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Factors associated with the successful completion of randomized controlled trials in gynecological oncology☆

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HIGHLIGHTS

- Within five years of registration on ClinicalTrials.gov, only 33.7% of randomized controlled trials had been published.
- 71.8% of completed randomized controlled trials resulted in publication of results in a peer-reviewed journal.
- Single-center trials were significantly more likely to result in completion.
- There was no difference in characteristics between published and unpublished randomized controlled trials.

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ABSTRACT

Purpose: The aim of our review was to ascertain factors associated with the successful completion of a randomized controlled trial in gynecological oncology.

Materials and methods: This retrospective cohort study utilized data collected from the National Institutes of Health's US National Library of Medicine database on ClinicalTrials.gov. Data was collected over a five year period (2009–2013). Utilizing the search terms under the National Institutes of Health recommended "Studies by Topics" gynecological oncology studies were identified. Randomized controlled trials were selected for based on intervention and randomization criteria. Elements were then compared with statistical analysis performed using SASS.

Results: As of September 1st 2018, 149 of the 318 identified randomized controlled trials were successfully completed over a median length of 44 months (IQR 30.0–55.0). Completed randomized controlled trials were more likely to be performed at single centers ($p < 0.005$). Interventional, drug and device trials were not significantly more likely to be completed. There was no difference in funding sources for completed or not completed randomized controlled trials.

Conclusions: Prospective randomized trials are essential for establishing the standard of care in clinical medicine. They are, however, time and resource intensive. Herein we have attempted to identify factors associated with successful and timely completion of gynecologic oncology randomized controlled trials including site of origin, number of participating sites, funding source, intervention type, enrollment size, and study length; however, none of these factors were observed to have an association with increased rates of trial publication.

1. Introduction

In 2000, ClinicalTrials.gov was established by the National Institutes of Health (NIH) and the U.S. Department of Health and Human Services to comply with the Food and Drug Administration Modernization Act of 1997. This law mandated a publicly accessible registry of new investigational drug trials [1]. Over the course of the next several years, journal editors as well as local, national, and international government organizations encouraged investigators to register a variety of trials on ClinicalTrials.gov [2,3]. As part of the Food and Drug Administration Amendments Act of 2007, clinical trials were further required to publish a summary of patient characteristics and trial outcomes on the site [4]. This step went into

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effect in September 2008. Previous studies have looked at the characteristics of trials registered on ClinicalTrials.gov and subsequently published in other fields of medicine [5,6]. This research demonstrated multi-center and international studies were more likely to be discontinued prior to completion. Completed studies with industry funding or sample sizes <100 were significantly less likely to be published [5,6].

Randomized controlled trials (RCTs) remain the most reliable method for testing new medical therapies and treatment protocols [7]. Increasing trial length, administrative burden, and decreasing funding have resulted in an environment for clinical research which limits the initiation and hinders the completion of studies [3,8–10]. Resources are inefficiently utilized in interventional trials if they are discontinued or not published—a known problem in other fields of research [9,11–13]. Research in gynecological oncology is underfunded compared to other malignancies when stratified by site-specific lethality [5,6]. It is necessary to ensure that research into gynecological oncology efficiently utilizes the limited available funding resources.

The objective of this analysis is to ascertain the variables associated with completion and publication of randomized controlled trials in gynecologic oncology. We theorized that single-site studies with sample sizes <100 were more likely to be completed, but less likely to be published when compared to larger completed trials.

2. Methods

This was an observational cohort study. The data is publicly available and was considered exempt by the Institutional Review Board at the McGovern Medical School at the University of Texas Health Science Center at Houston. The primary purpose of this study was to examine rates of completion and publication for randomized controlled trials in gynecological oncology. In this study, variables associated with successful trial completion or publication in previous research were investigated. These were defined as trial location, funding source, intervention type, single-center vs. multicenter participation, trial purpose, trial size, and trial length.

ClinicalTrials.gov was queried on a single day (August 28, 2018) for gynecological oncology trials registered from January 1, 2009 through December 31, 2013. The search was conducted by National Institutes of Health "Studies by Topics" under the "Urinary Tract, Sexual Organs, and Pregnancy Conditions" section Studies pertinent to gynecological oncology were further sub-selected by using search terms found in Appendix 1.

All identified studies were placed in a database that included study descriptors and design data reported on ClinicalTrials.gov. Two reviewers (AS, SW) independently reviewed the database and removed duplicates, studies that were not primarily focused on gynecological oncology, and studies that were non-randomized. In cases where there was a discrepancy, a third author (MG) reviewed the record and assisted in resolution.

All ClinicalTrials.gov records that were marked as "complete" or "unknown" were reviewed to identify links to study publications (other statuses included "withdrawn," "terminated," "recruiting," "active, not recruiting," "enrolling," and "suspended"). In the case of "complete" or "unknown" studies in which no link to publication was available, PubMed and Google Scholar were used to search for corresponding publications. Search terms included the ClinicalTrials.gov registry number, trial title, author names, and keywords. Matches were evaluated based on trial design, hypothesis, sample size, and trial dates. Trials and/or abstracts that were available in a peer-reviewed journal indexed in PubMed were considered to be both completed and published. Based on study methods, non-randomized trials were again removed from the databases. Date of publication and the impact factor of the journal were collected for studies that achieved publication. The sample median for impact factor was calculated, and data were split at the median. Journals with an impact factor above the median were classified as "high impact" journals and journals with an impact factor below the median were classified as "low impact."

Monte Carlo estimation of the exact Pearson Chi-Square test was used for comparison of categorical variables. Differences were considered to be significant if the p-value was <0.05. Descriptive statistics for trial length and enrollment were developed. Medians were compared analyzed using a two-sample *t*-test. Differences in least square means were calculated, for which 95% confidence intervals were developed. Results were considered to be significant if the 95% confidence interval did not cross zero. All statistical analyses were performed using IBM SPSS® software.

3. Results

A total of 2777 studies were initially identified through ClinicalTrials.gov. After removing duplicates, non-randomized trials, and those not focused primarily on gynecological oncology, 318 trials remained. Of these, 149 were completed and 107 were published. Median number of study participants was 159 (interquartile range 71–151). Of all RCTs, statuses listed as of the date of data capture were as follows: 149 completed; 96 recruiting; 31 unknown; 28 terminated; 9 withdrawn; 2 suspended; 2 active, not recruiting; and 1 enrolling by invitation (Table 1). This corresponds to an overall 12% discontinuation rate.

Table 2 shows characteristics associated with completion of RCTs. We found that single-center trials were more likely to be completed than multicenter trials (59.7% vs. 40.3%, $p = 0.005$). Additionally, we found that trials conducted over a short period were more likely to be completed than longer trials (44.0 months vs. 72.0 months, 95% CI: 23–38, $p < 0.001$). We found no significant difference between completed and non-completed trials based on trial location, funding source, intervention type, trial size, or trial purpose.

Completed trials were analyzed based on publication status. We found no significant difference between published and unpublished trials based on trial location, funding source, single-center vs. multicenter trials, intervention type, trial size, trial length, or trial purpose (Table 3). Multicenter trials were more likely to result in publication in higher impact journals (IF $\geq$5.157) when compared to single-center trials (75.6% vs. 35.0%, $p < 0.0001$).

4. Discussion

This paper examined studies in gynecological oncology over the first five years of federally-mandated trial registration on ClinicalTrials.gov. When ClinicalTrials.gov was queried, all RCTs had been registered in the database for a minimum of five years. Approximately five years after the latest included study date, nearly 1 in 8 trials was terminated, suspended, or withdrawn, less than half of all RCTs had been completed, and only 33% had published results—either on ClinicalTrials.gov or in the peer-reviewed literature. Our study did not demonstrate an effect of funding source or

Table 1
Trial status at time of data collection.

Status	Number of studies (%)
Completed	149 (46.8%)
Recruiting	96 (30.1%)
Unknown	31 (9.7%)
Terminated	28 (8.8%)
Withdrawn	9 (2.8%)
Suspended	2 (0.6%)
Active, not recruiting	2 (0.6%)
Enrolling by invitation	1 (0.3%)

Table 2
Characteristics associated with completion of randomized control trials.

Characteristic	Completed N (%) Median (IQR)	Not completed N (%) Median (IQR)	p-Value
Site of origin			1.0
US only or US + international	67 (45.0%)	75 (44.4%)	
International only	82 (55.0%)	94 (55.6%)	
Participating sites			
Single-center	89 (59.7%)	74 (43.8%)	**0.005***
Multi-center	60 (40.3%)	95 (56.2%)	
Funding			
Industry	49 (51.5%)	46 (48.4%)	0.32
Non-industry (federal, etc.)	100 (44.8%)	123 (55.2%)	
Intervention			
Drug/device/procedure	113 (44.1%)	143 (58.1%)	0.06
Other	36 (58.1%)	26 (41.9%)	
Purpose			0.125
Prevention	14 (56.3%)	18 (43.7%)	
Treatment	84 (41.8%)	117 (58.2%)	
Diagnostics	4 (50.0%)	4 (50.0%)	
Other	43 (55.8%)	34 (44.2%)	
Enrollment	146 (61–451)	170 (72–452)	0.226
Trial length	44.0 (30.0–55.0)	72.0 (47.0–96.0)	**<0.001***

Bold values indicates significance at $p < 0.05$.

any other analyzed variable on rates of publication. It is widely known that proportionally less funding is directed toward research involving gynecological malignancies when compared to other less common and less lethal cancer types. As such, accountability for the utilization of research funds allocated to gynecological cancers is paramount.

Our findings are consistent with results from similar analyses conducted in the general surgery and medical oncology literature. In a 2014 study published in the BMJ by Chapman, et al., 21% of all randomized controlled trials in general surgery registered on ClinicalTrials.gov were discontinued early, only 79% reached completion, and of completed studies, only 66% were published at approximately 5 years. Comparable to our findings, there was no association between funding type, intervention, sample size, number of participating centers, etc., and publication status [13]. A similar study was conducted in the medical oncology literature in 2016 and published in the European Journal of Cancer. In this study, Chen et al. found that only 66% of completed medical oncology studies achieved publication, with only 32% of these being published within 24 months of completion. Again, no association was found between trial location or funding and successful publication of results [14].

Table 3
Characteristics associated with publication of randomized control trials.

Characteristic	Published N (%) Median (IQR)	Not published N (%) Median (IQR)	p-Value
Site of origin			0.07
US or US + international	43 (64.2%)	24 (35.8%)	
International only	64 (78.0%)	18 (22.0%)	
Participating sites			0.57
Single-center	62 (69.7%)	27 (30.3%)	
Multi-center	45 (75%)	15 (25.0%)	
Funding			0.86
Industry sponsored	35 (72.9%)	13 (27.1%)	
Other	72 (71.3%)	29 (28.7%)	
Intervention			0.82
Drug/device/procedure	82 (72.6%)	31 (27.4%)	
Other	25 (69.4%)	11 (30.6%)	
Purpose			0.59
Prevention	12 (66.7%)	6 (33.3%)	
Treatment	59 (70.2%)	25 (29.8%)	
Diagnostics	4 (100.0%)	0 (0.0%)	
Other	32 (74.4%)	11 (25.6%)	
Enrollment	166 (99–597)	111 (53–191)	0.40
Trial length	41.5 (27.0–52.5)	47.0 (33.0–56.0)	0.10

Despite our finding that single-center trials and shorter trial length were associated with increased rates of completion, these studies were no more likely than their multi-center or more extended trial length counterparts to result in publication. While our study design did not support further analysis to this effect, this finding may suggest a publication bias amongst journals, where less sophisticated studies struggle to receive acceptance and publication. This is a finding that is documented in the oncologic literature. Krzyzanowska et al. found in 2003 that findings presented at annual meetings of the American Society of Clinical Oncology were less likely to be published if they conveyed statistically non-significant results [15]. Non-completion and non-publication of results of these trials represent a disservice to patients who volunteer their health and well-being for research that fails to yield usable data.

This study addresses the issue of non-completion and non-publication of randomized controlled trials in the gynecological oncology literature. Strengths of this study include the use of a national repository for study registration, and beginning the search with a wide catchment for reproductive tract disorders, and subsequently narrowing the focus to malignancies to ensure maximum data capture. Weaknesses of this study are associated with the incomplete nature of the ClinicalTrials.gov database. Despite mandatory reporting of trial status and results, the database was noted to have several coding errors that were identified and corrected by the researchers during data collection, with 11/318 records being recoded for publication status after finding publicly available results in the peer-reviewed literature. This finding is in keeping with previous studies which have noted incomplete reporting of study results by investigators in ClinicalTrials.gov [16,17]. Incomplete reporting may also account for the 30% of studies that are categorized as still in recruitment phase, some as many as 10 years from initiation.

This study highlights the fact that inherent difficulties exist at each stage of the research process, from funding to completion to publication. These difficulties, however, are not easily explained by discrete characteristics of the location, investigators, or study. Further research may benefit from taking a qualitative approach in determining and removing factors that investigators identify as comprising barriers to successful trial completion and publication. Improving trial completion and publication rates in gynecological oncology would do justice to patients who contribute their time and bodies by enrolling in trials irrespective of the outcomes, but do so regardless in the hope of improving the health of those that come after them.

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Declaration of competing interest

The authors report no conflict of interest.

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