

Brayden M. Rucker\*, BS, Nicholas B. Sajjadi, BS, Lacy S. Brame, DO, Matt Vassar, PhD and Micah L. Hartwell, PhD

# The impact of COVID-19 on otolaryngology research: a cross-sectional analysis of discontinued trials

<https://doi.org/10.1515/jom-2021-0278>

Received November 29, 2021; accepted March 9, 2022; published online April 1, 2022

## Abstract

**Context:** The COVID-19 pandemic has reduced the capacity to conduct medical research due to recruitment difficulties, supply chain shortages, and funding deficits. The clinical practice of otolaryngology was especially impacted due to a reduction in elective procedures, such as facial plastic surgeries and vocal fold injections.

**Objectives:** The primary objective was to examine the extent of clinical trial (CTs) disruption secondary to the COVID-19 pandemic in the field of otolaryngology.

**Methods:** On August 1, 2021, we conducted a systematic search utilizing ClinicalTrials.gov for CTs related to common otolaryngology disorders. We utilized the date range January 1, 2020 through August 1, 2021 to identify all trials potentially affected by the COVID-19 pandemic. Investigators performed screening and data extraction in a duplicate, masked fashion. Trials resulting from the search were extracted for trial status, condition treated, enrollment number, funding, study type, study design, last update posted date, and trial location. Trials that explicitly mentioned COVID-19 as a reason for discontinuation or suspension were coded as such. For trials that did not explicitly mention COVID-19, we coded the reason provided from ClinicalTrials.gov. The

Oklahoma State University Center for Health Science Institutional Review Board determined that this project did not qualify as human subject research.

**Results:** A total of 1,777 CTs met the inclusion criteria, and 223 CTs were discontinued between January 1, 2020 and August 1, 2021. Thirty-three (14.8%) of the 223 CTs reported discontinuation explicitly due to the COVID-19 pandemic. The 33 studies had 1,715 participants enrolled in total. Among the primary interventions, 11 (33.3%) were devices, 10 (30.3%) were drugs, 5 (15.2%) were behavioral, 4 (12.1%) were diagnostic tests, 1 (3.0%) was dietary, and 2 (6.1%) were labeled as “other.” Regarding the CT location, 20 (60.6%) were conducted in the United States, and 13 (39.4%) were conducted internationally. Of the 33 CTs, 19 (57.6%) were suspended, 9 (27.3%) were terminated, and 5 (15.2%) were withdrawn. The overall most common reason for trial disruption was recruitment difficulties (24.2%). Median enrollment for discontinued trials due to COVID-19 was 37 (interquartile range [IQR], 19–71) and for other reasons was 6 (IQR, 0–27), for which the Mann–Whitney test showed a statistically significant difference between the two ( $z = -3.913$ ,  $p < 0.001$ ). There were no significant associations between trial location, funding source, randomization, or whether a study involved masked vs unmasked participants.

**Conclusions:** The COVID-19 pandemic has incited an impact on clinical research in the field of otolaryngology. To preserve trial continuation amid future threats to participant interaction and communication, we recommend further exploration of remote monitoring practices and virtual procedures—those that will maintain the effectiveness and accuracy needed to establish novel therapeutics. We encourage future trials to gauge which remote assessments show the greatest validity, with the long-term goal of establishing innovative study designs resilient to future pandemics.

**Keywords:** clinical trials; COVID-19; ENT; otolaryngology; pandemic.

\*Corresponding author: **Brayden M. Rucker**, BS, Oklahoma State University Center for Health Sciences, 1111 W 17th Street, Tulsa, OK 74107, USA, E-mail: [brayden.rucker@okstate.edu](mailto:brayden.rucker@okstate.edu)

**Nicholas B. Sajjadi**, BS, Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA  
**Lacy S. Brame**, DO, Department of Otolaryngology – Head and Neck Surgery, Oklahoma State University Medical Center, Tulsa, OK, USA  
**Matt Vassar**, PhD and **Micah L. Hartwell**, PhD, Office of Medical Student Research, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA; and Department of Psychiatry and Behavioral Sciences, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA

The practice of evidence-based medicine combines clinical knowledge gained from experience with robust scientific evidence often provided by clinical trials (CTs) [1]. Findings from CTs are valuable to otolaryngologists, because they provide evidence for treating medical conditions such as tinnitus, rhinosinusitis, head and neck cancers, and many other ENT-related conditions [2]. The COVID-19 pandemic has reduced the capacity to conduct medical research by disrupting the progress of ongoing CTs in several fields of medicine [3–6]. In response to the pandemic, the United States Food and Drug Administration updated guidance on conducting CTs, prioritizing patient safety by limiting travel and accessibility of participants to study visits and follow-ups, minimizing interactions with social distancing, and halting drug supply chains [7]. Further, sponsoring institutions have introduced restrictions on developing trials, because funding has remained uncertain amid the unpredictable pandemic [3]. Together, many safety measures, while necessary, have hindered the progress of CTs.

The practice of otolaryngology also shifted dramatically during the COVID-19 pandemic. For example, ENT surgeons have been inundated with patients requiring tracheostomy tube placements due to prolonged intubation from COVID-19 complications, which has detracted from their usual focus of practice [8]. Additionally, procedures such as facial plastic surgeries, vocal fold injections, and other nonemergent procedures have been stalled after having been deemed “elective” by some institutions [9]. The shifting focus of otolaryngology practice brought about by the pandemic may have profound effects on CTs as well as other research studies in the field of otolaryngology. Moreover, ENT-related osteopathic techniques that can be utilized to combat upper respiratory infections, such as cervical myofascial release, cervical articulation, and lymphatic drainage techniques, declined due to the highly pathogenic nature of the coronavirus [10, 11]. In fact, a survey through the American Osteopathic Association revealed that 95% of osteopathic physicians experienced a decline in practice revenue as a result of the COVID-19 pandemic.

Gauging the long-term impact of the pandemic on otolaryngology research will depend on having first assessed the immediate impacts of the pandemic on otolaryngology-related CTs. Although protecting trial participants from COVID-19 has remained of the utmost importance, the effects of the pandemic on ENT CT progress remains unknown. Thus, we sought to examine the extent of otolaryngology CT disruption secondary to the COVID-19 pandemic. Findings from this study may highlight the importance of developing strategies for safely

continuing clinical research amid the possibility of future global emergencies.

## Methods

On August 1, 2021, we performed a systematic search of ClinicalTrials.gov, an international registry of both privately and publicly funded interventional studies [12], for trials related to otolaryngology disorders. Our search included the following terms: Acoustic Neuroma, Adenoidectomy, Ageusia, Allergic Rhinitis, Anosmia, Cochlear Implants, Craniofacial Injuries, Deafness, Diphtheria, Dysgeusia, Dysosmia, Ear Disorders, Ear Infections, ENT Disease, ENT Disorder, Head and Neck Cancer, Hearing Aids, Hearing Disorders, Hypopharyngeal Cancer, Laryngeal Cancer, Laryngitis, Laryngopharyngeal Cancer, Meniere’s Disease, Nasal Cancer, Nasopharyngeal Cancer, Nosebleed, Epistaxis, Oropharyngeal Cancer, Otitis Media, Otolaryngological Disease, Otorhinolaryngologic Diseases, Otolaryngologic Disorder, Paranasal Sinus Cancer, Pharyngeal Cancer, Pharyngitis, Presbycusis, Sinus Infection, Sinusitis, Snoring, Sore Throat, Strep Throat, Swimmer’s Ear, Thyroid Cancer, Tinnitus, Tonsillitis, Usher Syndrome, Vestibular Diseases, Vertigo, and Vestibular Schwannoma. We included interventional trials in any phase and in any country that were recruiting, active but not recruiting, enrolling by invitation, suspended, withdrawn, or terminated. The “last update posted” date was utilized as a proxy for trial status change. We utilized the date range January 1, 2020 through August 1, 2021 to identify all trials potentially affected by the COVID-19 pandemic. The search string is presented in Figure 1.

The trials resulting from the search were extracted for trial status, condition treated, enrollment number, funding, study type, study design, last update posted date, and trial location. Trials were then screened for relevance to the field of otolaryngology utilizing the “conditions treated,” and irrelevant studies were excluded. In a blinded, duplicate manner, two authors (B.M.R. and N.B.S.) manually extracted the reasons for discontinuation or suspension provided on the ClinicalTrials.gov website. Trials that explicitly mentioned “COVID-19” as a reason for discontinuation or suspension were coded as such. For these trials, study intervention was additionally extracted. For trials that did not explicitly mention the COVID-19 pandemic, we coded the reason provided from ClinicalTrials.gov. If a reason was not provided, the reason for discontinuation was coded as “not provided.”

A Mann–Whitney U test was utilized to examine whether significant differences in enrollment existed between trials discontinued due to the COVID-19 pandemic vs all other discontinued trials. We utilized a Mann–Whitney U test because enrollment numbers were nonnormally distributed among trials in our sample. We utilized Fisher’s exact tests to examine associations between trials that were canceled due to the COVID-19 pandemic and the funding source and trial location (US and non-US-based). If a study had multiple sites and any of them were listed in the United States, they were coded as US studies. Funding source was coded as either *US Government* (if any US Federal agency, Veterans Affairs, Department of Defense was reported), *Industry* (if any industry involvement was reported), or *Other* for registered CTs receiving funding from neither industry nor government. *Other* is a “funded by” category

**ClinicalTrials.gov:**

```
[Otolaryngologic Disorder OR Otolaryngological Disease OR ENT Disorder OR ENT Disease OR
Otorhinolaryngologic Diseases OR Achalasia OR Acoustic Neuroma OR Adenoidectomy OR Ageusia
OR Allergic Rhinitis OR Anosmia OR Cochlear Implants OR Craniofacial Injuries OR Deafness OR
Diphtheria OR Vertigo OR Dysgeusia OR Dysosmia OR Ear Disorders OR Ear Infections OR Esophageal
Cancer OR Esophagus Disorders OR Head and Neck Cancer OR Hearing Aids OR Hypopharyngeal
Cancer OR Laryngeal Cancer OR Laryngitis OR Laryngopharyngeal Cancer OR Meniere's Disease OR
Nasal Cancer OR Nasopharyngeal Cancer OR Nosebleed OR Epistaxis OR Oropharyngeal Cancer OR
Otitis Media see Ear Infections OR Paranasal Sinus Cancer OR Pharyngeal Cancer OR Pharyngitis OR
Presbycusis see Hearing Disorders and Deafness OR Sinus Infection OR Sinusitis OR Snoring OR Sore
Throat OR Strep Throat OR Swimmer's Ear see Ear Infections OR Thyroid Cancer OR Tinnitus OR
Tonsillitis OR Usher Syndrome OR Vestibular Diseases see Dizziness and Vertigo OR Meniere's
Disease OR Vestibular Schwannoma see ) AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch]
( "Recruiting" OR "Active, not recruiting" OR "Enrolling by invitation" OR "Suspended" OR
"Terminated" OR "Withdrawn" ) AND AREA[StudyType] EXPAND[Term] COVER[FullMatch]
"Interventional" AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[01/01/2020, 08/01/2021]
```

**Figure 1:** Search strategy to obtain clinical trials (CTs).

that investigators can select on ClinicalTrials.gov, and we applied this term as defined on ClinicalTrials.gov. If a study included *US Government* and *Industry*, it was coded as *US Government* due to superseding reporting guidelines, with the same hierarchy for studies with *Industry* and *Other*.

Statistical analyses were performed utilizing Stata 16.1 (Stata-Corp, College Station, TX). The Oklahoma State University Center for Health Science Institutional Review Board determined that this project did not qualify as human subject research as defined in 45 CFR 46.102 (d) and (f).

## Results

### Study characteristics

Our search returned 3,253 CTs, and 1,777 were retained after screening for relevance to our search (Figure 2). Among the 1,777 included CTs, the median enrollment was 59 (interquartile range [IQR], 27–128) with a total of 397,523 participants (range, 0–150,000). By trial location, 911 (51.4%) were in the United States and 866 (48.7%) were outside of the United States. By funding source, 524 (29.5%) were “Industry,” 221 (12.4%) were “US Government,” and 1,032 (58.1%) were “Other.” By trial status, 347 (19.5%) were “Active, not recruiting,” 58 (3.3%) were “Enrolling by invitation,” 1,149 (64.7%) were “Recruiting,” 41 (2.3%) were “Suspended,” 114 (6.4%) were “Terminated,” and 68 (3.8%) were “Withdrawn.”

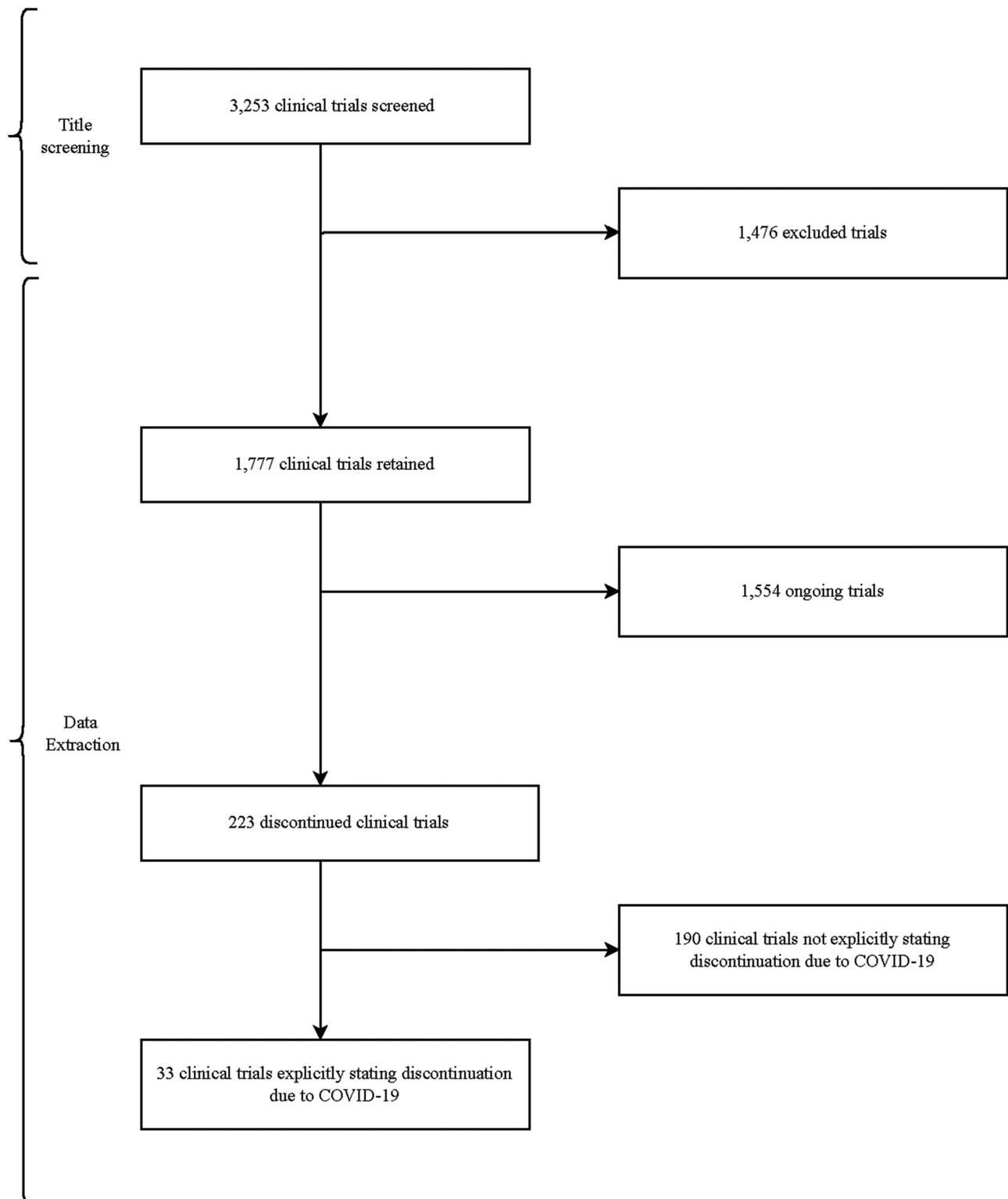
### Discontinued trials

Of the 1,777 included studies, 223 (12.4%) studies were discontinued between January 1, 2020, and August 1, 2021.

The median enrollment of the discontinued trials was 8 (IQR, 0–35) with a range of 0–1,110 participants. The total number of participants involved in prematurely terminated studies was 8,584. Among the discontinued studies, 135 (60.5%) were conducted in the United States and 88 (39.5%) were conducted outside of the United States. By funding source, 59 (26.5%) were *Industry*, 26 (11.7%) were *US Government*, and 138 (61.9%) were *Other*. Regarding study design, 107 (48.0%) studies were nonrandomized, and 116 (52.0%) studies were randomized. A total of 146 (65.5%) studies involved unmasked trial participants, while 77 (34.5%) studies involved masked trial participants. Of the 223 discontinued studies, the reported reasons for discontinuation were as follows: 59 (25.5%) recruitment and enrollment, 15 (6.7%) sponsor-related, 13 (5.8%) safety & efficacy, 17 (7.6%) principal investigator-related, 23 (10.3%) funding and resources, 34 (15.3%) design-related, 2 (0.9%) business decision, 9 (4.0%) lack of approval, 18 (8.1%) not provided, and 33 (14.8%) were discontinued explicitly due to the COVID-19 pandemic.

### COVID-19-related discontinuation

Of the 33 studies disrupted due to the pandemic, 9 (27.3%) were terminated, 19 (57.6%) were suspended, and 5 (15.2%) were withdrawn. The 33 studies discontinued due to the COVID-19 pandemic had 1,715 participants enrolled in total. Among the primary interventions, 11 (33.3%) were devices, 10 (30.3%) were drugs, 5 (15.2%) were behavioral, 4 (12.1%) were diagnostic tests, 1 (3.0%) was dietary, and 2 (6.1%) were labeled as “other.” Regarding the CT location, 20 (60.6%) were conducted in the United States, and 13



**Figure 2:** Flow diagram of trial selection.

(39.4%) were conducted internationally. A total of 8 (24.2%) out of 33 studies were discontinued due to recruitment difficulties, making it the most common reason for CT disruption. In addition, 3 (9.1%) were

discontinued due to reallocation of testing resources, 1 (3.0%) was discontinued due to lack of funding, 1 (3.0%) was discontinued due to screening safety concerns, and 20 (60.6%) were discontinued with unspecified explanations.

**Table 1:** Associations of reasons for discontinuation by trial characteristics.

Characteristic	Reason for discontinuation		p-Value
	Non-COVID-19	COVID-19	
Number of CTs	190	33	
Location			$\chi^2 (1)=0.004$
Non-US	75	13	0.948
US	115	20	
Funding source			$\chi^2 (2)=0.55$
Industry	52	7	0.758
US Government	22	4	
Other	116	22	
Randomization			$\chi^2 (1)=0.479$
No	93	14	0.489
Yes	97	19	
Masked			$\chi^2 (1)=1.07$
No	127	19	0.301
Yes	63	14	
Enrollment			Mann–Whitney U
Median (IQR)	6 (0–27)	37 (19–71)	$z=-3.913, p<0.001$

CT, clinical trial; IQR, interquartile range.

## Statistical associations

Median enrollment for discontinued trials due to COVID-19 was 37 (IQR, 19–71) and for other reasons was 6 (IQR, 0–27), for which the Mann–Whitney test showed a statistically significant difference between the two ( $z=-3.913, p<0.001$ ; Table 1). There were no significant associations between trial location, funding source, randomization, or whether a study involved masked vs unmasked participants. The association of reasons for discontinuation by trial characteristics is displayed in Table 1.

## Discussion

We found that at least 14.8% of registered otolaryngology-related CTs discontinued since the pandemic began were halted due to the COVID-19 pandemic, with the majority of these trials reporting recruitment problems. These trials discontinued due to the pandemic represent 1,715 participants who could not receive novel and potentially beneficial treatments because of the pandemic. A statistically significant association was found between COVID-19-related trial discontinuation and median enrollment number, suggesting that larger trials were more likely to be discontinued as a result of the pandemic. This disruption could have resulted from social-distancing protocols that placed limitations on the maximum capacity of facilities and social gatherings. Although no significant associations were found between

COVID-19 discontinuation and trial location, randomization, funding source, or masking strategy, any trial disruption poses important implications. Moreover, it is possible that reporting trial discontinuation due to the COVID-19 pandemic was underreported. The most common reason overall for trial discontinuation was recruitment difficulties, which may have been a consequence of shutdowns, stay-at-home orders, or social distancing policies. The lack of various associations with the likelihood of trialists reporting discontinuation due to the COVID-19 pandemic may simply suggest that all discontinued otolaryngology trials were impacted equally, regardless of differences in these measured variables.

The COVID-19 pandemic brought on new challenges to CT progress. For example, social distancing policies threatened trial discontinuation, especially for interventions involving person-to-person contact. Self-isolation policies can interfere with all phases of CTs, which warrants the exploration of novel protocols for use in pandemic situations. Virtualization, telecommunication, and at-home collection of data could all serve as possible solutions going forward [13]. In a systematic review assessing the impact of the COVID-19 pandemic on trial progress, Sathian et al. [14] suggested alternative methods of obtaining data amid self-isolation protocols—telephone-mediated questionnaires and at-home data collection. In addition, Xue et al. [15] surveyed CT investigators utilizing ClinicalTrials.gov data in May 2020 to determine the extent to which the pandemic altered the progress of ongoing trials. Investigators in the study reported that 57% of patient interactions and 79% of interactions between sponsors and contract research organizations took place remotely [15]. However, the integration of telemedicine poses its challenges; trial developers must consider the additional costs of technology, and they have to establish amendments protecting patient rights and procedure operations [16].

Premature trial discontinuation is often necessary for ethical reasons. Compromised patient safety, the presence of severe adverse events, and interventional futility are a few of the justifiable considerations for trial discontinuation [17]. If a trial exposes human subjects to more risks than benefits, the justification to continue research markedly diminishes. However, trials are often discontinued due to preventable circumstances, which greatly contributes to research waste [18]. In a retrospective cohort study utilizing randomized controlled trial (RCT) protocols approved between 2000 and 2003, Kasenda et al. [19] found that approximately one quarter of planned RCTs are prematurely discontinued primarily due to recruitment issues. RCTs have also been shown to be at a higher risk for discontinuation compared to

nonrandomized controlled trials, single-arm trials, and cohort studies [20]. These findings, as well as our own findings, suggest the need for improved contingency plans and strategies aimed at continuing trials that fail to adequately recruit participants, especially in the setting of a pandemic or other global emergency. By preventing trial discontinuation, or mitigating its impact, valid data and progress could be preserved and utilized as evidence for subsequent systematic reviews, meta-analyses, and other forms of medical evidence.

It is important to note the potential benefit that osteopathic treatment holds for diseases like COVID-19. Although hands-on osteopathic manipulation may have been hindered by the contact precautions and social isolation policies in place during the pandemic, video-instructed at-home exercises and techniques could hold some benefit to patients that are otherwise unable to access care. However, we encourage future studies to assess the impact of osteopathic treatment to nonhospitalized patients during the pandemic because manipulative therapy requires person-to-person interactions.

## Limitations

By the nature of our study design, trials were labeled as “COVID-19-related discontinuation” if COVID-19 was explicitly mentioned in the “Recruitment Status” box provided on ClinicalTrials.gov. This does not rule out the potential for other trials found in our search to have been disrupted from the COVID-19 pandemic. Therefore, our results could be underrepresenting the true impact of the COVID-19 pandemic on ENT research. Also, we cannot claim causality due to the nature of cross-sectional analysis, and our results should be interpreted accordingly. There may have been additional factors contributing to trial disruption, even among trials explicitly reporting the COVID-19 pandemic as a factor. For example, many CTs in otolaryngology may have been modified to support COVID-19 research efforts. Principal investigators may have reallocated funds to support COVID-19 research efforts when the National Institutes of Health (NIH) allowed for grant revisions at the start of the pandemic. However, we were not able to assess the extent of funding reallocation with the current methodology, limiting the ability to discuss the possibility of grant revision and protocol restructuring. Future studies are needed to assess the impact of funding reallocation on the progress of ENT trials during the pandemic. With many ENT trials discontinued during the pandemic period, it is likely that researchers could also reallocate time to write manuscripts. Thus,

future research may investigate whether the number of ENT manuscripts submitted or published showed significant changes during the pandemic. Lastly, our results are indicative only of the current pandemic time period and would benefit with further analysis of discontinued studies both prepandemic and postpandemic. We encourage the implementation of future studies to explore CT discontinuation statistics to aid in establishing a baseline for the data obtained in this study.

## Conclusions

Overall, the COVID-19 pandemic has incited an impact on clinical research in the field of otolaryngology. We believe that this manuscript is important for osteopathic students and resident physicians pursuing otolaryngology as a profession, especially in academic settings where clinical research occurs. Our study demonstrates the susceptibility of ENT CT design to global emergencies. We hope that the findings of this study inspire osteopathic students and residents entering otolaryngology to develop resilient CT methods that allow ENT research to continue safely during global health crises. Further, to preserve trial continuation amid future threats to participant interaction and communication, we recommend further exploration of remote monitoring practices and virtual procedures—those that will maintain the effectiveness and accuracy needed to establish novel therapeutics. We encourage future trials to gauge which remote assessments show the greatest validity, with the long-term goal of establishing innovative study designs resilient to future pandemics.

**Research funding:** None reported.

**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 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.

**Competing interests:** Dr. Vassar reports receipt of funding from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the US Office of Research Integrity, Oklahoma Center for Advancement of Science and Technology, and internal grants from Oklahoma State University Center for Health Sciences—all outside of the present work.

## References

- Ah-See KW, Molony NC. A qualitative assessment of randomized controlled trials in otolaryngology. *J Laryngol Otol* 1998;112:460–3.
- Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: developing guidance for clinical trials. *Otolaryngol Head Neck Surg* 2006;135:S31–80.
- Asaad M, Habibullah NK, Butler CE. The impact of COVID-19 on clinical trials. *Ann Surg* 2020;272:e222–3.
- Desai S, Manjaly P, Lee KJ, Li SJ, Manjaly C, Mostaghimi A. The impact of COVID-19 on dermatology clinical trials. *J Invest Dermatol* 2021;141:676–8.
- Upadhaya S, Yu JX, Hodge J, Campbell J. COVID-19 impact on oncology clinical trials: a 1-year analysis. *Nat Rev Drug Discov* 2021;20:415.
- Moon SJE, Dabbs AD, Hergenroeder AL, Vendetti ML, Jones KB, Willey BM, et al. Considerations for assessing physical function and physical activity in clinical trials during the COVID-19 pandemic. *Contemp Clin Trials* 2021;105:106407.
- Center for Drug Evaluation, Research. Guidance for industry, investigators, and institutional review boards. Published 2021. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency> [Accessed 16 Jul 2021].
- McGrath BA, Brenner M, Warrillow SJ, Pandian V, Arora A, Cameron TS, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Respir Med* 2020;8:717–25.
- Wright B, McKenna C, Reddy C. The effect of the COVID-19 pandemic on non-elective otolaryngology admissions and a positive change in clinical practice. *Ann R Coll Surg Engl* 2021; 103:496–8.
- MacDonald CW, Lonnemann E, Petersen SM, Rivett DA, Osmotherly PG, Brismée JM. COVID 19 and manual therapy: international lessons and perspectives on current and future clinical practice and education. *J Man Manip Ther* 2020;28: 134–45.
- American Osteopathic Association. 95% of osteopathic physicians experienced a decline in practice revenue during pandemic. Published June 16, 2020. Available from: <https://osteopathic.org/2020/06/16/40-of-physician-practices-lost-half-their-revenue-during-pandemic/> [Accessed 2 Mar 2022].
- NIH. U. S. National Library of Medicine. ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/> [Accessed 15 Jul 2021].
- Greenough MC, Sajjadi NB, Rucker B, Vassar M, Hartwell M. The use of telecommunication and virtualization among ongoing and discontinued COVID-19 clinical trials: a cross-sectional analysis. *Contemp Clin Trials* 2022;114: 106681.
- Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER, et al. Impact of COVID-19 on clinical trials and clinical research: a systematic review. *Nepal J Epidemiol* 2020;10: 878–87.
- Xue JZ, Smietana K, Poda P, Webster K, Yang G, Agrawal G. Clinical trial recovery from COVID-19 disruption. *Nat Rev Drug Discov* 2020;19:662–3.
- Izmailova ES, Ellis R, Benko C. Remote monitoring in clinical trials during the COVID-19 pandemic. *Clin Transl Sci* 2020;13:838–41.
- Deichmann RE, Krousel-Wood M, Breault J. Bioethics in practice: considerations for stopping a clinical trial early. *Ochsner J* 2016; 16:197–8.
- Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Obstet Gynecol* 2009;114: 1341–5.
- Kasenda B, von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA* 2014;311:1045–51.
- Blümle A, Schandelmaier S, Oeller P, Kasenda B, Briel M, von Elm E, et al. Premature discontinuation of prospective clinical studies approved by a research ethics committee - a comparison of randomised and non-randomised studies. *PLoS One* 2016;11: e0165605.