Journal of Hand Surgery Global Online 5 (2023) 673–676

Contents lists available at ScienceDirect

Journal of Hand Surgery Global Online

journal homepage: www.JHSGO.org

Original Research

Analysis of Terminated Hand and Wrist-Related Clinical Trials

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ARTICLE INFO

Article history:
Received for publication February 12, 2023
Accepted in revised form April 13, 2023
Available online May 10, 2023

Key words:
Clinical trials
Hand surgery
Randomized controlled trial
Study termination
Wrist surgery

Purpose: While clinical trials provide high-quality evidence guiding medical decision-making, early trial termination can result in both lost time and resources. Our purpose was to investigate the rate of and reasons for clinical trial termination for hand and wrist-related conditions and identify study characteristics associated with early trial termination.

Methods: The ClinicalTrials.gov database was queried for all hand and wrist-related clinical trials. All terminated and completed trials were reviewed, with characteristics and reasons for termination recorded. Study characteristics included type, purpose, intervention assessed, enrollment, group allocation, blinding, trial phase, sponsor type, and geographic region. Chi-square test was used to identify associations between trial characteristics and terminated versus completed status.

Results: A total of 793 hand and wrist-related clinical trials were identified, with 77 trials (10%) terminated prior to completion. The most common reason for termination was "recruitment/retention difficulty," reported in 37 (48%) terminated trials. In comparing competed versus terminated trials, primary purpose (nonobservational studies), enrollment (<50 patients), and geographic region (North America) were all significantly more likely to be terminated. Terminated trials were more likely to have an intervention type investigating a specific device or drug.

Conclusions: Early trial termination for hand and wrist-related conditions is common (10%), with patient recruitment and retention identified as the leading cause of termination. Trials involving potential commercial incentives (those investigating a device or drug) were associated with an increased rate of trial termination.

Clinical relevance: An emphasis on patient enrollment during study design may aid in mitigating the most common cause of early clinical trial termination.

Clinical trials are experimental studies designed to prospectively evaluate the efficacy of a specific treatment. Because of their rigorous study design with randomization and blinding, these studies provide high-quality evidence and can aid in guiding clinical decision-making.[1] These trials frequently comprise guideline-level treatment recommendations, including the American Academy of Orthopaedic Surgeons Clinical Practice Guidelines.[2,3] In executing these trials, investigators often face financial, administrative, regulatory, and participant-related barriers, including securing funding, allocating staff, distributing research materials, and recruiting and maintaining the study population.[4] If these issues are unable to be successfully addressed, the trial may be terminated prior to completion.

The trial termination is associated with substantial cost, lost resources, and wasted effort by study investigators and patients.[5–7] Identifying the reasons behind the trial termination may help to guide future trial designs. Previous studies have investigated trial characteristics associated with trial termination outside hand and wrist surgery.[8–13] Although previous investigations have identified risk factors across various surgical subspecialties, there remains a paucity of literature regarding trials in hand and wrist surgery.[8–13]

The purpose of this investigation was to perform a cross-sectional analysis of clinical trials for conditions on the hand and

Declaration of interests: No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

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https://doi.org/10.1016/j.jhsg.2023.04.003

wrist. We aimed to quantify completed and terminated clinical trials and reasons for termination. In addition, we aimed to identify trial characteristics associated with early termination status. We hypothesized trial termination would be common among hand- and wrist-related clinical trials.

Materials and Methods

An Institutional Review Board exemption was obtained for this investigation. A search of hand and wrist clinical trials on ClinicalTrials.gov was conducted on May 3, 2022, using the search terms describing common hand and/or wrist-related conditions (Appendix 1, available on the *Journal*'s website at www.jhsgo.org). ClinicalTrials.gov is a web database that provides the public with access to information on publicly and privately supported clinical trials.7 The principal investigator or the sponsor provided the information listed on the website, which was updated throughout the study or after the study had been completed.

Each term was searched separately on ClinicalTrials.gov. A list of studies, as well as their descriptive data, was compiled. Duplicates were removed. Trials were then identified by completion status, and those with either a completed status or terminated status were included for review. Trial titles were manually screened by the reviewers. Trials were excluded if they were unrelated to the hand and/or wrist. The trial parameters of interest were the primary purpose, study type, primary sponsor, intervention, enrollment, allocation, blinding, study phase, and region. ClinicalTrials.gov provides explanations for each characteristic within the "Glossary of Common Site Terms." 7 Reviewers manually retrieved any missing information from ClinicalTrials.gov for the parameters of interest. For the study phase, any study within phase 1 (including combined phase 1 and 2 studies) was categorized within the phase 1 group. Studies that were either only phase 2, phase 3, or combined phases 2 and 3 were categorized into the phase 2/3 group. For additional descriptions, the "other" classification within the primary sponsor category was recategorized and broken down further into the following classification groups: University, Hospital or Health System, Individual, Professional Society, Specialized Medical Center, Research Center, and Private Foundation. For statistical analysis, categories italicized in Table 1 under primary purpose, intervention, study phase, sponsor, and region were collapsed into one group within these parameters.

A chi-square test was performed to assess whether there were associations between completed or terminated studies and the parameters of interest. P values of $< .05$ were used to determine the statistical significance. Pairwise comparisons were conducted using Fisher exact test to determine which category within the parameter was most significantly associated with completion status. Bonferroni adjustment was used to determine the P value of statistical significance for pairwise comparisons.

A post hoc power analysis of chi-square analysis was also performed with the effect and combined sample sizes to determine the probability that we obtained a significant result given an alpha level of 0.05. Cramer's V was used to measure the association or effect size between the completion status and parameters of interest. Adequate statistical power was defined as a power of $\geq$80%.

Various post hoc power analyses for chi-square were performed to detect an association between completion status and the parameters of interest at a significance level of $P = .05$ and a sample size of N = 793. The analysis revealed that this study achieved 100% power to detect a 19% association with enrollment, 20% association with regional status, and 36% association with intervention type and completion status. This study was 98% powered to detect a 16% association between primary purpose and completion status.

Results

In total, 793 clinical trials were identified and included in this study. The Figure presents a flowchart depicting the included and excluded studies. Of those included, 716 were listed as completed, and 77 (9.7%) were terminated.

The reasons for trial termination are listed in Table 2. The most common cause for study termination was recruitment/retention difficulty, with 37 (48%) studies terminated. Administrative/conduct issues (n = 15; 19%) and business decisions (n = 7; 9%) were the next most common reasons for study termination. Ten studies (13%) were terminated for unknown reasons.

Study characteristics of the completed and terminated trials are shown in Table 1. Both categories of trials presented similar characteristics in that the majority of completed and terminated trials were interventional (79% and 83%), randomized (62% and 65%), and not blinded (52% and 58%), respectively. In both trial categories, treatment was the most common primary purpose for the trial. The primary trial purpose was also significantly associated with completion status ($P < .001$). The primary sponsors for both trial types were universities, with 41% of completed trials and 38% of terminated trials funded by a university. Hospitals or health systems were the next most common type of sponsor for both completed (n = 244; 34%) and terminated trials (n = 26, 34%). Enrollment status had a significant association with completion status, with the majority of completed trials (n = 309; 43%), although at a smaller proportion, and most terminated trials (n = 57; 74%) enrolling <50 participants ($P < .001$). Of the terminated studies, a large proportion was conducted in North America (73%), whereas only 41% of completed trials took place in the North American region. The region also demonstrated a significant relationship with the completion status of the trial ($P < .001$). No significant association was found between the clinical trial completion status and study type, allocation, blinding, study phase, or primary sponsor.

The primary purpose, intervention type, enrollment, and region were significantly associated with the clinical trial completion status. Pairwise comparisons were conducted between specific parameter categories using a Bonferroni-adjusted alpha of 0.01667 for the primary purpose, enrollment, and region, as well as a Bonferroni-adjusted alpha of 0.005 for intervention type. Within the primary purpose, treatment and nontreatment/observational studies were significantly associated with termination compared with observation ($P < .001$). North America was significantly associated with a terminated trial compared to Europe and non-North American/European regions ($P < .001$). Enrollment of <50 participants was significantly associated with termination compared with both treatments having 50–100 participants and >100 participants ($P < .001$). Finally, trials with drug interventions were significantly associated with termination compared with interventions that were nonprocedure/device/drugs ($P < .005$).

Discussion

Trial termination occurred in 9.7% of hand- and wrist-related clinical trials. This rate is consistent with the previous investigations from other fields and subspecialties. In a cross-sectional study of all trials reported on Clinicaltrials.gov, Williams et al observed a 12% termination rate.[10] Within orthopedics, termination rates were found to be 8% and 13% for shoulder- and elbow-related trials, respectively, and 6.8% to 14% for spine-related trials.[8,9,11] The leading reason for termination was patient recruitment/retention, which occurred in nearly half of the trials, a finding that has been noted in reviews of all clinical trials within this database and subspecialty-specific investigations.[8–11] This echoes the findings of other authors, who reported this rate to be between

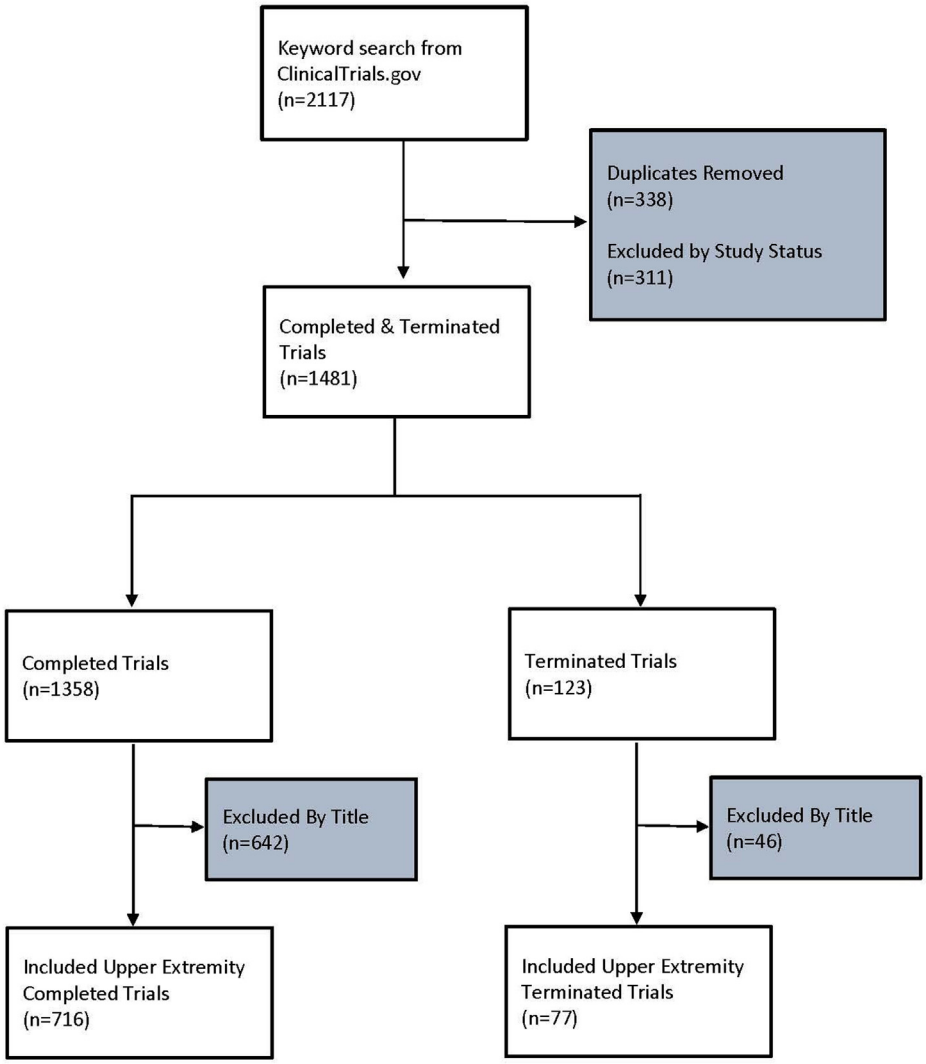

Figure. Flowchart of article inclusion for the analysis of hand- and wrist-related clinical trials.

33.8% and 56.5%.[8–10,12] Poor recruitment is likely a multifactorial problem, but it has been suggested that narrow eligibility criteria, investigator-led (rather than industry-led) trials, and high-burden interventions may be responsible.[14] The awareness of this issue has led to the development of strategies aimed at improving patient recruitment and retention. A recent Cochrane review concluded high-grade evidence to support the use of open-label trials, telephone reminders to nonresponders, and information pamphlets to increase enrollment.[15] Strategies that increase patient enrollment and retention will be critical to the success of future clinical trials.

There were several trial characteristics associated with termination. Observational trials were more likely to be completed, whereas treatment studies were more likely to be terminated. This difference may be because of patient concerns regarding participating in clinical trials, such as fears about randomization and treatment side effects.[16] Terminated trials were also more likely to be performed in North America, accounting for nearly three-quarters of all terminated trials. This was also observed as a significant factor for early termination in oncologic trials.[13] We believe that this increased rate of North American study termination may be attributable to academic pressures to publish, resulting in the creation of clinical trials without the sufficient resources and planning needed for successful trial completion.

Trials where the intervention type was a device or a drug were significantly more likely to be terminated. This was also reported in shoulder-related clinical trials, in which 59% of terminated trials involved a device or drug.[8] Additionally, industry-sponsored studies were terminated at a rate of 22% and were also found to be more common among terminated trials.[8] In our series, clinical trials with an industry sponsor were more likely to be terminated (13% vs 8% respectively), but these results were not statistically significant. Caruana et al[9] found that industry-sponsored spine-related trials were terminated at a higher rate, accounting for over 50% of terminated trials. The exact reason for these observations remains unclear but may be related to patient enrollment, where narrow patient eligibility criteria designed to maximize the product's effect may limit patient participation.[17] Added scrutiny to trial design and feasibility of patient inclusion/exclusion criteria may be warranted for these trials to reduce trial termination.

Limitations of the study must be acknowledged. First, data were exclusively obtained from ClinicalTrials.gov. Although reporting on this site is mandatory in the United States,[18] it is not mandatory globally; therefore, some international trials may have been missed. Second, 10% of trials were terminated for a reason listed as unclear. Furthermore, it is possible that our search terms, though designed to be comprehensive, did not capture all relevant hand and wrist-related trials and, therefore, some trials may have been omitted.

Table 1
Study Characteristics of Completed and Terminated Clinical Trials

Characteristics	Completed Trials, n (%) n = 716	Terminated Trials, n (%) n = 77	*P* Value
Study type			
Interventional	564 (79)	64 (83)	.372
Observational	152 (21)	13 (17)	
Primary purpose			
Treatment	469 (66)	60 (78)	<.001
Observational	153 (21)	1 (1)	
Nontreatment/observational	94 (13)	16 (21)	
Other	27 (4)	2 (3)	
Diagnostic	17 (2)	6 (8)	
Supportive care	17 (2)	-	
Prevention	12 (2)	3 (4)	
Health services research	10 (1)	1 (1)	
Basic science	8 (1)	-	
Screening	3 (0)	-	
Not listed	-	4 (5)	
Intervention type			
Procedure	188 (26)	18 (23)	
Device	176 (24)	24 (31)	.020
Drug	133 (19)	22 (29)	
None	18 (3)	3 (4)	
Nonprocedure/device/drug	203 (28)	10 (13)	
Diagnostic test	87 (12)	2 (3)	
Rehabilitation	47 (7)	1 (1)	
Behavioral	44 (6)	5 (6)	
Radiation	10 (1)	-	
Indeterminate	15 (2)	2 (3)	
Enrollment			
<50	309 (43)	57 (74)	<.001
50–100	222 (31)	8 (10)	
>100	185 (26)	12 (16)	
Allocation			
Randomized	446 (62)	50 (65)	.649
Nonrandom	270 (38)	27 (35)	
Blinding			
None	375 (52)	45 (58)	.177
Single	148 (21)	14 (18)	
Double	108 (15)	8 (10)	
Triple	48 (7)	9 (12)	
Quadruple	37 (5)	1 (1)	
Study phase			
Phase 1	29 (4)	2 (3)	.541
Phase 2/3	90 (13)	11 (14)	
Phase 4	47 (7)	8 (10)	
Not Listed	550 (77)	56 (73)	
Primary sponsor type			
University	296 (41)	29 (38)	.714
Hospital/health system	244 (34)	26 (34)	
Nonuniversity/hospital	176 (25)	22 (29)	
Industry	58 (8)	10 (13)	
NIH	25 (4)	3 (4)	
Individual	49 (6)	5 (6)	
Specialized medical center	12 (2)	2 (3)	
Research center	16 (2)	1 (1)	
Private foundation	8 (1)	-	
Government agency	7 (1)	-	
Professional society	1 (0)	1 (1)	
Region			
North America	290 (41)	56 (73)	<.001
Europe	224 (31)	15 (19)	
Non-North America/Europe	202 (28)	6 (8)	
Middle East	72 (10)	3 (4)	
Asia	71 (10)	1 (1)	
South America	30 (4)	1 (1)	
Africa	24 (3)	1 (1)	
Oceania	5 (1)	-	

For statistical analysis, categories italicized under the primary purpose, intervention, study phase, sponsor, and region with were collapsed into one group within these parameters.

Future investigations or reviews should aim to explore more effective ways to conduct clinical trials with the goal of exploring best practices with respect to recruiting and retaining study participants.

Table 2
Reasons for Study Termination of Clinical Trials

Reasons for Termination	Total Terminated Clinical Trials, n (%) n = 77
Recruitment/retention difficulty	37 (48)
Administrative/conduct issues	15 (19)
Business decision	7 (9)
Data from trial	2 (3)
Insufficient recruitment for analysis	-
Recall/cessation of investigational product	2 (3)
COVID-19 related	3 (4)
External information	-
Unclear reason for termination	10 (13)
Difficulty obtaining study materials	3 (4)
Loss of funding	4 (5)

In conclusion, an early trial termination for hand and wrist conditions is common. The leading reason for termination was because of patient recruitment and retention. Trial characteristics, such as sponsor, study purpose, and intervention type, may be factors associated with trial termination. With the cost and effort demanded to conduct clinical trials, studies should be designed with an emphasis on patient enrollment to increase trial completion.

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