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The impact of the COVID-19 pandemic on early termination of ophthalmology clinical trials: A cross-sectional analysis of ClinicalTrials.gov

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Abstract

Objective: To study the effect of the COVID-19 pandemic on the early termination of ophthalmology clinical trials.

Methods: On June 10, 2022, we searched ClinicalTrials.gov and identified clinical trials pertaining to eye diseases. We included trials last updated between January 1, 2020 and June 8, 2022, as ones possibly impacted by the pandemic. We selected all interventional trials in any stage and country that were "recruiting," "active, not recruiting," "enrolling by invitation," "suspended," "terminated," "completed," or "withdrawn" and excluded trials that had been completed or discontinued before 2020, had incomplete data, trials in which the eye was not the primary focus of the trial (e.g., Chediak-Higashi syndrome, myasthenia gravis). The following trial-level characteristics were collected: location, trial status, enrollment count, ocular condition, sponsors, intervention purpose, trial phase (I–IV), randomization, number of arms, and reasons for discontinuation. In addition to calculating descriptive statistics, we assessed whether trial characteristics differed between ophthalmology clinical trials canceled due to COVID-19 and those canceled for other reasons.

Results: Following the screening, 2280/12,679 (18%) ophthalmology clinical trials were retained. Of these, 142 (6.2%) were discontinued between January 1, 2020 and June 8, 2022. Moreover, 34 out of 142 (23.9%) ophthalmology clinical trials were discontinued due to COVID-19. These trials were more likely to be sponsored by academic medical centers (26/34, 76.5% vs 57/108, 52.8%, $p = 0.03$) and were not assigned to a specific study phase, indicating they were not investigational new drugs (22/34, 64.7% vs 46/108 42.6%, $p = 0.003$).

Conclusions: COVID-19-related trial discontinuations were more likely to be reported by academic medical centers and associated with trials investigating fully approved drugs, medical devices, procedures, diagnostic imaging, and behavioral changes. Further investigation of these characteristics may lead to a more robust and resilient understanding of the causes of early termination of these clinical trials.

Keywords

COVID-19 pandemic, ophthalmology, intervention study and clinical trial, early termination of clinical trials, Clinicaltrials.gov

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Introduction

Ophthalmology clinical trials (OCTs) are essential for the development and assessment of drugs, devices, and surgical procedures. OCTs require immense investment as the average cost per study from phases I–IV was $69.4 million in 2014 with a median cost of $23,893 per enrolled patient.[1,2] These high costs cause concerns about resource waste when trials are discontinued or results are unpublished.

To increase public awareness and access to clinical trials, Congress passed the Food and Drug Administration (FDA) Modernization Act of 1997 directing the Department of Health and Human Services to create ClinicalTrials.gov, a registry of clinical trials of FDA-regulated products.[3] Since launching in 2000, ClinicalTrials.gov has become the largest, open-source clinical trial database with detailed information about individual trials including location, design, recruitment status, and outcome measures.[4]

The coronavirus disease 2019 (COVID-19) pandemic greatly altered clinical and research practices in ophthalmology. In March 2020, the FDA-recommended sponsors considered the risks of trial continuation while the American Academy of Ophthalmology recommended any non-emergent patient care be discontinued.[5,6] These measures led to disrupted clinic visits, the reassignment of physicians to other clinical services, a surgical backlog, and a shift to telehealth care.[7,8] Most academic medical centers (AMCs) also paused trials that were non-essential, leading to difficulties in patient enrollment and follow-up.[9] Consequently, managing sight-threatening eye diseases became challenging and worsened the progression of myopia as the gap between follow-up visits increased.[10,11]

Previous research on OCTs characterized publication rates, geographic disparities, and design characteristics.[12–14] The effects of the COVID-19 pandemic on OCT discontinuation are unclear. A greater understanding of trials discontinued due to the pandemic may aid the design and management of future trials, leading to reduced resource waste. Therefore, this study aims to describe the characteristics and discontinuation rate of OCTs potentially affected by COVID-19.

Methods

Study design and setting

This cross-sectional study of OCTs followed the Strengthening the Reporting of Observational Studies in Epidemiology Report (STROBE) guidelines.[15] The University of Texas Southwestern Institutional Review Board (UTSW-IRB) deemed that this study does not meet the definition of human subjects research and thus exempted this study from IRB approval and oversight (Waiver#: Y1-22-1247). Furthermore, informed consent was not performed as all data were publicly available, no individual patient data were reviewed, and no human subjects were involved in this research.

On June 10, 2022, ClinicalTrials.gov was accessed through the Aggregate Content of ClinicalTrials.gov (AACT), a comprehensive, relational database of ClinicalTrials.gov that is updated daily.[16] We searched the AACT using terms listed on the "Eye Diseases" page of ClinicalTrials.gov and downloaded a dataset containing every registered OCT. As performed by similar studies,[17–19] we used the "last update posted date" as a proxy to identify trials possibly affected by COVID-19 and to track changes in trial recruitment status. We included trials last updated between January 1, 2020 and June 8, 2022, the latest version of the database.

All interventional trials in any stage and country that were "recruiting," "active, not recruiting," "enrolling by invitation," "suspended," "terminated," "completed," or "withdrawn" were selected (Definitions in Supplemental Table 1). We excluded trials that had been completed or discontinued before 2020, had "not started recruiting," incomplete data, or trials in which the eye was not the primary focus of the trial (e.g., Chediak-Higashi syndrome, myasthenia gravis). A flow chart of our screening process is shown in Figure 1.

Clinical trial characteristics

For the included trials, we recorded the following characteristics: location, randomization, enrollment, ocular condition, sponsor, trial phase, recruitment status, intervention purpose, and reason for discontinuation. The definitions for these characteristics were derived from the Protocol Data Element Definition and Glossary pages of ClinicalTrials.gov and can be seen in Supplemental Table 1.[20,21]

As described by Brewster et al.,[22] we categorized sponsors as "government" for US Governmental agencies, "industry" for pharmaceutical or medical device companies, "academic medical center" for teaching hospitals or universities, or "other" for sponsors such as charities, research networks, or private practices. Trials with multiple sponsors were characterized by the lead sponsor. Similar to other studies,[17–19] we coded trials as U.S. studies if any trial facility was in the United States and non-U.S. studies if all facilities were outside the United States. Furthermore, early phase I trials were categorized as phase I, phase I–II trials were categorized as phase II, and phase II–III trials were categorized as phase III. Trials were characterized as randomized or non-randomized, and trials that declared themselves as "N/A" to randomization were recorded as non-randomized.

Due to the variety of disease conditions, any condition appearing in $\leqslant 5$ trials were categorized as "other." Furthermore, intervention purposes were categorized as "therapeutic" for trials related to treatment or supportive care or "non-therapeutic" for trials related to basic science, health services, prevention, device feasibility, diagnostics, or other.

Unlike the other characteristics described above, the reason for discontinuation characteristic is a free-response entry for trial sponsors when they are documenting information about their trial listing on ClinicalTrials.gov. Therefore, to

Table 1. Characteristics of ophthalmology clinical trials discontinued due to COVID-19 versus non-COVID-19 reasons.

Characteristic	COVID-19 ($n = 34$)	Non-COVID-19 ($n = 108$)	Total ($n = 142$)	p-Value[a]
Location				
U.S. Studies, *n* (%)	12 (35.3)	58 (53.7)	70 (49.3)	0.06
Non-U.S. Studies, *n* (%)	22 (64.7)	50(46.3)	72 (50.7)	
Sponsor				
AMC[d], *n* (%)	26 (76.5)	57 (52.8)	83 (58.5)	0.03[b,c]
Industry, *n* (%)	6 (17.6)	45 (41.7)	51 (35.9)	
Other, *n* (%)	2 (0.6)	6 (0.6)	8 (5.6)	
Government, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Trial status				
Suspended, *n* (%)	7 (20.6)	18 (16.7)	25 (17.6)	0.68
Terminated, *n* (%)	16 (47.1)	45 (41.7)	61 (43.0)	
Withdrawn, *n* (%)	11 (32.4)	45 (41.7)	56 (39.4)	
Trial phase				
Phase 1, *n* (%)	0 (0.0)	11 (10.2)	11 (7.7)	0.003[b,c]
Phase 2, *n* (%)	3 (8.8)	20 (18.5)	23 (16.2)	
Phase 3, *n* (%)	1 (2.9)	20 (18.5)	21 (14.8)	
Phase 4, *n* (%)	8 (23.5)	11 (10.2)	19 (13.4)	
Not applicable, *n* (%)	22 (64.7)	46 (42.6)	68 (47.9)	
Number of arms				
Single, *n* (%)	6 (17.6)	36 (33.3)		0.08
Multiple, *n* (%)	28 (82.4)	72 (66.7)		
Randomization				
Randomized, *n* (%)	23 (67.6)	65 (60.2)	88 (62.0)	0.43
Non-randomized, *n* (%)	6 (32.4)	43 (39.8)	49 (34.5)	
Conditions				
Glaucoma, *n* (%)	6 (17.6)	14 (13.0)	20 (14.1)	0.20[c]
ARMD[e], *n* (%)	1 (2.9)	15 (13.9)	16 (11.3)	
Dry eye, *n* (%)	7 (29.6)	9 (8.3)	16 (11.3)	
Cataract, *n* (%)	3 (8.8)	10 (9.3)	13 (11.3)	
Refractive issue, *n* (%)	2 (5.9)	5 (4.6)	7 (4.9)	
Other, *n* (%)[f]	15 (44.1)	55 (44.1)	70 (49.3)	
Intervention purpose				
Therapeutic, *n* (%)	26 (76.5)	91 (84.3)	117 (82.4)	0.30
Non-therapeutic, *n* (%)	8 (23.5)	17 (15.7)	25 (17.6)	
Enrollment, *n* (median, IQR)	477 (11, 26)	7418 (1, 24)	7895 (2, 26.5)	0.50[g]

[a]*p*-Values are from chi-square tests otherwise noted.
[b]Significant difference ($p < 0.05$).
[c]Fisher's exact test.
[d]Academic Medical Center.
[e]Age-related macular degeneration.
[f]30 other conditions, of which there were ⩽5 trials, were categorized as other. Examples include amblyopia diabetic retinopathy, macular edema, uveal melanoma, uveitis, blepharitis, optic neuropathy, Fuchs' endothelial dystrophy, and entropion.
[g]Mann–Whitney-*U* Test.

standardize the characteristic for analysis, two investigators (SK and SV) independently read and categorized each "reason for discontinuation" entry as one of the following: (1) COVID-19, (2) the principal investigator, (3) recruitment, (4) funding, (5) logistics, (6) safety and efficacy, (7) lack of approval, (8) sponsor, (9) early completion due to interim results, (10) multiple reasons, or (11) unspecified. Disagreements in categorization were resolved with a third investigator (AA) breaking a tie. Reasons for discontinuation were also further categorized as COVID-19-specific or non-COVID-19-specific discontinuation.

Statistical analysis

Descriptive statistics were used to report trial-level characteristics and the rate of OCT discontinuation. We used chi-Square, Fisher–Freeman–Halton, and Mann–Whitney-*U* tests, as appropriate, to assess whether trial characteristics

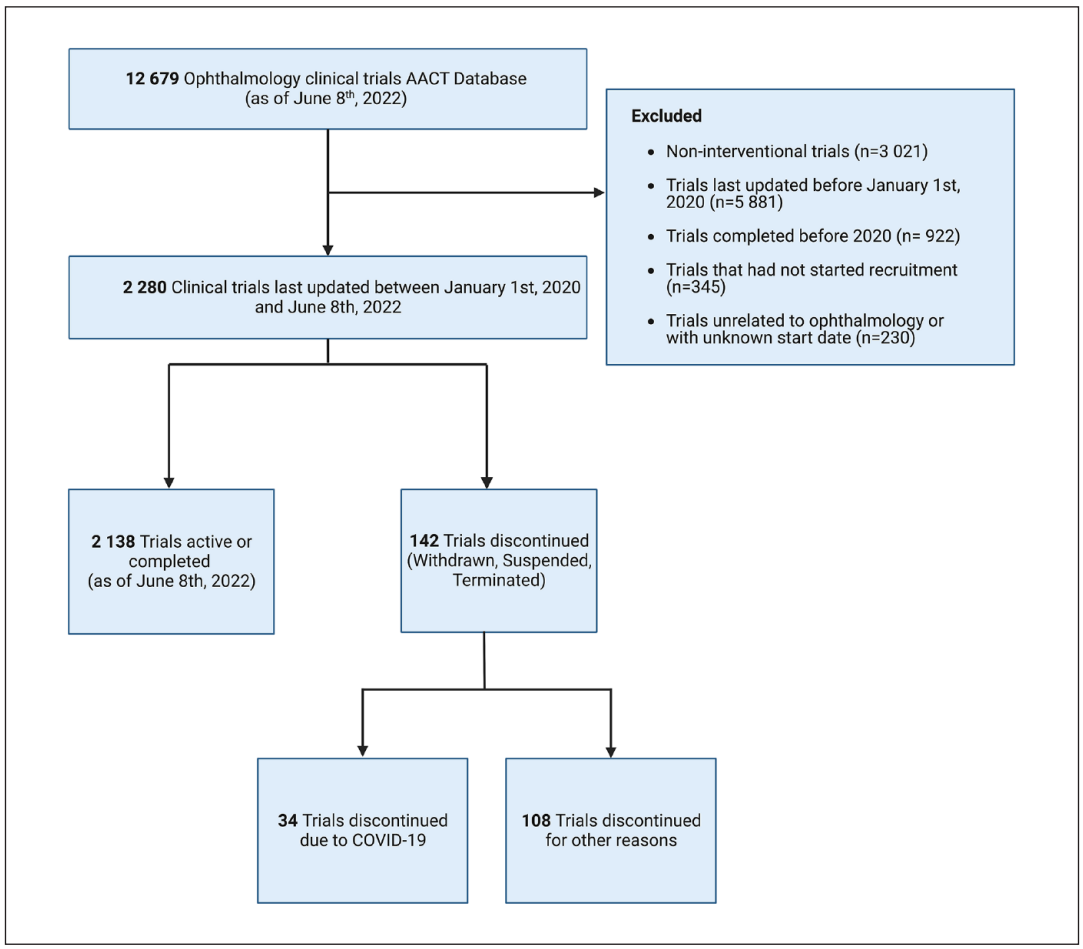

Figure 1. Inclusion/exclusion flow chart of clinical trials (created with Biorender.com).

differed between OCTs discontinued explicitly due to COVID-19 and OCTs discontinued due to non-COVID-19 reasons. All data processing and statistical analysis were performed using Microsoft Excel 16.64 (Redmond, WA, USA), IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA), and RStudio 2022.07.1 (Boston, MA, USA). $p < 0.05$ was considered significant and all analyses were two-sided.

Results

Study characteristics

Of the 12,679 OCTs in our complete dataset, 2280 (18.0%) trials were retained following screening (Figure 1). Based on location, 1013 (44.4%) trials were U.S. studies and 1267 (55.6%) were international. A total of 371,877 (mean, 381.4; SD, 7209) patients were enrolled in these trials. Based on sponsor type, AMCs sponsored 1214 (53.3%) trials, industry sponsored 904 (39.7%) trials, the US government sponsored 19 (0.8%) trials, and other entities sponsored 142 (6.2%) trials. In terms of status, 1103 trials (48.4%) were recruited, 652 (28.6%) were completed, 327 (14.3%) were active but not recruiting, 61 (2.7%) were terminated, 56 (2.5%) were enrolled by invitation, 56 (2.5%) were withdrawn, and 25 were suspended (1.1%).

Reasons for discontinuation

Of the 2280 retained trials, 142 (6.2%) were discontinued between January 1, 2020 and June 8, 2022. These trials were discontinued due to (a) COVID-19 (34, 23.9%), (b) recruitment (20, 14.1%), (c) the sponsor (19, 13.4%), (d) safety and efficacy (17, 12.0%), (e) funding (12, 8.5%), (f) logistics (11, 7.8%), (g) study design (7, 4.9%), (f) the principal investigator (5, 3.5%), (h) lack of approval (3, 2.1%), (i) results being achieved after interim analysis (2, 1.4%), (j) multiple reasons (1, 0.7 %), or (k) unspecified reasons (11, 7.7%). The characteristics of these trials are described in Table 1.

Discontinued trials

In all, 34 trials (23.9% of 142 discontinued trials, 1.5% of 2280 retained trials) were discontinued explicitly due to COVID-19. Of these, seven trials (20.6%) were suspended, 16 (47.1%) were terminated, and 11 (32.4%) were withdrawn. The earliest discontinuation was recorded on June 9,

2020, and the latest discontinuation was on May 17, 2022, less than 1 month from the date of our search. Of 7418 enrolled patients affected by all trial cancelations, 477 (6.4%, median = 11, IQR = 26) were affected by COVID-19-related discontinuations.

Furthermore, AMCs sponsored 26 (76.5%) OCTs, industry sponsored 6 (17.6%), other entities sponsored 2 (5.9%), and the US government sponsored none of the discontinued trials. In terms of location, 12 (35.3%) trials were U.S. studies while 22 (64.7%) were international. The primary purpose of 26 (76.5%) trials was therapeutic, whereas 8 (23.5%) trials were non-therapeutic. There were 23 (67.6%) trials that were randomized in design and 11 (32.4%) that were non-randomized. Among the ocular conditions studied, 6 (17.6%) were related to glaucoma, 1 (2.9%) to age-related macular degeneration, 7 (20.6%) to dry eye, 3 (8.8%) to cataracts, 2 (5.9%) to refractive issues, and 15 (44.1%) to various other conditions. None of the trials were in phase I, 3 (8.8%) were in phase II, 1 (2.9%) was in phase III, 8 (23.5%) were in phase IV, and 22 (64.7%) not assigned to any phase. Trials canceled due to COVID-19 were more likely to be sponsored by AMCs (26/34,76.5% vs 57/108, 52.8%, $p = 0.03$) and be in a non-applicable (N/A) clinical trial phase (22/34, 64.7% vs 46/108, 42.6%, $p = 0.003$) compared to trials canceled due to other reasons.

Discussion

Our cross-sectional study focusing on the effect of the COVID-19 pandemic on the discontinuation of ophthalmology-related clinical trials found between January 1, 2020 and June 9, 2022, 142 (142/2280 total trials, 6.8%) OCTs were discontinued. Of the discontinued trials, 34 (23.9%) were due to COVID-19, indicating considerable disruption in the ophthalmology clinical trial landscape.

Our study adds to the growing literature assessing the impact of COVID-19 on clinical trials registered on ClinicalTrials.gov.[17–19,23] We found 34 (34/2280, 1.49%) OCT discontinuations due to the pandemic. Our results are similar to other fields such as autism (15/197, 7.6%), otolaryngology (33/1777, 1.9%), anesthesia (24/823, 2.9%), and depressive disorders (5/56, 8.9%).[17–19,23] Likewise, we found government-sponsored OCTs to be less affected by the pandemic compared to non-government-sponsored OCTs.

In addition to sponsoring the most OCTs (1214/2280, 53.3%), AMCs were also more likely to report trial discontinuations due to COVID-19 (26/34,76.5%, $p = 0.03$). In comparison, AMC-sponsored OCTs between 2007 and 2019 were less likely to be discontinued.[12,13] This suggests COVID-19 was more burdensome for AMCs compared to industry, government, and other sponsors. AMCs typically house a variety of clinical specialties with large patient volumes, which likely led to stricter restrictions on clinical practice and research across all specialties.[24] According to Bauer et al.,[24] AMCs also faced issues with funding and research-staff allocation. These limitations led them to shift resources away from non-COVID trials, such as OCTs, to more urgent COVID-19 trials.

Trials discontinued due to COVID-19 were more likely to be not associated with specific study phases (I–IV), assigned to investigational new drugs (INDs), compared to trials discontinued for other reasons (22/34, 64.7% vs 46/108, 42.6%, $p = 0.003$). Since AMCs typically fund these non-IND trials, they may have been canceled due to shifts in funding and resources as previously discussed.[12] Industry sponsors, who typically make large investments in drug development, may have been less willing to make such shifts in funding.[12] Furthermore, since ophthalmology devices are placed surgically, the decline in surgical cases and clinic visits during the pandemic may have also further contributed to early trial discontinuation.[9]

There are limitations to our study. First, due to our study's cross-sectional design and the daily updates of ClinicalTrials.gov, we were unable to assess trial discontinuation rates before the pandemic and thus were unable to compare between periods. Second, due to the self-reported requirements for discontinuation, some sponsors cited non-COVID-19 reasons for discontinuation even if they had been affected by the COVID-19 pandemic. In addition, some reasons cited for discontinuation such as difficulty recruiting patients may have also been indirectly related to the pandemic. This limitation likely led our study to underestimate the number of trials discontinued due to COVID-19. Third, ClinicalTrials.gov limits the documentation for study discontinuation to only 250 characters, which limits detailed reason(s).[20] As a result, we are also unable to assess whether non-discontinued OCTs have lower recruitment than expected or delayed recruitment. Fourth, this study is conducted within the framework of ClinicalTrials.gov and does not include trials not registered with the site; therefore, our findings may not be adequately generalizable, especially for international trials. Future studies could gain a further understanding of OCT disruption by surveying principal investigators, clinical trial staff, and sponsors of discontinued trials. A more comprehensive understanding of trial discontinuation could allow for the creation of safeguards and protocol changes for more robust trials that can avoid discontinuation whether it be due to black swan events such as a pandemic or more routine causes.

Conclusion

Our findings indicate the COVID-19 pandemic played a considerable role in the discontinuation of OCTs. Trials conducted at AMCs and trials investigating fully approved drugs, medical devices, procedures, diagnostic imaging, and behavioral changes were especially vulnerable to early discontinuation. Further research is required to better prepare the research community for unexpected calamities and to assess the setbacks in the progress of new treatments for patients.

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Declaration of conflicting interests

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Ethics approval

The University of Texas Southwestern Institutional Review Board (UTSW-IRB) deemed that this study does not meet the definition of human subjects research and thus exempted this study from IRB approval and oversight (Waiver#: Y1-22-1247)

Informed consent

Informed consents were not performed as all data were publicly available, no individual patient data were reviewed, and no human subjects were involved in this research.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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