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Clinical Trials Related To The Spine & Shoulder/elbow: Rates, Predictors, & Reasons For Termination

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Clinical Trials Related to the Spine & Shoulder/Elbow:

Rates, Predictors, & Reasons for Termination

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

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Abstract: Clinical Trials Related to the Spine & Shoulder/Elbow: Rates, Predictors, & Reasons for Termination

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Clinical trials are key to the advancement of products and procedures related to musculoskeletal conditions. Unfortunately, many trials are terminated prior to completion. ClinicalTrials.gov is a registry and results database maintained by the National Library of Medicine that catalogs trial characteristics and tracks overall recruitment status (e.g., ongoing, completed, terminated) for each study as well as reasons for termination. Reasons for termination have not been specifically evaluated for musculoskeletal trials and those related to the spine and shoulder/elbow were selected for characterization and assessment of independent predictors of termination by comparing characteristics of completed and terminated trials.

The ClinicalTrials.gov database was queried for all completed and terminated interventional studies using search terms built into the ClinicalTrials.gov search engine related to the spine on June 20, 2021 and those related to the shoulder/elbow on August 6, 2021, respectively. Trial characteristics and reasons for termination were abstracted. Univariate and multivariate analyses were performed to determine independent predictors of trial termination.

For clinical trials related to the spine, a total of 969 were identified and characterized, of which 136 (14%) were terminated. Insufficient rate of participant accrual was the most frequently reported reason for trial termination, accounting for 33.8% of terminated trials. Multivariate analysis demonstrated increased odds of trial termination for industry-

sponsorship (odds ratio [OR] = 1.59) relative to sponsorship from local groups, device studies (OR = 2.18) relative to investigations of drug or biological product(s), and phase II (OR = 3.07) relative to phase III studies ($p < 0.05$ for each).

For clinical trials related to the shoulder, a total of 662 were identified and characterized, of which 51 (8%) were terminated. Difficulties with participant recruitment and/or retention was the individual reason most frequently reported for trial termination, accounting for 51% of terminated clinical trials related to the shoulder. For clinical trials related to the shoulder, multivariate analysis of primary trial characteristics demonstrated increased odds of trial termination for industry-sponsorship (OR = 4.2, $p = 0.001$) relative to sponsorship from local groups, and blinded studies (OR = 45.8, $p = 0.0003$) relative to studies that did not implement any form of blinding.

For clinical trials related to the elbow, a total of 126 were identified and characterized, of which 16 (13%) were terminated. Difficulties with participant recruitment and/or retention was the individual reason most frequently reported for trial termination, accounting for 38% of terminated clinical trials related to the elbow. For clinical trials related to the elbow, logistic regression did not reveal any of the primary trial characteristics evaluated to be correlated with odds of termination.

Clinical trials related to the spine, shoulder, and elbow were terminated at a rate of 14%, 8%, and 13%, respectively. Overall, difficulties in the recruitment and/or retention of trial participants was the reason most frequently reported for trial termination. With significant resources put into clinical trials and the need to advance scientific objectives, independent predictors and reasons for trial termination should be considered and addressed, when possible, to optimize the completion rate of trials that are initiated.

Acknowledgements

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Introduction

Clinical trials are key to the advancement of products and procedures related to the musculoskeletal conditions. Unfortunately, trials may be terminated before completion. Trials that are not completed have financial costs, administrative and patient burden, and may not achieve their original objectives.

ClincialTrials.gov is a public registry and results database of clinical trials information that was launched in September 2008 to implement Section 801 of the United States Food and Drug Administration Amendments Act of 2007 (FDAAA 801), which requires the submission of "basic results" for certain clinical trials.[1,2] These basic results include tabular summarization of the following: the progress of participants through each stage of the study; baseline characteristics (e.g., demographic data, study-specific measures), outcome measures and statistical analyses, and adverse event information, though submission of adverse event information was optimal before required reporting as of September 2009.

Data such as the Overall Recruitment Status of the trial must be periodically updated to reflect whether subject enrollment is ongoing or has halted. ClinicalTrials.gov considers a study completed when "the study has concluded per study protocol; participants are no longer receiving intervention or being examined (i.e., the last participant's last [study-related] visit has occurred)" whereas Overall Recruitment Status is updated to reflect termination when the "study has halted

prematurely and will not resume; participants are no longer being examined or receiving intervention."[3]

In February 2007, ClinicalTrials.gov made the data element *Why Study Stopped* available as a free-text field for reporting of a brief explanation of the reason or reasons why a clinical study was stopped before the planned completion as initially anticipated by the study protocol. Completion of the *Why Study Stopped* data element is now required if the study Start Date occurred on or after January 18, 2017.[3]

Rates and reasons for termination of clinical trials have been previously assessed in a 2015 cross-sectional study of the ClinicalTrials.gov results database wherein reasons for termination of all terminated trials registered—without regard for the condition or disease in which the investigational product was being trialed—as of February 2013 (i.e., the date the ClincialTrials.gov results database was queried for the study) were grouped as related to scientific data gathered from the trial itself, reasons other than scientific data from the trial being conducted, and termination reason not provided. The most common reason for trial termination of all trials assessed was insufficient study participant accrual rate, reported as the reason for termination for 56.5% of terminated clinical trials.[4] However, reasons for trial termination and trial characteristics associated with trial termination have not been specifically evaluated for musculoskeletal trials, nor have the rates of

termination for musculoskeletal trials been compared to rates of termination for clinical trials overall.

Statement of Purpose

Building on prior studies related to reasons for termination of clinical trials for the ClinicalTrials.gov results database overall[4] and the fate of clinical trials related to the spine, which tracked overall recruitment status and termination rate of spine trials without reporting reasons for termination specific to musculoskeletal conditions of the spine,[5] the current study was performed to assess clinical trials related to the spine and shoulder/elbow for characterization and assessment of independent predictors of termination by comparing characteristics of completed and terminated trials.

Methods

Author Contributions

Author DLC was responsible for conceptualization of the work presented herein under mentored supervision by author JNG. Conceptualization involved formulation and modification of research goals and aims. DLC was responsible for querying the ClinicalTrials.gov clinical trials results database using pre-set search terms related to conditions/diseases of the spine, shoulder, and elbow for which clinical trials related to the spine, shoulder, and elbow, are registered, respectively.

Next, DLC independently curated the resulting clinical registration data, performed univariate statistical analyses, and, utilizing the R computer coding language and R studio computational software, performed multivariate logistic regression analyses to identify trial characteristics independently predictive of trial termination. DLC then generated the tables and figures contained herein.

All authors (i.e., DLC, MJG, WMM, JNG) contributed to review of relevant published literature and writing of the original manuscript draft. Review and editing of the original draft were performed by authors DLC and JNG to meet submission criteria for journals *Clinical Spine Surgery* and *Journal of Shoulder and Elbow Surgery*. All authors completed final review and approval of the work presented here.

Ethics Statement

The Yale Institutional Review Board (IRB) has determined studies utilizing the ClinicalTrials.gov results database to be exempt from review, as the database exports trial registration data that do not meet the criteria for research involving human subject research. The authors, their immediate family members, and any research foundations with which they are affiliated have not received any financial renumeration or other benefits from any commercial entity related to the subject of this doctoral thesis.

Methods Description

Study Sample of Musculoskeletal Clinical Trials

Each cohort of clinical trials (i.e., for spine, shoulder, and elbow) was generated using the Advanced Search feature of the *Find a study* search engine at ClinicalTrials.gov to impose eligibility requirements on clinical trials to be investigated in this study and utilized the "Condition or disease" data entry field to query ClinicalTrials.gov for clinical trials associated with musculoskeletal conditions.

This study included only trials with study type designated as "Interventional Studies (Clinical Trials)" with Overall Recruitment Status as completed or terminated; observational and expanded access studies were not included in any of the trial cohorts for spine, shoulder, or elbow. Registration data for ongoing clinical trials related to the spine and shoulder/elbow were not captured to avoid introducing bias in evaluation of correlation of trial characteristics with odds of trial termination since the ultimate endpoint (completed vs. terminated) has yet to be determined for ongoing clinical trials.

Following each query of the ClinicalTrials.gov database, duplicate clinical trial records were isolated using the unique National Clinical Trial number for each trial and removed from each dataset. Clinical trials related to the spine, shoulder, and elbow were grouped by Overall Recruitment Status as either completed or terminated.

Data for clinical trials related to the spine were abstracted from ClinicalTrials.gov on June 20, 2021. ClinicalTrials.gov was queried for all completed and terminated clinical trials registered to date with at least one of the available search terms preconfigured into the ClinicalTrials.gov search engine to contain the word “spine:”

> “Spine, Cleft,” “Spine, Open,” “Spine; Angulation,” “Spine; Arthrosis,” “Spine; Deformity, Congenital,” “Spine; Instability,” “Spine Arthritis,” “Spine Cancer,” “Spine Compression Fracture,” “Spine Deformity,” “Spine Degeneration,” “Spine Disease,” “Spine Fracture,” “Spine Fusion,” “Spine Infection,” “Spine Injuries and Disorders,” “Spine Injury,” “Spine Juvenile Osteochondroses,” “Spine Malformation,” “Spine Metastases,” “Spine or Vertebra; Arthritis, Ankylosing,” “Spine or Vertebra; Arthritis, Infectious or Infective,” “Spine or Vertebra; Disorder, Tuberculous (Etiology),” “Spine or Vertebra; Fracture, Cervical,” “Spine or Vertebra; Fracture, Lumbar,” “Spine or Vertebra; Fracture, Sacral,” “Spine or Vertebra; Osteochondrosis, Juvenile,” “Spine Osteoarthritis,” “Spine Osteochondroses,” “Spine Rheumatoid Arthritis,” “Spine Spondylosis Thoracic,” “Spine Stiffness,” “Spine Tb,” and “Spine Tumor.”

Data for clinical trials related to the shoulder were abstracted from ClinicalTrials.gov on August 6, 2021. ClinicalTrials.gov was queried for all completed and terminated clinical trials registered to date with at least one of the

available search terms preconfigured into the ClinicalTrials.gov search engine to contain the word “shoulder:”

> “Shoulder, Milwaukee,” “Shoulder; Adhesion,” “Shoulder; Anomaly,” “Shoulder; Deformity, Congenital,” “Shoulder; Dislocation, Chronic,” “Shoulder Adhesive Capsulitis,” “Shoulder and Upper Arm Injury; Shoulder Arthritis,” “Shoulder Arthropathy Associated with Other Conditions,” “Shoulder Blade Fracture,” “Shoulder Bursitis,” “Shoulder Calcific Tendinitis,” “Shoulder Capsulitis,” “Shoulder Deformity,” “Shoulder Disease,” “Shoulder Dislocation,” “Shoulder Dislocation Closed Traumatic,” “Shoulder Dislocation or Subluxation,” “Shoulder Dystocia,” “Shoulder Fracture,” “Shoulder Frozen,” “Shoulder Girdle Dystocia,” “Shoulder Girdle Neuropathy,” “Shoulder Girdle Syndrome,” “Shoulder Hand Syndrome,” “Shoulder Impact,” “Shoulder Impingement,” “Shoulder Impingement Syndrome,” “Shoulder Injuries,” “Shoulder Injuries and Disorders,” “Shoulder Instability Subluxation Bilateral,” “Shoulder Joint—Dislocation,” “Shoulder Joint Disorder,” “Shoulder Lesions,” “Shoulder Luxation,” “Shoulder Muscle Strain,” “Shoulder Osteoarthritis,” “Shoulder Pain,” “Shoulder Pain Chronic,” “Shoulder Region Dislocation Anterior,” “Shoulder Region Dislocation Traumatic,” “Shoulder Region Dislocation Traumatic Closed,” “Shoulder Sprain,” “Shoulder Strain Deltoid Muscle,” “Shoulder Strain Muscle,” “Shoulder Subluxation,” “Shoulder Syndrome,” “Shoulder Syndrome Impingement,” and “Shoulder Tendinitis.”

Data for clinical trials related to the elbow were abstracted from ClinicalTrials.gov on August 6, 2021. ClinicalTrials.gov was queried for all completed and terminated clinical trials registered to date with at least one of the available search terms preconfigured into the ClinicalTrials.gov search engine to contain the word “elbow:”

> “Elbow Arthritis,” “Elbow Arthropathy,” “Elbow Broken,” “Elbow Bursitis,” “Elbow Contracture,” “Elbow Deformity (Acquired),” “Elbow Disease,” “Elbow Dislocation,” “Elbow Epicondylitis,” “Elbow Epicondylitis Medial,” “Elbow Flexion Contracture,” “Elbow Fracture,” “Elbow Golfers,” “Elbow Injuries and Disorders,” “Elbow Injury,” “Elbow Joint Contracture,” “Elbow Luxation” “Elbow Nursemaid,” “Elbow Osteoarthritis,” “Elbow Sprain,” “Elbow Strain,” “Elbow, Tennis,” “Elbow Tendinitis,” “Elbow Tendinopathy,” “Elbow Tenosynovitis.”

Clinical trials with Overall Recruitment Status designated as either completed or terminated were grouped. Duplicate clinical trial records were removed from the dataset.

Trial Characteristics

Trial characteristics were abstracted from ClinicalTrials.gov as categorical variables. Some trial characteristics were grouped to facilitate interpretation and definitions are provided below.

Lead sponsor organization was the primary sponsoring group. Studies were categorized as sponsored by local groups (which included individuals, universities, and community-based organizations), industry, National Institutes of Health (NIH), or other U.S. federal government agency.

Intervention types were categorized according to the "process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include non-invasive approaches, such as education or modifying diet and exercise."[4] Clinical trials were categorized by intervention as investigating a drug or biological product, device, procedure, or other (other included the following intervention types: behavioral, radiation, diagnostic testing, genetic, and other).

Phase of study captured the study design. Phase I captured what was included in the data as early phase I and phase I studies. Phase II captured what was included in the data set as phase II and I/II studies. Phase III captured what was included in the data set as phase III and II/III studies.

Studies were also categorized as randomized (i.e., "yes" or "no") and blinded (i.e., "yes" or "no"). Blinding was abstracted as a dichotomous variable (i.e., "yes" or "no") to indicate whether at least one of the following study entities had been

blinded: the participant, care provider, investigator, and/or outcomes assessor were blinded.

Secondary trial characteristics were also abstracted or spine-, shoulder-, and elbow- related clinical trials. These included group assignment (allocation), primary purpose, gender eligibility, and age group eligibility.

Reasons for Trial Termination

Reasons for trial termination were abstracted from the *Why Study Stopped* data element and classified into one of ten general categories for clinical trials related to the spine and one of nine general categories for clinical trials related to the shoulder/elbow. General categories of termination reasons were adapted from a previous cross-sectional analysis of terminated trials to specifically capture reasons for termination reported for clinical trials of the spine and shoulder/elbow.[4]

For clinical trials related to the spine, termination reason categories included (1) insufficient participant accrual rate; (2) business decision or strategic reasons (e.g., “sponsor decision,” “change in clinical strategy”); (3) regulatory or conduct issues (e.g., protocol compliance issues or site-related issues, expiration of institutional review board approval); (4) scientific data from trial (e.g., lack of efficacy of the investigational product, unfavorable risk-benefit profile); (5) sufficient participant recruitment for analysis; (6) recall or cessation of production of the investigational

product; (7) inadequate funding/resources; (8) reasons related to the coronavirus disease 2019 public health emergency (e.g., laboratory shutdown, safety restrictions); (9) external information (e.g., changes in standard of care or data from other trials resulted in the study becoming inconsequential); (10) unclear reasons or reasons missing (i.e., not reported to ClinicalTrials.gov by either the sponsor or principal investigator).

For clinical trials related to the shoulder and elbow, termination reason categories included (1) difficulties in recruitment and/or retention of trial participants; (2) administrative or conduct issues; (3) business decision or strategic reasons; (4) scientific data from trial; (5) sufficient participant recruitment for analysis; (6) recall or cessation of production of the investigational product; (7) reasons related to the coronavirus disease 2019 public health emergency; (8) external information; and (9) unclear reasons or reason missing.

Statistical Methods

Analyses were done separately for clinical trials of the spine, shoulder, and elbow. Univariate χ^2 analyses were performed to compare the distribution of primary and secondary trial characteristics among completed and terminated clinical trials. Multivariate logistic regression was then used to determine independent predictors of trial termination as a function of these trial characteristics.

Statistical analyses were performed with RStudio (version 1.4.1717, Public Benefit Corporation, Boston, MA, USA). Significance was set to 0.05. A forest plot was used for the presentation of the multivariate analyses (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA).

Results

Spine-related Clinical Trial Characteristics

For spine-related clinical trials, 969 were identified, of which 136 (14%) were terminated. Primary trial characteristics are shown in Table 1. The captured clinical trials related to the spine were most frequently sponsored by local groups—accounting for 59.6% of all clinical trials related to the spine; evaluated either a drug/biological product (36.6%) or device (20.3%); were blinded (53.5%); employed parallel assignment of study groups (70.0%); phase III (20.0%), where applicable; randomized (70.5%); and blinded (53.4%). On univariate analysis, lead sponsor and intervention type correlated with trial termination ($p < 0.05$ for both).

Table 1. Spine-related primary characteristics of trials that were completed and terminated.

Total number of trials	**N=833 trials**	**N=136 trials**	
	Completed N (%)	**Terminated N (%)**	**P value**
Lead sponsor			
Local groups	512 (61.5%)	66 (48.5%)	
Industry	312 (37.5%)	69 (50.7%)	**0.013**
NIH or U.S. Fed	9 (1.1%)	1 (0.7%)	
Intervention type			
Drug or Biological	377 (45.3%)	55 (34.9%)	
Device	153 (18.4%)	44 (32.4%)	**<0.001**
Procedure	106 (12.7%)	19 (14.0%)	
Other*	197 (23.6%)	18 (13.2%)	
Phase			
Phase I	35 (4.2%)	4 (2.9%)	
Phase II	93 (11.2%)	25 (18.4%)	
Phase III	174 (20.9%)	20 (14.7%)	0.097
Phase IV	136 (16.3%)	24 (17.6%)	
Not applicable	395 (47.4%)	63 (46.3%)	
Randomized?			
Yes	585 (70.2%)	98 (72.1%)	
No	235 (28.2%)	38 (27.9%)	0.336
Not provided	13 (1.6%)	0 (0.0%)	
Blinded?			
Yes	453 (54.4%)	64 (47.1%)	
No	371 (44.5%)	72 (52.9%)	0.108
Not provided	9 (1.1%)	0 (0.0%)	

*Intervention type "Other" includes the following intervention types: other, behavioral, radiation, diagnostic testing, and genetic. *NIH*=National Institutes of Health; *U.S. Fed*= United States federal agency other than the National Institutes of Health.

Spine-related secondary trial characteristics are shown in Table 2. The captured clinical trials related to the spine most frequently used parallel group assignment (70.0%), focused on treatment (78.1%), and enrolled all sexes (98.4%) as well as adults and older adults (74.5%). None of these secondary trial characteristics were correlated with termination of spine-related clinical trials by univariate analysis.

Table 2. Spine-related secondary characteristics of trials that were completed and terminated.

Total number of trials	N=833 trials	N=136 trials	
	Completed N (%)	Terminated N (%)	P value
Assignment			
Parallel	579 (69.5%)	99 (72.8%)	
Single group	201 (24.1%)	31 (22.8%)	
Crossover	30 (3.6%)	3 (2.2%)	0.730
Sequential	8 (1.0%)	1 (0.7%)	
Factorial	7 (0.8%)	2 (1.5%)	
Information missing	8 (1.0%)	0 (0.0%)	
Primary Purpose			
Treatment	643 (77.2%)	114 (83.8%)	
Prevention	43 (5.2%)	4 (2.9%)	
Supportive care	38 (4.6%)	5 (3.7%)	
Diagnostic	27 (3.2%)	4 (2.9%)	
Health services research	17 (2.0%)	2 (1.5%)	
Basic science	12 (1.4%)	3 (2.2%)	
Screening	7 (0.8%)	0 (0.0%)	0.488
Device feasibility	1 (0.1%)	0 (0.0%	
Not provided	21 (2.5%)	0 (0.0%)	
Gender eligibility			
All	785 (94.2%)	134 (98.5%)	
Female	32 (3.8%)	2 (1.5%)	
Male	12 (1.4%)	0 (0.0%)	0.194
Not provided	4 (0.5%)	0 (0.0%)	
Age group eligibility			
Child	29 (3.5%)	4 (2.9%)	
Child, adult	61 (7.3%)	5 (3.7%)	
Child, adult, older adult	52 (6.2%)	4 (2.9%)	0.285
Adult	73 (8.8%)	10 (7.4%)	
Adult, older adult	610 (73.2%)	112 (82.4%)	
Older adult	8 (1.0%)	1 (0.7%)	

Spine-related Clinical Trials: Reasons for Termination

Of the spine-related clinical trials found to be terminated, the reasons for termination were tabulated (Table 3). Insufficient rate of participant accrual the most frequently reported reason for trial termination, accounting for 46 of 136 terminated trials (33.8%).

Table 3. Spine-related clinical trials: categorization of reasons for trial termination.

Termination reason category*	Number of Trials	Percentage of Trials
Total terminated	136	100%
Insufficient accrual rate	46	33.8%
Business decision or strategic reasons	23	16.9%
Regulatory or conduct issues	21	15.4%
Scientific data from trial	16	11.8%
Sufficient recruitment for analysis	4	2.9%
Product recall or cessation of production	4	2.9%
Inadequate funding/resources	3	2.2%
Related to COVID-19 pandemic	3	2.2%
External information	2	1.5%
Reason not provided or uninformative	14	10.3%

*Reasons for trial termination are listed in order of decreasing frequency other than reason not provided or uninformative, which was placed at the bottom of the list.

Other reasons for termination of spine-related clinical trials included business decision or strategic reasons (16.9%), regulatory or conduct issues (15.4%), and scientific data from trial (11.8%). Other less common reasons for trial termination are detailed in Table 3. Of note, termination was either missing or the reason provided was uninformative regarding categorization for 10.3% of terminated trials.

Spine-related Clinical Trials: Independent Predictors of Trial Termination

For spine-related clinical trials, multivariate analysis was performed to determine independent predictors of trial termination using primary trial characteristics in Table 1. Odds ratios (OR), 95% confidence intervals (CI), and P-values are shown in Figure 1.

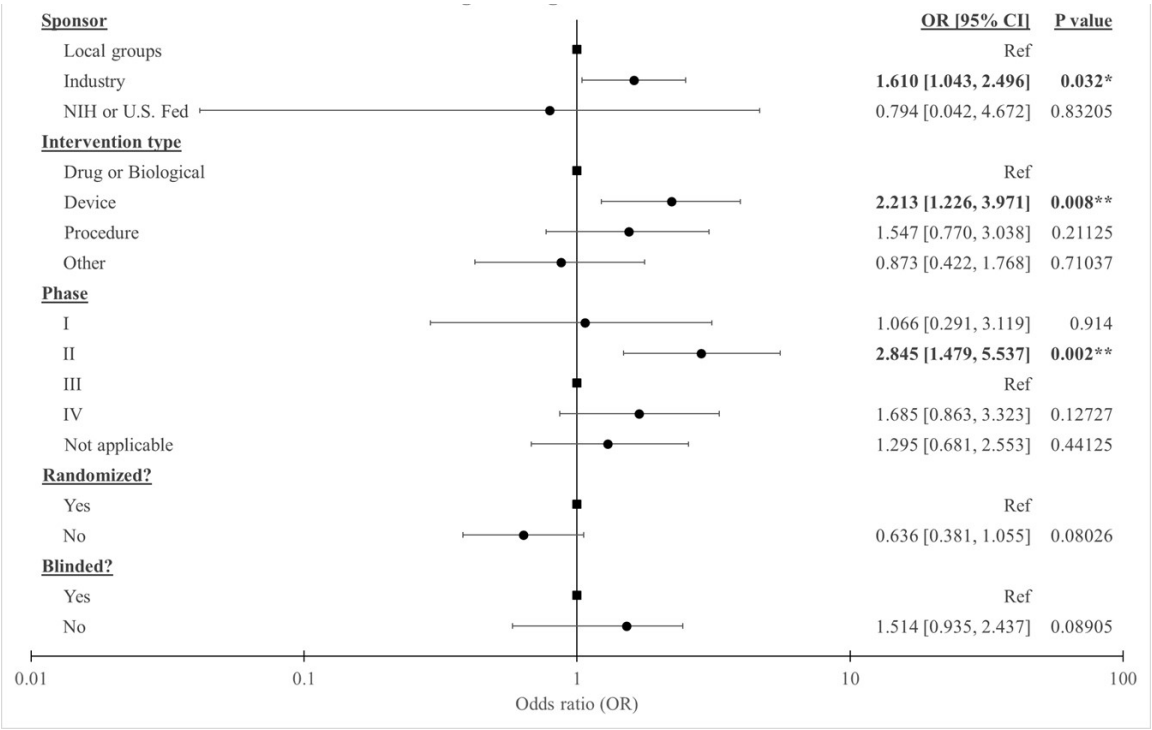

Figure 1. Forest plot for spine-related clinical trials showing the results of a multivariate logistic regression assessing for correlation between trial characteristics and odds of trial termination. *CI*=confidence interval; *NIH*=National Institutes of Health; *U.S. Fed*=United States federal agency other than the National Institutes of Health; *Ref*=reference. Significance levels: *$p < 0.05$; **$p = 0.001$; ***p

< 0.001. **Boldface** formatting has been used to indicate odds ratios with 95% confidence interval not overlapping with 1 and $p < 0.05$.

Spine-related clinical trial termination was independently associated with industry-sponsorship relative to studies sponsored by local groups (OR = 1.610, 95% CI: 1.043, 2.496, $p = 0.032$), intervention type device relative to investigations of drug or biological product(s) (OR = 2.213, 95% CI: 1.226, 3.971, $p = 0.008$), and phase II relative to phase III studies (OR = 2.845, 95% CI: 1.479, 5.537, $p = 0.002$).

Shoulder and Elbow-related Clinical Trial Characteristics

For shoulder-related clinical trials, 662 were identified and characterized, of which 51 (8%) were terminated. For elbow-related clinical trials, 126 were identified and characterized, of which 16 (13%) were terminated.

Shoulder and elbow-related clinical trial primary characteristics are shown in Table 4. The captured clinical trials were most frequently sponsored by local groups—accounting for 89% of shoulder-related clinical trials and 87% of elbow-related clinical trials; evaluated either a drug/biological product (22% shoulder, 29% elbow) or device (18% shoulder, 21% elbow); were phase III (26% shoulder, 56% elbow), where applicable; randomized (84% shoulder, 87% elbow); and blinded (70% shoulder, 67% elbow).

Table 4. Shoulder and elbow-related primary trial characteristics of trials that were completed and terminated.

Total trials:	Shoulder (N=662)			Elbow (N=126)		
	Completed N (%)	**Terminated N (%)**	**P value**	**Completed N (%)**	**Terminated N (%)**	**P value**
	611 (100.0%)	**51 (100.0%)**		**110 (100.0%)**	**16 (100.0%)**	
Lead sponsor						
Local groups	555 (90.8%)	35 (68.6%)		95 (86.4%)	14 (87.5%)	
Industry	50 (8.2%)	15 (29.4%)	**<0.001**	14 (12.7%)	2 (12.5%)	0.929
NIH or U.S. Fed	6 (1.0%)	1 (2.0%)		1 (0.9%)	0 (0.0%)	
Intervention type						
Drug or Biological	128 (20.9%)	14 (27.5%)		33 (30.0%)	4 (25.0%)	
Device	101 (16.5%)	16 (31.4%)	**0.007**	23 (20.9%)	4 (25.0%)	0.809
Procedure	166 (27.2%)	13 (25.5%)		22 (20.0%)	2 (12.5%)	
Other*	216 (35.4%)	8 (15.7%)		32 (29.1%)	6 (37.5%)	
Phase						
Phase I	22 (3.6%)	4 (7.8%)		0 (0.0%)	0 (0.0%)	
Phase II	38 (6.2%)	4 (7.8%)		10 (9.1%)	1 (6.3%)	
Phase III	45 (7.4%)	4 (7.8%)	0.625	17 (15.5%)	3 (18.8%)	0.975
Phase IV	68 (11.1%)	5 (9.8%)		4 (3.6%)	1 (6.3%)	
N/A	438 (71.7%)	34 (66.7%)		79 (71.8%)	11 (68.8%)	
Randomized?						
Yes	511 (83.6%)	42 (82.4%)		94 (85.5%)	15 (93.8%)	
No	99 (16.2%)	9 (17.6%)	0.926	16 (17.0%)	1 (6.3%)	
Not provided	1 (0.2%)	0 (0.0%)		—	—	
Blinded?						
Yes	434 (71.0%)	26 (51.0%)		74 (67.3%)	10 (62.5%)	
No	175 (28.6%)	25 (49.0%)	**0.009**	36 (32.7%)	6 (37.5%)	0.705
Not provided	2 (0.3%)	0 (0.0%)		—	—	

*Intervention type "Other" includes the following intervention types: other, behavioral, radiation, diagnostic testing, and genetic. *N/A*=not applicable; *NIH*=National Institutes of Health; *U.S. Fed*=United States federal agency other than the National Institutes of Health.

On univariate analysis of shoulder-related clinical trials, trial termination was correlated with lead sponsor (p = 0.0001), intervention type (p = 0.007), and blinding (p = 0.009). On univariate analysis of elbow-related clinical trials, trial termination was not correlated with any of the primary trial characteristics.

Shoulder and elbow-related secondary trial characteristics for trials that were completed and terminated are shown in Table 5. The captured clinical trials most frequently used parallel group assignment (79% shoulder, 77% elbow), focused on treatment (81% shoulder, 91% elbow), and enrolled all genders (93% shoulder, 96% elbow) as well as adults and older adults (73% shoulder, 76% elbow).

Of the secondary trial characteristics evaluated for shoulder-related clinical trials, trial termination only correlated with age group eligibility. For clinical trials related to the elbow, trial termination was not found to be correlated with any of the secondary trial characteristics assessed.

Table 5. Shoulder and elbow-related secondary trial characteristics of clinical trials that were completed and terminated.

Total trials:	Shoulder (N=662)			Elbow (N=126)		
	Completed N (%)	**Terminated N (%)**	**P value**	**Completed N (%)**	**Terminated N (%)**	**P value**
	611 (100.0%)	**51 (100.0%)**		**110 (100.0%)**	**16 (100.0%)**	
Assignment						
Parallel	482 (78.9%)	43 (84.3%)		84 (76.4%)	13 (81.3%)	
Single group	92 (15.1%)	8 (15.7%)		16 (14.5%)	2 (12.5%)	
Factorial	18 (2.9%)	0 (0.0%)	0.658	4 (3.6%)	0 (0.0%)	0.877
Crossover	16 (2.6%)	0 (0.0%)		6 (5.5%)	1 (6.3%)	
Sequential	2 (0.3%)	0 (0.0%)		—	—	
Not provided	1 (0.2%)	0 (0.0%)		—	—	
Primary Purpose						
Treatment	492 (80.5%)	45 (88.2%)		100 (90.9%)	15 (93.8%)	
Prevention	50 (8.2%)	3 (5.9%)		3 (2.7%)	0 (0.0%)	
Supportive care	23 (3.8%)	1 (2.0%)		1 (0.9%)	0 (0.0%)	
Diagnostic	17 (2.8%)	0 (0.0%)		1 (0.9%)	0 (0.0%)	
Basic Science	4 (0.7%)	0 (0.0%)		1 (0.9%)	1 (6.3%)	
Health services research	2 (0.3%)	0 (0.0%)	0.782	—	—	0.699
Screening	2 (0.3%)	0 (0.0%)		—	—	
Device feasibility	—	—		2 (1.8%)	0 (0.0%)	
Other	12 (2.0%)	2 (3.9%)		2 (1.8%)	0 (0.0%)	
Not provided	9 (1.5%)	0 (0.0%)		—	—	
Gender eligibility						
All	567 (92.8%)	49 (96.1%)		105 (95.5%)	16 (100.0%)	
Female	38 (6.2%)	2 (3.9%)	0.617	2 (1.8%)	0 (0.0%)	0.685
Male	6 (1.0%)	0 (0.0%)		3 (2.7%)	0 (0.0%)	
Age group eligibility						
Child	3 (0.5%)	0 (0.0%)		6 (5.5%)	1 (6.3%)	
Child, adult	13 (2.1%)	0 (0.0%)		2 (1.8%)	0 (0.0%)	
Child, adult, older adult	46 (7.5%)	1 (2.0%)	**0.046**	3 (2.7%)	0 (0.0%)	0.758
Adult	100 (16.4%)	5 (9.8%)		17 (15.5%)	1 (6.3%)	
Adult, older adult	441 (72.2%)	42 (82.4%)		82 (74.5%)	14 (87.5%)	
Older adult	8 (1.3%)	3 (5.9%)		—	—	

Shoulder- and Elbow-related Clinical Trials: Reasons for Termination

For shoulder-related clinical trials, the most common reason for trial termination was difficulties with participant recruitment and/or retention, accounting for 51% of terminated clinical trials related to the shoulder (Table 6). Less common reasons for termination of clinical trials related to the shoulder are detailed in Table 6. Notably, a reason for termination was either missing (not reported) or the reason provided was uninformative regarding categorization for 12% of terminated clinical trials related to the shoulder.

Table 6. Shoulder- and elbow-related clinical trials: categorization of reasons for trial termination.

	Shoulder		Elbow	
Total clinical trials terminated:	N=51	100.0%	N=16	100.0%
Termination reason category:				
Recruitment and/or retention difficulties	26	51.0%	6	37.5%
Administration or conduct issues	7	13.7%	3	18.8%
External information	4	7.8%	—	—
Related to COVID-19 public health emergency	3	5.9%	—	—
Business decision or strategic reasons	2	3.9%	2	12.5%
Scientific data from trial	2	3.9%	1	6.3%
Sufficient recruitment for analysis	1	2.0%	2	12.5%
Recall of investigational product	—	—	1	6.3%
Reason not provided or uninformative	6	11.8%	1	6.3%

COVID-19=coronavirus disease 2019.

For elbow-related clinical trials, the most common individual reason for trial termination was also difficulties with participant recruitment and/or retention, accounting for 38% of trial terminations (Table 6). Other, less common reasons for termination of clinical trials related to the elbow were administration or conduct issues (19%) followed by business decision or strategic reasons (13%) and determination of recruitment as sufficient for interim analysis that warranted trial termination (13%).

Shoulder- and Elbow-related Clinical Trials: Independent Predictors of Trial Termination

Multivariate analysis was performed to determine independent predictors of trial termination for clinical trials related to the shoulder and elbow using primary trial characteristics in Table 4.

For shoulder-related clinical trials, termination was found to be independently associated with industry sponsorship relative to studies sponsored by local groups (OR = 4.7, 95% confidence interval [CI] 1.7, 10.0; p = 0.001) and trials implementing any form of blinding (single, double, triple, or quadruple) relative to studies that did not use blinding (OR = 45.8, 95% CI 9.1, 841.4; p = 0.0003). ORs, 95% Cis, and p values are presented using a forest plot in Figure 2.

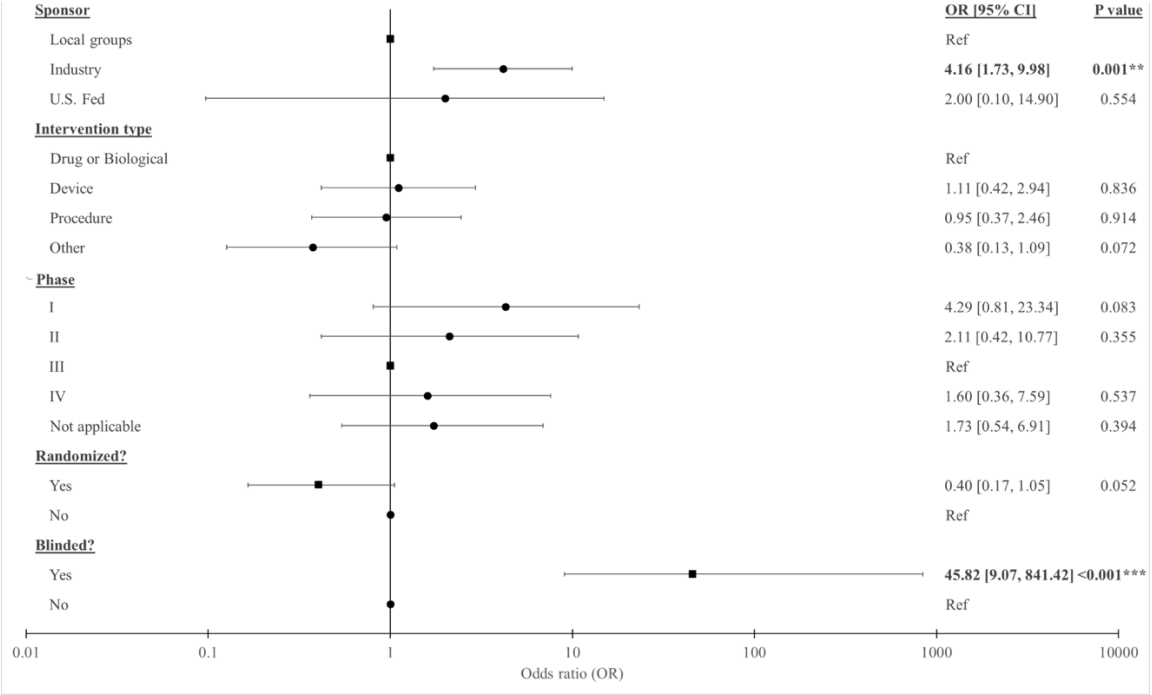

Figure 2. Forest plot for shoulder-related clinical trials showing a multivariate logistic regression assessing for correlation between trial characteristics and odds of trial termination. Multivariate logistic regression for termination of clinical trials related to the shoulder. Sponsorship by local groups includes individual, university, and community-based organizations as the leading source of trial funding. The reference used for sponsor, intervention type, phase, randomization, and blinding were sponsorship by local groups, device, phase III, not randomized, and not blinded, respectively. *CI*=confidence interval; *U.S. Fed*=United States federal agency (includes National Institutes of Health and other United States federal agencies); *OR*=odds ratio; *Ref*=reference; *p<0.05; **p=0.001; ***p<0.001.

For elbow-related clinical trials, multivariate logistic regression did not reveal any of the primary trial characteristics evaluated to be independently correlated with odds of trial termination. Notably, there were fewer trials for this analysis.

Discussion

General Discussion surrounding Musculoskeletal Clinical Trials

Clinical trials are key to the advancement of science and technologies in all areas of clinical medicine, including those related to conditions of the musculoskeletal system. Prior studies have evaluated the rate of trial termination on ClinicalTrials.gov. One previous cross-sectional study evaluating all interventional trials by Williams et al. found that 11.8% clinical trials posted to ClinicalTrials.gov as of February 2013 were terminated.[4]

The current study features a cross-sectional analysis of clinical trials related to the spine, shoulder, and elbow registered with ClinicalTrials.gov and found that those related to the spine, shoulder, and elbow were terminated at a rate of 14%, 8%, and 13%, respectively. These termination rates included trials terminated for reasons related to the responsible conduct of research (e.g., interim analysis demonstrating an unfavorable risk-benefit profile of the intervention under active investigation, achievement of study end points prior to planned completion per protocol, and termination following interim power analysis that determines recruitment as sufficient).

Although termination of clinical trials for these reasons is usually unavoidable, difficulties in the recruitment and/or retention of participants was the reason most frequently reported for trial termination for clinical trials related to the spine, shoulder, and elbow. From a clinical perspective, this finding should be

encouraging, as it underscores the need for ongoing communication between sponsors, investigators, and study sites to determine appropriate strategies to bolster enrollment—these could include but are not limited to clarifying study aims and eligibility criteria among clinical research teams at enrolling sites, opening additional sites, and/or revising eligibility criteria that may exclude participants that may stand to benefit from the intervention under active investigation.

In summary, improved understanding of trial termination rates, which trials are being terminated, reasons reported by clinical trial sponsors and investigators for trial termination, and trial characteristics independently correlated with increased odds of trial termination is crucial to facilitating successful completion of clinical trials related to musculoskeletal conditions.

Spine-related Clinical Trials

A 2015 study by Ohnmeiss evaluated clinical trials related to the spine registered with ClinicalTrials.gov and found a lesser percent of clinical trials to be terminated [18/263 (6.8%)].[5] However, the study denominator for that study was different, as it included trials with all types of recruitment status (including ongoing studies that had not yet declared themselves). If instead one were to evaluate the prior 2015 study through the lens of only completed and terminated clinical trials related to the spine, then 18/90 (20%) of the trials were terminated.

Multivariate analysis was used to evaluate for study characteristics independently predictive of termination because of the overlapping nature of various trial characteristics. Logistic regression demonstrated increased odds of trial termination for industry sponsorship (OR=1.59) relative to sponsorship from local groups. This contrasts with a study of cardiovascular clinical trials in which trials funded by universities had increased odds of termination relative to industry-sponsored trials. The group asserts that "unlike trials funded by NIH/US federal agencies or industry, trials conducted by universities may not be able to count on sufficient funding to afford an adequate research infrastructure and a dedicated staff."[6] While this may be true for some studies, perhaps there are additional opportunities for funding that have since become available to clinical trials sponsored by local groups and not to industry-sponsored trials.

The findings of the current study also contrast with a 2014 study of surgical randomized controlled trials in the ClinicalTrials.gov database; using an adjusted binary logistic regression, Chapman et al found that industry funding did not affect trial termination rate.[7] While comparison is limited in that the current study includes both randomized and nonrandomized studies and adjusts for randomization through multivariate analysis, the finding that industry-sponsored clinical trials related to the spine have increased odds of termination, may suggest that clinical trials related to the spine funded by industry are more susceptible to termination than surgical trials in general.

Multivariate analysis also found device studies to have greater odds of termination (OR = 2.18) relative to investigations of drug or biological product(s). Reasons for this may include difficulties related to consenting participants for device studies, protocol compliance issues related to proper use of devices, recall of devices because of safety-related issues, and/or changes in the standard of care that result the device becoming obsolete. Of note, cardiovascular clinical trials did not have an increased odds of trial termination associated with device studies relative to those with drug as the intervention type; thus, increased odds of termination in association with device studies may be specific to clinical trials related to the spine.[6]

Finally, multivariate analyses found phase II studies to be associated with greater odds of termination (OR = 3.07) relative to phase III studies. Phase II studies primarily assess the efficacy and adverse effects of the intervention under investigation. Recruitment of trial participants may prove to be challenging because of limited safety data gathered from phase I and preclinical studies when compared with recruitment to phase III studies for which additional efficacy and safety data is provided by phase II studies.

The current study then went on to evaluate reasons for trial termination. Insufficient accrual rate was the most frequently reported individual reason for trial termination (33.8% of the terminated trials). This finding was in line with but actually a bit lower than that found by prior studies that have looked at all trials on

ClinicalTrials.gov (found 56.5% be terminated because of insufficient accrual rate),[4] cardiovascular clinical trials (53.6% were terminated because of insufficient accrual rate),[6] and surgical randomized controlled trials (44% terminated because of poor recruitment).[7] This underscores the need for asking broad enough clinical questions, ensuring adequate patient recruitment strategies, designing appropriate eligibility criteria, and engaging sufficient centers with the needed clinical volumes. The ability of centers to recruit participants that meet eligibility criteria must be considered.

Interestingly, only 13.3% of the terminated trials cited trial data (e.g., lack of efficacy, adverse safety profile, or clinical inferiority of the investigational product to standard of care) as the reason for termination as well as termination because of information external to the trial (e.g., changes in the standard of care, the results of another clinical trial render an ongoing investigation moot). This percentage of terminated trials may be unavoidable, as it reflects the responsible conduct of research and ethical responsibilities—namely beneficence and nonmaleficence—governing patient care.

Shoulder- and Elbow-related Clinical Trials

Multivariate analysis was used to evaluate for study characteristics independently predictive of termination due to the overlapping nature of various trial characteristics. Primary trial characteristics were independently correlated with

increased odds of termination for clinical trials related to the shoulder but not for those related to the elbow (where the number of clinical trials is noted to be lesser).

For clinical trials related to the shoulder related trials, logistic regression demonstrated increased odds of trial termination for industry sponsorship relative to sponsorship from local groups (OR = 1.59). This contrasts with a study of cardiovascular trials in which clinical trials funded by universities had increased odds of termination relative to industry-sponsored trials, citing possible difficulties with maintaining needed support of such studies.[6] Although this may be true for some studies, perhaps there are additional opportunities for funding support from the public and private sector that have since become available to trials sponsored by local groups and not to industry-sponsored trials. Moreover, a limitation arises in associating the odds of trial termination with lead sponsor type: this study as well as the study referenced here both do not account for collaborations between public and private sources of funding that may contribute to trial success. Further study is needed to determine the impact of collaboration on the completion rate of clinical trials related to the shoulder and elbow.

Logistic regression also demonstrated increased odds of termination for clinical trials related to the shoulder that employed blinding of any form (i.e., single, double, triple, or quadruple blinding) relative to studies that did not use any form of blinding (OR=45.82). This may underscore the challenges associated with blinding of surgical trials. To this end, a prior review of the randomized controlled trials

published in the *Journal of Bone and Joint Surgery* from 1988 through 2000 found at least two-thirds of the surgical trials did not blind outcome assessors, patients, or data analysts.[8]

Reasons for trial termination were evaluated. Difficulties in recruitment or retention of participants was the most common individual reason for termination responsible for termination of 51% and 38% of shoulder- and elbow-related clinical trials, respectively. This finding was in line with prior studies that have looked at all trials on ClinicalTrials.gov (found 57% to be terminated because of insufficient accrual rate)[4] and cardiovascular clinical trials (found 54% to have terminated because of insufficient accrual rates).[6] This finding is supported by ‘‘Lasagna’s law,’’ or an investigator’s overestimation of the incidence of patients who meet the inclusion criteria.[9] This highlights the need to set achievable enrollment targets, ensure adequate patient recruitment and retention strategies, design appropriate eligibility criteria, and engage sufficient centers with the needed clinical volumes.

Limitations

This study has several limitations. Cross-sectional sampling of trials registered at ClinicalTrials.gov limits data collection to a single time point (i.e., the point at which the ClinicalTrials.gov database is queried) as well as to “applicable clinical trials” as defined by the Final Rule for Clinical Trials Registration and Results Information Submission (i.e., generally, phase II through IV trials investigating FDA-regulated drugs, biological products, or devices that are conducted in the United States).[10].

Though all preset search terms containing the terms “spine,” “shoulder,” and “elbow” were used to generate a study sample of clinical trials related to the spine, shoulder, and elbow, respectively, such sampling is limited to keywords built into the search engine at ClinicalTrials.gov (i.e., the *Find a study* tool). As a result, the study sample of clinical trials related to the spine is predominantly composed of adult pathology; therefore, further research focused on reasons for termination of pediatric spine trials is necessary.

Each study sample of clinical trials related to the spine and shoulder/elbow is heterogeneous in composition, which potentially limits interpretation of study findings and application of lessons learned to study of specific musculoskeletal conditions.

In terms of reporting reasons for trial termination, the *Why Study Stopped* data element is the only method to track reasons for trial termination at ClinicalTrials.gov and is optional for clinical trials started before January 18, 2017. Reporting may also be influenced by external factors, such as commercial interests. Moreover, the *Why Study Stopped* data element limits free-text reporting to 250 characters;[3] free-text reporting may be uninformative (not aiding in clear interpretation nor categorization for analysis).

Conclusion

In summary, clinical trials related to the spine, shoulder, and elbow were terminated at a rate of 14%, 8%, and 13%, respectively. Difficulties in the recruitment and/or retention of trial participants was the reason most frequently reported for trial termination. Thus, ensuring reasonable enrollment targets should be a paramount consideration in study design for clinical trials evaluating interventions related to diseases and disorders of the musculoskeletal system. Given the ethical considerations and opportunity costs associated with terminated studies, independent predictors, and reasons for termination of clinical trials should be addressed to optimize rates of trial completion.

Dissemination

- Caruana, D.L., Gouzoulis, M.J., McLaughlin, W.M., Grauer, J.N. (2022, Apr). Analysis of the frequency, characteristics, and reasons for termination of shoulder- and elbow-related clinical trials. Journal of Shoulder and Elbow Surgery, S1058-2746(22), 00339-1.

  PMID: 35398166. Publication Status: Published
- Caruana, D.L., Nam-Woo Kim, D., Galivanche, A., Wyatt, D.B., Justen, M.A., Moushey, A.M., Sheth, A.H., Paranjpe, M.D., Grauer, J.N. (2022, Mar). Analysis of the Frequency, Characteristics, and Reasons for Termination of Spine-Related Clinical Trials. Clinical Spine Surgery, 35(7), E596-E600.

  PMID: 35351841. Publication Status: Published
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