one source. In those instances, trials were given the "multiple" funding sources classification. The funding categories listed in the database include "NIH", "industry", "US Fed", and "other". The US Fed comprised non-NIH government funding such as the Center for Disease Control or the Food and Drug Administration. The "other" category primarily included private funding from universities or philanthropy. For the purposes of analysis, participant enrollment was treated as a binary condition where trials had either enrolled no participants or had enrolled at least one participant.

Trial assignments: surgical versus nonsurgical

To allow for a substantially larger sample size and to replace manual review, trials were automatically assigned to "surgical" and "nonsurgical" groups according to an algorithm derived for this project. Surgical keywords were generated by pooling the titles from 10,000 US trials obtained by searching the term "surgery" in clinicaltrials.gov. After omitting proper nouns and articles, individual terms from these titles were ranked by frequency of occurrence. Keywords were selected based on frequency and likelihood of being exclusive to surgical trials (i.e., laparoscopy is relatively unlikely to appear in nonsurgical trials whereas nonsurgical trials frequently reference "surgery"). A trial was defined as surgical if its title or description contained any of the surgical keywords and was also either within the "device" or "procedure" categories of the database. Keywords included the following: "Surg", "laparoscop", "ectomy", "resect", "plasty", "operat", "bariatric", and "bypass". Shortened words with wildcard search terms were chosen to allow for flexibility within the search syntax. For example, the keyword "Operat" is able to capture "operation", "operative", and "operate" and include matching trials into the defined categories.

A validation of this algorithm was performed by randomly sampling trials according to automatic assignment from each broad category (ongoing, completed, and discontinued). Three independent investigators were blinded to algorithm assignments and asked to manually assign trials to "surgical" or "nonsurgical" groups based on trial titles and available descriptions. Assignments were compared across investigators. Any discrepancies in assignment were passed to an additional blinded investigator. If discrepancies persisted, the investigators met to review the trials, and assignment was made by consensus. The number of trials sampled from each category was produced at random from between 100 and 150 trials from each subcategory (surgical *versus* nonsurgical for each of