General Original Article

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Delayed discovery: the COVID-19 pandemic's influence on osteoarthritis clinical trials

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Abstract

Context: The COVID-19 pandemic disrupted clinical research in many medical and surgical fields, resulting in research waste and loss of treatment for patients. Although other areas have been explored, the extent of the pandemic's influence on osteoarthritis (OA) trials is currently unknown.
Objectives: This study aims to explore the reasons for termination of clinical trials investigating OA during the COVID-19 pandemic.
Methods: We searched ClinicalTrials.gov for OA trials and characterized their reason for discontinuation, noting where trialists directly cited the COVID-19 pandemic as the reason for trial discontinuation. We also coded other common reasons for trial discontinuation. Descriptive and inferential statistics were performed to determine the difference in enrollment, funding source, trial phase, allocation, and intervention type between the trials terminated early due to pandemic and nonpandemic reasons.
Results: Out of 135 clinical trials, 119 were included and 27 (22.7 %) of them reported the COVID-19 pandemic as a primary reason for discontinuation, which was the overall most common reason for OA trial discontinuation during the study period. We found statistically significant differences for trials discontinued due to pandemic vs. non–pandemic-related reasons, with trials having sites outside the United States, randomized allocation, and drug or device intervention type being most affected. However, there was no statistically significant difference between groups regarding trial phase, funding source, or enrollment.
Conclusions: This study highlights the impact of the COVID-19 pandemic on the clinical trials related to OA. We found that many trials reported discontinuation directly due to the pandemic, which may lead to the loss or delay of novel treatments for OA. To avoid such discontinuation in the future, alternative methods for conducting OA-related clinical trials should be explored and implemented.

Keywords: clinical trials; COVID-19; orthopedics; osteoarthritis

Osteoarthritis (OA) is a common, seriously impairing orthopedic condition responsible for substantial societal and personal costs. Current estimates suggest that more than 32.5 million US adults, the majority being older than 65 years of age, have received a medical diagnosis of OA [1, 2]. The economic burden associated with OA has nearly doubled over the last decade, now surpassing $137 billion annually [3]. Adding to the financial burden of the disease, OA also contributes to depression and social isolation [4], limitations in physical activity [5], and limiting one's ability to work [6]. Due to a rise in OA diagnoses and the significant financial and social implications of the disease, medical management and decision-making must be based on robust and reliable evidence.

In the field of orthopedic surgery, well-designed, randomized controlled trials are regarded as Level I evidence, sitting atop the evidence hierarchy [7]. Results from these influential studies help driven shared medical decision-making, and are often referenced as supporting evidence upon which clinical practice guideline recommendations are based [8, 9]. Although clinical trials serve an

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important role in medical research, including orthopedic surgery, trial discontinuation may be considered unethical and contribute to significant research waste [10, 11]. Previous studies have reported that trial discontinuation may be necessary due to circumstances that may pose a risk to patient safety, poor trial efficacy, and feasibility of completion [12]. However, other reasons for trial discontinuation may be preventable [12]. Regardless of the reasoning, trial discontinuation may jeopardize the patient-physician relationship, limit the advancement of clinical research, and subject participants to potentially harmful interventions.

Previous research has shed light on the frequency and reasoning behind clinical trial discontinuation, including OA trial discontinuation [13, 14]. However, the COVID-19 pandemic has altered the manner in which clinical trials are conducted, in addition to altering the overall accessibility to emerging clinical trials [15]. In fact, the US Food and Drug Administration (FDA) made changes to their guidelines governing clinical trials. These changes were aimed to decrease the risk of disease exposure and transmission, and the FDA advised clinical trialists to either make necessary changes to trial design to mitigate risks associated with the COVID-19 pandemic or to discontinue the trial altogether [16]. Clinical trials in the field of orthopedic surgery and other surgical subspecialties likely faced unique challenges when elective, nonemergent procedures were canceled in an effort to preserve medical resources and mitigate potential exposure [17]. Lastly, physician manpower was reallocated to assist with pandemic efforts, thereby limiting time spent either in the operating room or conducting clinical research [15, 17]. To better understand the extent of influence that the COVID-19 pandemic had on OA research, we sought to determine the frequency that clinical trials focusing on the management of OA were discontinued secondary to the COVID-19 public health crisis. We also sought to determine whether specific trial characteristics were associated with the likelihood of trialists reporting discontinuation due to the pandemic. Findings from this study may inform future OA clinical trial design and implementation.

Methods

On December 15, 2022, we searched ClinicalTrials.gov for interventional trials investigating treatments for OA. We utilized the search term "osteoarthritis" in the condition search box on ClinicalTrials.gov to obtain the most broad and inclusive initial search. Studies had to be interventional clinical trials in any phase that were evaluating any intervention type (Behavioral, Biological, Device, Dietary Supplement, Drug, Procedure, Radiation, or Other) for the treatment of OA in any joint in the body. Intervention types are determined by trialists at the time of registration. We did not limit the search by the bodily site of OA, trial phase, trial location, funding source, allocation, intervention type, or enrollment. We searched for trials that were *Suspended*, *Terminated*, or *Withdrawn* utilizing the *Last Update Posted* date as a proxy for the date of discontinuation. *Terminated* studies were permanently discontinued with no intention of restarting at a later date. *Suspended* trials were temporarily discontinued with the intention to start at a later date, but may have been terminated later if the study was unable to continue. Withdrawn studies were registered but were discontinued before the trial could begin. This information gives insight into the various stages of a clinical trial during which it was discontinued reportedly due to the pandemic. We limited our search to trials with *Last Update Posted* dates between January 01, 2020 and December 15, 2022 to capture all trials possibly influenced by the COVID-19 pandemic at the time of our investigation. All resulting trials and all available variables, including intervention type, were downloaded verbatim directly from ClinicalTrials.gov in CSV format.

We screened the resulting trials for relevance to OA, excluding trials that did not focus on the treatment of OA. Then, utilizing a pilot-tested Google Form, the authors reviewed each included trials registry page and extracted the verbatim reason for discontinuation reported by trialists on the page. The Google Form is available to qualified researchers upon request to the corresponding author. Studies that mentioned the COVID-19 pandemic as the primary reason for discontinuation were coded as such. Trials that did not mention the pandemic as a factor for discontinuation also had their reasons for discontinuation coded. Non-pandemic reasons are based on previous studies [18, 19] and are as follows: *Recruitment or Enrollment*, *Funding or Resources*, *Design-Related*, *Safety or Efficacy*, *PI-Related (Principal Investigator)*, *Sponsor/Business Decision*, and *Not Provided*.

We utilized Fisher's exact test to assess for differences in categorical trial characteristics between trials that were explicitly discontinued due to the pandemic and those that did not mention the pandemic. We utilized the Wilcoxon rank sum test when testing for differences in enrollment, because preliminary data analysis revealed that enrollment was not normally distributed among trials. We provide descriptive statistics for the reasons for discontinuation reported for all trials during this time. All statistical analysis was performed utilizing R (version 4.2.2) and RStudio as well as the *gtsummary* [20], *tidyverse* [21], and *flextable* [22] packages. This study did not qualify as human subjects research and did not require institutional review board (IRB) oversight.

Results

Discontinued trial characteristics

Our systematic search returned 135 discontinued clinical trials, 16 of which were excluded because they did not focus on the treatment of OA. Regarding the 119 included trials, the median enrollment was 13 with an interquartile range (IQR) of 0–74 and involved 7,483 participants. By status, 11 trials were *Suspended*, 61 were *Terminated*, and 47 were *Withdrawn*. By location, 68 trials had sites in the

United States, 35 h ad no US sites, and 16 trials did not report site locations. Regarding allocation, 96 trials were randomized, 8 were non-randomized, and 15 were *Not Applicable*. By intervention type, 8 were *Behavioral*, 9 were *Biological*, 33 were *Device*, 2 were *Dietary Supplement*, 40 were *Drug*, 15 were *Procedure*, 1 was *Radiation*, and 11 were *Other*. The remaining descriptive statistics for all included trial variables, overall and stratified by whether the pandemic was a reason for discontinuation, are displayed in Table 1.

Table 1: OA clinical trial characteristics and associations with being discontinued due to COVID-19.

Characteristic	Discontinued due to the COVID-19 pandemic		Overall, n=119[a]	p-Value[b]
	Yes, n=27[a]	No, n=92[a]		
Status				0.002
Suspended	7 (26 %)	4 (4.3 %)	11 (9.2 %)	
Terminated	14 (52 %)	47 (51 %)	61 (51 %)	
Withdrawn	6 (22 %)	41 (45 %)	47 (39 %)	
Phases				0.21
Early phase 1	1 (3.7 %)	1 (1.1 %)	2 (1.7 %)	
Phase 1	1 (3.7 %)	1 (1.1 %)	2 (1.7 %)	
Phase 2	4 (15 %)	16 (17 %)	20 (17 %)	
Phase 3	0 (0 %)	10 (11 %)	10 (8.4 %)	
Phase 4	3 (11 %)	16 (17 %)	19 (16 %)	
Not applicable	18 (67 %)	48 (52 %)	66 (55 %)	
Funding source				0.24
US Government	1 (3.7 %)	4 (4.3 %)	5 (4.2 %)	
Industry	8 (30 %)	43 (47 %)	51 (43 %)	
Other	18 (67 %)	45 (49 %)	63 (53 %)	
Sites in United States				**0.01**
Yes	12 (44 %)	56 (61 %)	68 (57 %)	
No	14 (52 %)	21 (23 %)	35 (29 %)	
Not provided	1 (3.7 %)	15 (16 %)	16 (13 %)	
Allocation				**0.032**
Randomized	19 (70 %)	77 (84 %)	96 (81 %)	
Nonrandomized	5 (19 %)	3 (3.3 %)	8 (6.7 %)	
Not applicable	3 (11 %)	12 (13 %)	15 (13 %)	
Intervention type				**0.018**
Behavioral	5 (19 %)	3 (3.3 %)	8 (6.7 %)	
Biological	2 (7.4 %)	7 (7.6 %)	9 (7.6 %)	
Device	7 (26 %)	26 (28 %)	33 (28 %)	
Dietary supplement	1 (3.7 %)	1 (1.1 %)	2 (1.7 %)	
Drug	6 (22 %)	34 (37 %)	40 (34 %)	
Procedure	1 (3.7 %)	14 (15 %)	15 (13 %)	
Radiation	1 (3.7 %)	0 (0 %)	1 (0.8 %)	
Other	4 (15 %)	7 (7.6 %)	11 (9.2 %)	
Enrollment	15 (2–61)	10 (0–76)	13 (0–74)	0.69[c] (z=1,181)

[a]n (%); median (intequartile range [IQR]). [b]Fisher's exact test; [c]Wilcoxon rank sum test. Bold values are statisitically significant results.

Discontinuation due to the COVID-19 pandemic

Of the 119 included trials, 27 (22.7 %) reported the COVID-19 pandemic as a primary reason for discontinuation. The 27 trials had a median enrollment of 15 (IQR: 2–61) and involved 1,051 participants. By status, 7 trials were *Suspended*, 14 were *Terminated*, and 6 were *Withdrawn*. By location, 12 trials had sites in the United States, 14 had no US sites, and 1 trial did not report site locations. Regarding allocation, 19 trials were randomized, 5 were nonrandomized, and 3 were *Not Applicable (not applicable or not reported)*. By intervention type, 5 were *Behavioral*, 2 were *Biological*, 7 were *Device*, 1 were *Dietary Supplement*, 6 were *Drug*, 1 was *Procedure*, 1 was *Radiation*, and 4 were *Other*. The reasons for discontinuation for all trials are as follows: 19 (16 %) *Recruitment or Enrollment*, 19 (16 %) *Funding or Resources*, 22 (18.5 %) *Design-Related*, 6 (5 %) *Safety or Efficacy*, 8 (6.7 %) *PI-Related*, 11 (9.2 %) *Sponsor/Business Decision*, 7 (5.9 %) *Not Provided*, and 27 (22.7 %) *Explicitly Stated COVID-19*. The results are depicted in Figure 1.

Statistical analysis

We found statistically significant differences between trials reporting an influence from the pandemic and those that did not report an influence by trial status (p=0.002), whether the trial had sites in the US (p=0.01), allocation (p=0.032), and intervention type (p=0.018). There were no statistically significant differences between groups regarding trial phase, funding source, or enrollment (Table 1).

Discussion

General findings

We found that the COVID-19 pandemic was the most commonly reported discontinuation reason among OA clinical trials discontinued since the pandemic began, with nearly a quarter of trials in our sample referencing the pandemic. The trials discontinued due to the pandemic involved over 1,000 participants. These findings highlight the severe impact of the pandemic on OA research, the implications of which are not fully known. Studies in other fields have demonstrated the significant influence of the pandemic on clinical research, and the magnitude of influence on OA trials is large in comparison. For example, clinical trials in Ear, Nose, and Throat (ENT) [23],

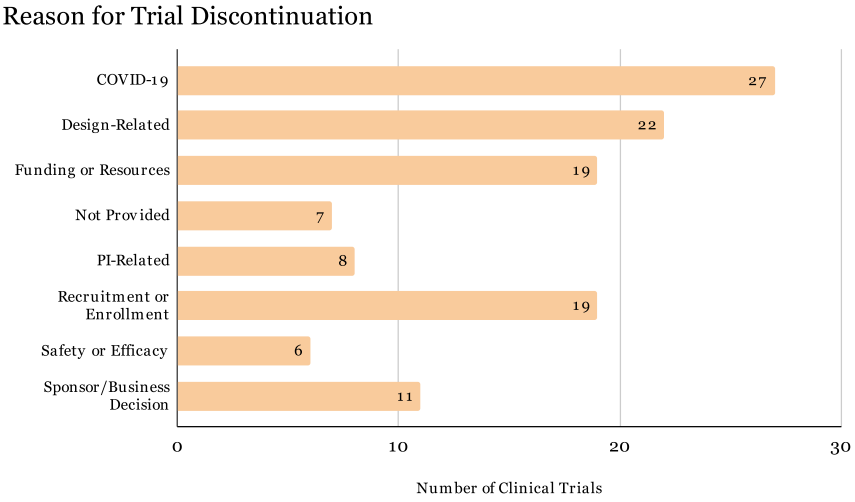

Figure 1: The number of clinical trials in the sample that reported specific reasons for discontinuation during the pandemic.

Anesthesiology [19], Depressive Disorders [24], and Autism Spectrum Disorder [25] had 223, 146, 56, and 15 trials discontinued, respectively. However, the relative amount specifically discontinued due to the pandemic for OA was the highest of these examples. The delay in OA clinical research will likely impede the development of treatment options that are more effective than standard-of-care and may have a lasting impact on the way OA clinical trials are conducted in the future [26]. In the following paragraphs, we discuss our findings in the context of previous research and offer recommendations for future investigations.

Factors associated with discontinuation due to the COVID-19 pandemic

The COVID-19 pandemic ubiquitously and negatively impacted clinical trials [26]. Trials in our cohort referencing the pandemic had a higher rate of suspended status (vs. terminated or withdrawn) compared to the other discontinued trials, possibly reflecting trialists' intention to continue trials in the future. Among the trials in our cohort that were discontinued due to the pandemic, device and drug trials were impacted more frequently. The increased likelihood of device trials being discontinued due to the pandemic is multifactorial. First, it has been reported that medical device manufacturers and innovators had to pause clinical trials and studies because of the need to reallocate resources for pandemic efforts [27]. Second, device trials requiring surgical implantation were likely considered elective. Many elective surgeries, including orthopedic surgeries [28], were postponed during the height of the pandemic. Regarding drug-based interventions, drug trials treating COVID-19 took precedence over other drug trials to maintain a focus on the pandemic [29]. Although many drugs utilized to treat OA are unlikely to have been utilized to treat COVID-19, lack of drug manufacturing resources due to the pandemic could have influenced OA research. Also, drug trials often require in-person administration and monitoring, which may have been prohibited due to local and national lockdown policies [30]. We also found that studies reporting an influence from the pandemic were less likely to have trial sites in the United States compared to those that did not reference the pandemic. It is likely that low-resource countries in Africa, Southeast Asia, and Central America were unable to continue conducting clinical trials and were impacted disproportionally compared to sites in North America [31, 32]. Finally, we found that trials discontinued due to the pandemic had a higher proportion of nonrandomized trials compared to trials that did not reference the pandemic. In our cohort, most of the nonrandomized trials referencing the pandemic in our cohort were device trials. The difficult nature of randomizing interventional device trials may explain why both nonrandomization and device-intervention types were risk factors for discontinuation due to the pandemic in our cohort [33]. Interestingly, we found that behavioral trials were more frequently discontinued due to COVID-19 than what has been seen in another study of similar methodology regarding psychiatric disorders [24]. In that study, we posited that behavioral studies were less likely to be discontinued due to COVID-19 due to their inherent capability to be performed via telecommunication/video chat. However, this does not appear to be the case with OA interventions, and future studies may explore how to make the behavioral OA trials more amenable to virtual methods. Trial phase, source of funding, and number of participants were not predisposing factors for discontinuation due to the pandemic.

Reasons for discontinuation during the pandemic

The second most commonly reported discontinuation reason, second only to the pandemic, was design-related because it included technical difficulties, protocol changes, inadequate methodology, trial site changes, or lack of ethical approval. Following closely behind design issues were equally recruitment/enrollment issues and lack of funding/resources. Our finding of frequent recruitment difficulties is in keeping with previous research. Recruitment issues are the overall most common reason for clinical trial termination irrespective of pandemic conditions [34]. The pandemic likely exacerbated the already frequent incidence of discontinuation due to accrual issues and even surpassed recruitment as the most commonly reported discontinuation reason. Recruitment may have been more difficult during the pandemic, due to local and national stay-at-home orders and social distancing protocols. Additionally, the fear of contracting COVID-19 could have influenced patients' desire to participate in clinical trials that would require entering public settings or leaving their homes [35]. The pandemic also altered the focus for research. With more resources and funding being allocated toward COVID-19 trials, research toward other conditions may have taken a pause [29]. Nearly 10 % of trials stated that discontinuation was due to business decisions. We believe that this verbiage is not specific and does not afford any valuable insight into why a trial was canceled, and trialists should explicitly state the cause of discontinuation.

Recommendations for future osteoarthritis trials

There is substantial literature discussing the use of telemedicine and other virtual or distanced methods to aid in the conduct of patient care and clinical trials as a result of the pandemic [15, 36–38]. We recommend that the use of distanced methods be explored for OA clinical trials, which may support trial conduct during future global emergencies. Distanced methods can be utilized for recruitment, monitoring, or in some cases, as an intervention. For example, a 2018 systematic review found that telephone-based interventions were as effective as person-to-person interventions at reducing pain intensity and disability in patients with hip and knee OA [39]. Telemedicine in clinical trials does have challenges. These challenges, as discussed by Naito et al. [40], include: (1) variations in state licensure requirements for telehealth; (2) disparities in access to telehealth among disadvantaged populations; (3) lack of consistency among individual IRBs. The cost of implementation and reimbursement presents another challenge [15]. The use of distanced methods in OA clinical trials should be explored further.

Strengths and limitations

Our study has strengths and limitations. Regarding strengths, it is the first study to our knowledge to explore how the COVID-19 pandemic influenced the conduct of OA trials. Moreover, data extraction was conducted in a masked, duplicate fashion to mitigate bias and extraction error, as recommended by Cochrane [41]. Regarding limitations, this study is cross-sectional in nature and in no way can it establish causality, and our results should be interpreted accordingly. Further, certain trials may not have reliably reported having been affected by the COVID-19 pandemic in the "Recruitment Status" box provided on ClinicalTrials.gov. As a result, we may have underestimated the extent to which COVID-19 played in halting OA research.

Conclusions

OA is a very common, debilitating condition for which effective treatments and prevention strategies are necessary. We sought to determine the impact of the COVID-19 pandemic on OA clinical trials. We found that nearly a quarter of OA trials registered on ClinicalTrials.gov that were discontinued during the pandemic explicitly stated that the pandemic was the primary cause for discontinuation. There were several trial characteristics associated with the trial explicitly referencing the pandemic as a cause for discontinuation. We recommend that the use of virtual and distanced methods for conducting clinical trials be explored for use in OA clinical trials. We also recommend that trialists utilize our findings to inform trial design.

Author contributions: All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors contributed to the analysis and interpretation of data; all authors gave final approval of

the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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