

***Running Title:*** COVID-19 and its Impact on Clinical trials

**Title:** COVID-19 Crisis: An Update on the Disruption of Clinical trials

Vijay Kumar\*

Amity Institute of Neuropsychology & Neurosciences, Amity University, Noida, UP- 201303,  
India

Orcid Id: [0000-0002-3621-5025](https://orcid.org/0000-0002-3621-5025)

*\*Address for Correspondence*

Vijay Kumar, PhD

Assistant Professor

Amity Institute of Neuropsychology & Neurosciences,  
Amity University, Noida, UP- 201313, India

E-mail: [vkumar33@amity.edu](mailto:vkumar33@amity.edu)

## Abstract

COVID-19 is causing major turmoil around the globe, and the clinical trial industry is likely to face unprecedented challenges to health and business sectors. In an effort to find a suitable treatment and prevention options for COVID-19, several COVID-19 clinical trials are being planned and initiated, while a large number of clinical trials for non- COVID-19 indications are suffering delays. With over more than 1000 trials being disrupted and more trials being added to this category daily, there is a direct impact on trial site activation and patient enrolment. This analysis deals with the specific impacts of the COVID-19 pandemic on the clinical trial and pharmaceutical industry. The objective of this study is to provide an updated information of the disrupted clinical trials and its impact on various therapeutic areas and different drugs. Among the severely affected clinical trials, oncology and CNS trials are the hardest hit therapy areas.

This article will certainly emphasize the need for advanced and innovative approaches to maintain the health of the clinical trial ecosystem by continuing the existing trials and the start of the new studies. We have to take and follow necessary actions to guarantee that the initiatives will not be locked during the COVID-19 pandemic, both for the treatment of patients and for the researchers to conduct decision-relevant clinical trials.

**Keywords:** COVID-19; Clinical Trials; disruption; non-COVID-19 clinical trials; drugs; therapeutic area

## 1. INTRODUCTION

The world is currently experiencing a global pandemic “Coronavirus Disease 2019” (COVID-19) caused by the novel coronavirus SARS-CoV-2, which, as of the middle of May 2020 is known to have infected more than 4 million people and resulted in nearly 3 lakhs deaths in more than 200 different countries. This novel virus spread mainly through respiratory droplets and close contact and showed to cause characteristic features of acute respiratory distress syndrome and the involvement of multiple organs [1]. With the pandemic of COVID-19 affecting the way of life across the globe, there has been an increased urgency to accelerate the clinical development of a vaccine or a therapeutic drug for the COVID-19 outbreak [2-6]. The scientific community, clinical centres, pharmaceutical companies, and regulatory agencies has risen to the Covid-19 challenge and working hard for the speedy progress and authorisation of anti-COVID-19 treatments. The result is an impressive and growing list of clinical trials looking for candidate drugs and vaccines [7-10]

Rather than the usual timeline of 12 to 24 months from clinical trial concept to first patient enrolled, however, in the last three months, over 1500 clinical trials have been registered. At the same time, when we see an alarming increase in the clinical trials for COVID-19, a large number of clinical trials for non-COVID-19 indications are suffering delays [11]. Since early March, over a hundred pharmaceutical industries have publicly announced disruptions to planned and ongoing clinical trials. These industries have delayed the initiation of planned trials or completely withdrawn these trials, as well as suspended enrolment in ongoing trials or terminated these trials [12].

The shift of interest of the many regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) which now offering accelerated approval for COVID-19 therapeutics and vaccines, could be a reason in part that sponsors have shifted focus and research onto the current pandemic. But the majority of trial disruption could be

attributed to patient safety, strict lockdown, social distancing, and the high demand for health care professionals to fight against COVID-19.

These large numbers of suspended clinical trials due to COVID-19 caused a setback for entire human research programmes, possibly delaying the advent of new drugs, evidence of drug's efficacy in new indications or combinations, or revealing negative results.

There are only a few publications available that highlight the extensive closures of clinical trials that have occurred in the COVID-19 era, however, the extent to which this stoppage has affected the medical research and health innovations is uncertain [13, 14]. This article will represent an attempt to quantify the number of clinical trials that have been terminated, suspended, or withdrawn due to COVID-19 and summarize their impact on drug development and different sponsors in the project of clinical research on humans.

## **2. CURRENT CLINICAL TRIALS ON COVID-19: AN OVERVIEW**

As of May 16, 2020, well over 1500 clinical trials have been registered on the clinical trials registry at the U.S. National Library of Medicine. Of these trials, 300 trials are conducted in the USA, followed by 243 in France, 101 in China, 87 in Italy, 73 in Spain, and 53 in the UK. Of note, 86 of these studies are in Phase I trials, 356 are in Phase II, 231 are in Phase III, and 52 are in Phase IV.

The Covid-19 Dashboard on the Pharma Intelligence Centre [15] vigorously tracks the trials from the Clinical Trials Database. According to this dashboard (accessed on May 15, 2020), of the 1,580 active trials, 187 are in Phase I trials, 783 are in Phase II, 420 are in Phase III, and 179 are in Phase IV (**Figure 1A**). Most trials are focussing on treatment rather than prevention (943 trials in total), followed by trials that aim to treat or prevent pneumonia caused by SARS-CoV-2 (583 trials), and trials that focus on complications of SARS-CoV-2 infection such as ARDS, Cytokine storm, AKI, sepsis etc (509 trials) (**Figure 1B**). Moreover, 92 trials are intended to use vaccines to treat COVID-19 and 40 trials are enrolling healthy control subjects

(**Figure 1B**). Accordingly, there are 328 drugs in development to treat or prevent COVID-19. Most of these are in the pre-clinical stage (296), whereas 4 drugs are in Phase I, 23 drugs are in Phase II, and 5 drugs are in Phase III (**Figure 1C**).

A quite old data from GlobalData Healthcare collected on April 26, 2020 indicates the exponential increase in the number of clinical trials during April, 2020 (**Supporting Information Figure S1**). Of these 1,167 trials, 50 are multinational trials whereas, ~1,000 trials are operated by a single country. Also, out of these 1,167 trials, 439 trials are from the pharma or biotechnology industry. Most of the clinical trials (273) are on chloroquine or hydroxychloroquine as a possible drug for the treatment of COVID-19, followed by Lopinavir/ritonavir (84), Interferon (57), Favipiravir (28), and Remdesivir (18) (**Supporting Information Figure S1**). There were 75 trials which are investigating vaccine for the treatment of COVID-19.

Despite a remarkable progress in the global Covid-19 clinical trial landscape, many scientists [4, 16, 17] consider it unfortunate and suspect that due to the absence of comprehensive trial coordination mechanisms, many of these trials will not provide robust results that could support patient-level treatment decisions. The questions asked very early on during the pandemic is still valid: “Do we need this many trials? And do we really use the resources intelligently?” As of May 15, 2020, more than 2,000 interventional and non-interventional COVID-19 trials have been registered worldwide [18].

### **3. DISRUPTED CLINICAL TRIALS DUE TO COVID-19**

While the healthcare community has united together globally to develop vaccines and therapeutics for COVID-19, there are several other clinical trials for the other life-threatening diseases are forgotten completely. This section attempts to quantify the volume of clinical trials that have been disrupted due to COVID-19 and their impact.

Very recently, a daily-updated "living paper" that aims to quantify the effects of Covid-19 on the clinical trials reported over 1,200 clinical trials worldwide have come to halt due to the COVID-19 pandemic [19]. This analysis based on the American trial registry shows that the number of trials that are being terminated, suspended, or withdrawn has more than doubled since the onset of the pandemic. Between the beginning of December 2019 to mid-May, 2,633 clinical trials registry entries on ClinicalTrials.gov were stopped (suspended, terminated or withdrawn). Of these, 1,167 (44%) trials cite COVID-19 as the reason for discontinuation (**Figure 2** and **Table 1**). A total of 47,436 patients were enrolled in trials stopped due to COVID-19 that provide actual enrolment figures on the registry.

Strikingly, a comparison of clinical trial disruption figures for the same months in 2017-2018 shows a 105% increase in trial discontinuations, suggesting a huge increase in the number of trials affected by the pandemic. It should be noted that this figure is likely an underestimate, as the data only includes trials listed on one trial registry, ClinicalTrials.gov.

**Table 1** shows the sample characteristics for all clinical trials stopped by Covid-19 arms indicates that out of these 1,167 trials, 1134 (97%) are suspended, 21 (2%) are terminated, and 12 (1%) are withdrawn. Furthermore, 168 (14%) of the trials stopped are in Phase 1, 158 (14%) are in Phase 2, 84 (7%) are in Phase 3, and 67 (6%) are in Phase 4 stage. Among disrupted trials, the trials for oncology affected most (319, 27%), followed by cardiovascular (132, 11%), Neurology (97, 8.3%), and pain (60, 5.1%). Moreover, among the disrupted clinical trials, 522 trials were testing drugs or biologicals affecting a total of 555 unique drugs or biologicals. The remaining affected trials were testing devices, procedures, behavioural interventions, laboratory analyses, diagnostic tests, etc. The draft report, figures, and data of this "Living Paper" are available at [20].

According to another updated report of May 14, 2020 [21], GlobalData found that 70% of the clinical trials were disrupted due to the suspension of enrolment, followed by 17.3% due to slow enrolment, and finally 12.8% due to delayed initiation as shown in **Figure 3A**. This report shows that the number of disrupted clinical trials has almost doubled from April with more than 1,100 trials. Of these disrupted trials, the majority are in Phase II, at 43% (compared to 44.8% in previous month, April), followed by Phase III with 24.5% (21.7% in April), Phase I with 22.6% (26.1% in April), and Phase IV with 9.8% (7.4% in April) (**Figure 3B**).

Of all the therapeutic area, Oncology has the highest number of disrupted clinical trials with 31.2% (33.3%), followed by Central Nervous System at 17.5% (16.1%), Gastrointestinal at 8.5% (9.1%), Infectious Disease at 8.1% (9.3%), and Cardiovascular at 8.1% (6.7%) (**Figure 3C**). This observed trend is similar to other reports also, where the most affected trials are from Oncology and CNS, however, Gastrointestinal trials usually falls outside the top five and generally seen at number six. Within this therapeutic area, Inflammatory Bowel Disease is the highest indication, which is frequently treated with immune suppressant drugs like TNF inhibitors. Interestingly, this may indicate that the Gastrointestinal trials are more affected than others due to the high risk of COVID-19 to patients with a lowered immune system.

Within oncology area, an indication breakdown shows that over 50% of disrupted trials are contributed by five tumor types and these are lung cancer (15.6%), breast cancer (11.9%), multiple myeloma (8.3%), myelodysplastic syndrome (8.3%), and prostate cancer (8.3%). Interesting to note that, 66% of all non-oncology disrupted trials are sponsored by the industry, compared to 51% of oncology trials.

The report also says that almost 830 organisations stopped their clinical trials, which is more than double when compared from the last month when there were 322 organisations. Of these 826 organisations, 463 are private or public companies, located mainly in the US (>50%), UK (8.2%), France (5%), Spain (6%), Germany (5%), Switzerland (4%), and in Canada (3%).

Particularly, the organisations like Boehringer Ingelheim reported the maximum number of disrupted trials, followed by Eli Lilly, Shire, Novartis, and UCB. Of the contract research organisation (CRO), Sarah Cannon Research Institute has reported the maximum number of affected clinical trials, followed by IQVIA, Pharmaceutical Product Development, Covance, and PRA Health Sciences. The top three countries with affected companies are the US, UK, and France.

The COVID-19 has shaken up clinical trials globally. Medidata (*medidata.com*) is continuously monitoring COVID-19's global impact on clinical trials. Medidata recently released enrolment data from nearly 4,600 current clinical trials and more than 182,000 study sites worldwide to determine how the COVID-19 pandemic has affected research [22]. The report shows a 79% global decrease in the number of new patient's enrolment year-over-year during April, 2020 compared to the same time frame last year (**Table 2**).

The worldwide decrease was 65% in March. Among the countries, the maximum decrease was seen in India (97%) and UK (95%). The data clearly indicates that the impact of the pandemic on new patient enrolment in most countries continues to grow. However, in the countries which are returning to normalcy, like China and South Korea, there was a clear improvement from March to April, highlighting the direct impact of COVID-19. In China, there was a 33% decrease in new patients enrolment in April as compared to 68% in March, which clearly indicates the beginnings of the recovery. Moreover, the other important observations reported through this analysis is that the effect of COVID-19 is not uniform across the therapeutic areas and some are more affected than others (**Table 2**). Enrolment in studies for oncology was decreased by 60%, whereas a 95% decline was observed for studies of cardiovascular diseases. Other areas also showed a decline in the number of enrolment and include infectious disease (66%), central nervous system (76%), respiratory diseases (86%), diseases of the endocrine



system (88%), and dermatology (91%). Also, the enrolment number decrease varies from the previous month, i.e. March data, suggesting high variation during the COVID-19 period.

Evaluate Vantage (<https://www.evaluate.com/vantage>) conducted an analysis where it looks for industry-sponsored phase I to III trials on clinicaltrials.gov, and notes every change made to each entry between January 2019 to April 2020 [23]. This analysis reported a 15-fold increase in trial suspensions, irrespective of the reason given, in the past two months (March-April) (**Figure 4**). The study shows that, in an average month around 50 trials tend to be suspended for any reason. But, come March when the world is still fighting with the pandemic, the number of suspended trials saw a jump to 280 studies, and this mounted to 731 in April (**Figure 4A**). However, there is no obvious impact on trial terminations in the COVID-19 era. Neither do the 'primary completion dates' appear to have been affected. Just over 3,000 and 2,000 trials had their completion dates delayed in March and April, respectively, figures that are similar to the average delay across the previous 14 months (**Figure 4B**). However, it should be noted that in many cases primary completion dates on clinicaltrials.gov are mere estimates, and are frequently at odds with reality.

According to another study from the publication BioPharma Dive [24], nearly 100 companies reported an interruption to at least one clinical trial because of the pandemic. The study showed that most affected are the small biotech companies (companies worth less than \$1 billion) compared to that of large biotech or pharma (capitalization of \$10 billion or more). Also, the most affected trials are Phase1 clinical trials (117) as compared to Phase 2 (66) and Phase 3 (56). The data includes only those trials which were specifically mentioned by companies. The list of the pharmaceutical companies which has stalled progress on clinical

trials of drug development for other diseases during the COVID-19 pandemic provided by Biopharma drive as on May 15, 2020 is provided in Supporting Information, **Table S1**.

Another current survey by Continuum Clinical in association with the Association of Clinical Research Professionals (ACRP) indicates 31% of clinical research study sites fear complete shutting due to COVID-19. Nearly 80% of these sites informed the termination or suspension of at least one of their current clinical trials. These data are from the survey from April 1-4 conducted on the 297 responding US sites and clearly indicate that COVID-19 non-related clinical trials have been seriously affected by the global healthcare crisis. Continuum Clinical is a global clinical trial enrolment company, and ACRP is a non-profit organization with more than 13,000 clinical research members across over 70 countries.

#### **4. IMPACT ON CLINICAL TRIALS EVALUATING NEUROLOGY INDICATIONS**

According to GlobalData Healthcare report [25], a total of 81 clinical trials with a definite neurological sign were affected as of April 15, 2020. Of these 81 trials, mental health conditions and pain are the most dominant, contributing to 21% and 19%, respectively (**Figure 5**). To make the representation simpler, mental health indications include the symptoms related to depression, psychiatric disorders, psychosis, schizophrenia, and other unspecified disorders. Clinical trials evaluating various forms of addiction such as those related to alcohol, opium, and nicotine also feature in the top five neurology indications, accounting for 11% of trials impacted by the pandemic. Besides, trials involving Parkinson's disease and dementia including Alzheimer disease are also influenced by the crisis (**Figure 5**). This report also reveals that of the trials that are affected, 59% are sponsored by industry, while the remaining are initiated by academic institutes.

The COVID-19 pandemic is profoundly affecting the clinical trials for rare disease patient communities. Rare disease patient organizations are facing a broad range of organizational challenges, including research slowdown, reduced funding, cancelled fundraising events etc.

## **CONCLUSION**

COVID-19 is causing major turmoil around the globe, and the clinical trial industry is currently facing unprecedented challenges to health care and business continuity. Across the world, the pandemic results in the speeding of research into potential COVID-19 drugs and vaccines, but at the same time the pandemic has slowed or stopped the clinical trials for other life-threatening diseases. Clinical trials for many investigational drugs are now on hold, but for patients with other lethal diseases, that means putting hope on hold too. The FDA has suggested many methods including virtual visits, phone interviews, self-administration, and remote monitoring for the smooth conducting of the clinical trials during the COVID-19 pandemic. However, the upward trend for clinical trial disruptions is expected to continue. In conclusion, for the sake of current and future patients, clinical trials must continue.

## **DISCLOSURE STATEMENT**

No potential conflict of interest was reported by the authors.

## REFERENCES

- [1] Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; Niu, P.; Zhan, F.; Ma, X.; Wang, D.; Xu, W.; Wu, G.; Gao, G.F.; Tan, W., A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*, **2020**, 382, (8), 727-733.
- [2] Thorlund, K.; Dron, L.; Park, J.; Hsu, G.; Forrest, J.I.; Mills, E.J., A real-time dashboard of clinical trials for COVID-19. *Lancet Digit Health*, **2020**.
- [3] Tu, Y.F.; Chien, C.S.; Yarmishyn, A.A.; Lin, Y.Y.; Luo, Y.H.; Lin, Y.T.; Lai, W.Y.; Yang, D.M.; Chou, S.J.; Yang, Y.P.; Wang, M.L.; Chiou, S.H., A Review of SARS-CoV-2 and the Ongoing Clinical Trials. *Int J Mol Sci*, **2020**, 21, (7).
- [4] Eichler, H.G.; Cavaleri, M.; Enzmann, H.; Scotti, F.; Sepodes, B.; Sweeney, F.; Vamvakas, S.; Rasi, G., Clinical trials for Covid-19: can we better use the short window of opportunity? *Clin Pharmacol Ther*, **2020**.
- [5] Sanders, J.M.; Monogue, M.L.; Jodlowski, T.Z.; Cutrell, J.B., Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, **2020**.
- [6] Lythgoe, M.P.; Middleton, P., Ongoing Clinical Trials for the Management of the COVID-19 Pandemic. *Trends Pharmacol Sci*, **2020**, 41, (6), 363-382.
- [7] World Health Organisation (WHO) website: <https://www.who.int/teams/blueprint/covid-19>
- [8] Covid-19 clinical trials registry. <https://www.covid-trials.org/>.
- [9] U.S. National Library of Medicine-Clinical Trials. Available online.: <https://clinicaltrials.gov/ct2/results?cond=COVID-19>.
- [10] European Union Clinical Trials Register. Clinical trials for covid-19. <https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19>.
- [11] Mullard, A., COVID-19 brings drug development to a halt. *Nat Rev Drug Discov*, **2020**, 19, (5), 298.
- [12] Covid-19 Dashboard. Pharma Intelligence Centre <https://pharmaintelligence.informa.com/resources/key-topics/coronavirus>.
- [13] Thornton, J., Clinical trials suspended in UK to prioritise covid-19 studies and free up staff. *BMJ*, **2020**, 368, m1172.
- [14] Ledford, H., Coronavirus shuts down trials of drugs for multiple other diseases. *Nature*, **2020**, 580, (7801), 15-16.
- [15] The Covid-19 Dashboard. <https://pharmaintelligence.informa.com/resources/key-topics/coronavirus?type=Topics&value=coronavirus>.
- [16] Mullard, A., Flooded by the torrent: the COVID-19 drug pipeline. *Lancet*, **2020**, 395, (10232), 1245-1246.
- [17] Gaborit, B.J.; Bergmann, J.F.; Mussini, C.; Arribas, J.R.; Behrens, G.; Walmsley, S.; Pozniak, A.; Raffi, F., Plea for multitargeted interventions for severe COVID-19. *Lancet Infect Dis*, **2020**.
- [18] WHO International Clinical Trials Registry Platform (ICTRP). <https://www.who.int/ictrp/en/>.
- [19] Carlisle, B.G., Clinical trials stopped by Covid-19. *Open Science*, **2020**, <https://covid19.bgc Carlisle.com/published/full-report-2020-05-13.html>.
- [20] Carlisle, B.G., Covid-19 Trial Tracker. Codeberg.org Available at: <https://codeberg.org/bgc Carlisle/Covid-19TrialTracker> **2020**.
- [21] Update on clinical trials disrupted due to Covid-19. *GlobalData Healthcare*, <https://www.clinicaltrialsarena.com/comment/disrupted-clinical-trials-covid-19/>.

[22] COVID-19 and Clinical Trials: The Medidata Perspective. Release 4.0

[23] Evaluate Vantage COVID-19 Report. <https://www.evaluate.com/thought-leadership/vantage/evaluate-vantage-covid-19-report>.

[24] A guide to clinical trials disrupted by the coronavirus pandemic. <https://www.biopharmadive.com/news/coronavirus-clinical-trial-disruption-biotech-pharma/574609/>.

[25] GlobalData Healthcare. <https://www.clinicaltrialsarena.com/comment/neurology-clinical-trials-covid-19/>.

**Figure Legends:**

**Figure 1.** A summary of the trials for the treatment or prevention of Covid-19. (A) Clinical trials and their Phases. (B) Role of trials as found in Trialstrove, and (C) Overview of drug development as found in Pharmaprojects. Source of data is from *Reference 15*.

**Figure 2.** Clinical trials that were suspended, terminated or withdrawn since 2019-12-01. Green shade indicates a stoppage of clinical trials relating to Covid-19. Grey shade indicates clinical trials stopped without explicitly related to Covid-19. Adapted from *Reference 19*.

**Figure 3.** Clinical trials disrupted due to COVID-19 (as of May 14, 2020). (A) Nature of trial disruption, (B) Disrupted clinical trials distributed by Phases, and (C) Disrupted clinical trials distributed according to therapeutic area. Source of data is from *Reference 21*.

**Figure 4.** Clinical trial disruption according to Evaluate Vantage data (accessed on May 14, 2020). (A) The distribution of clinical trials according to their terminations, withdrawals, or suspension, (B) Delays of primary completion of clinical trials. Adapted from *Reference 23*.

**Figure 5.** Impact of COVID-19 pandemic on clinical trials evaluating various neurology indications. Percentage disruption of various neurological conditions observed as of April 15, 2020. Adapted from *Reference 25*.

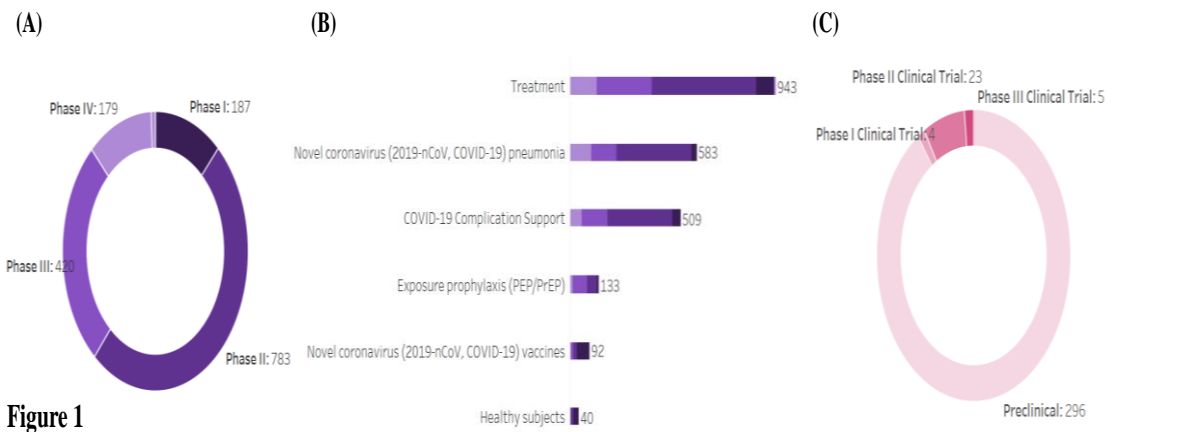


Figure 1

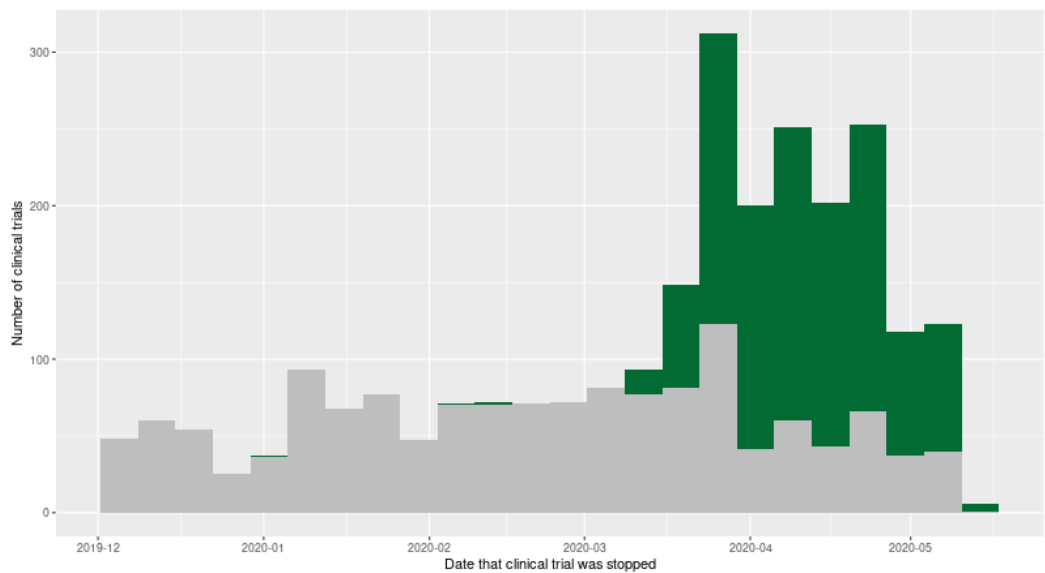


Figure 2

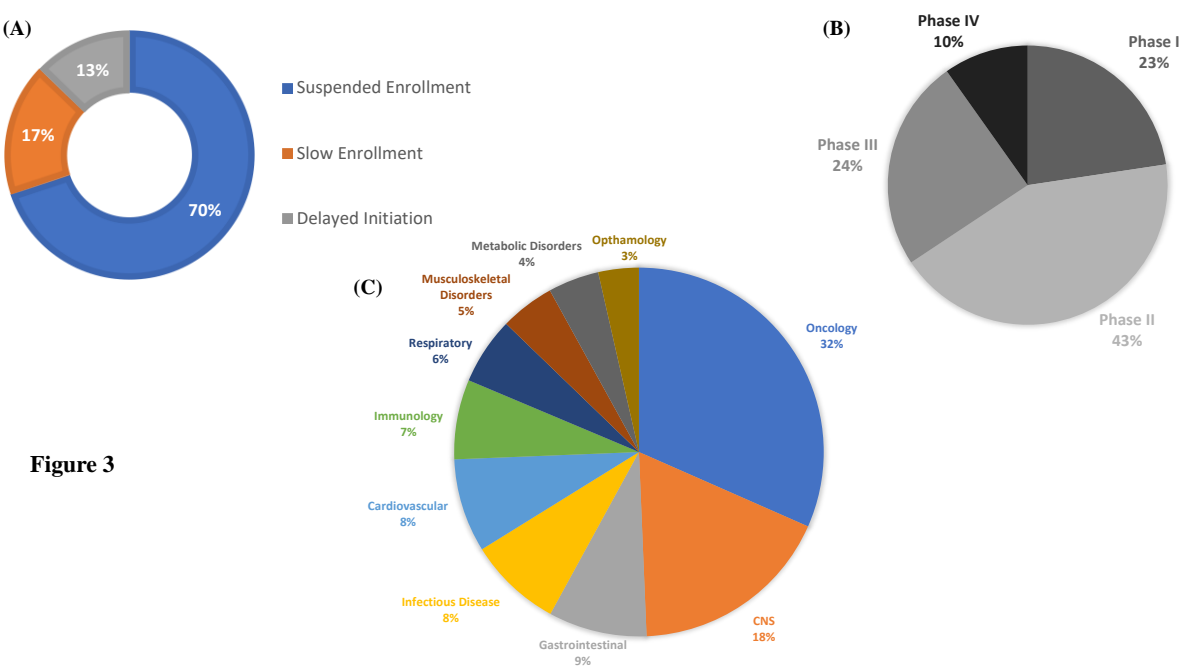


Figure 3

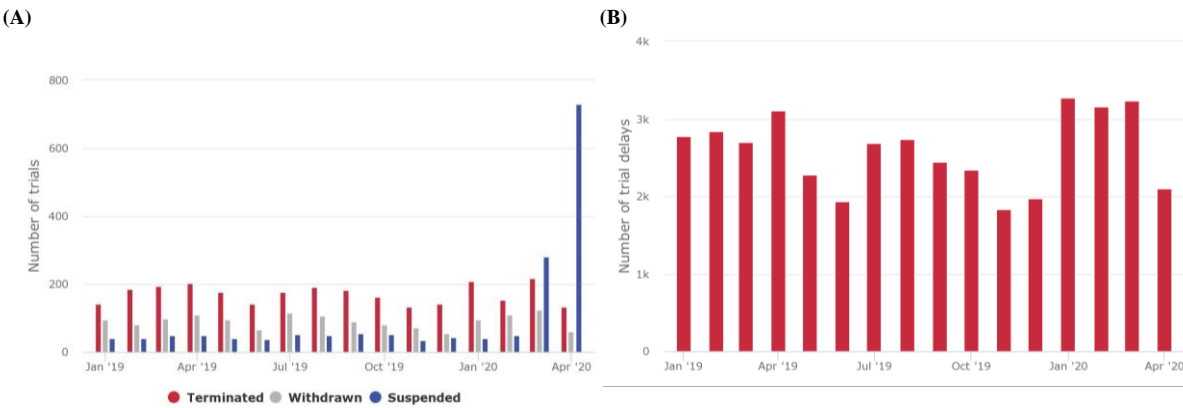


Figure 4



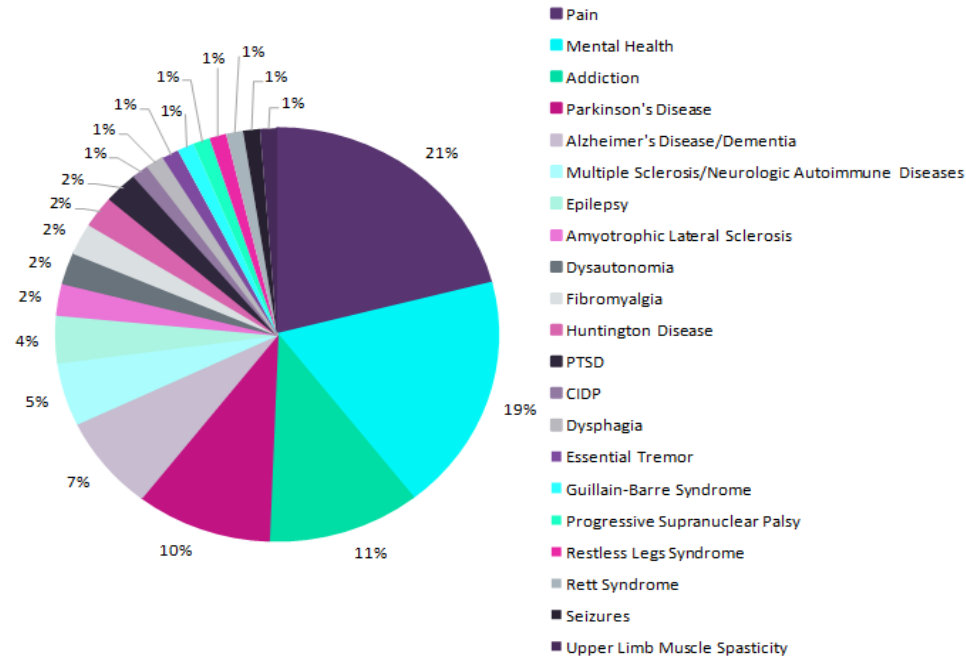


Figure 5

**Table 1.** Sample characteristics for all clinical trials in the COVID-19 period (January, 2020 to May, 2020) regardless of reason for stopping versus trials stopped with an explicitly stated reason citing COVID-19. (From *Reference 19*)

	<b>Trials stopped between Jan 2019-May 2020 (any reason)</b>	<b>Trials stopped between Jan 2019-May 2020 (due to COVID-19)</b>
<b>Trials</b>	2,623	1,167
Actual enrolment	624,351	47,436
Anticipated enrolment	4,359,579	4,114,080
<b>Status when stopped</b>		
Suspended	1350 (51%)	1134 (97%)
Terminated	830 (32%)	21 (2%)
Withdrawn	443 (17%)	12 (1%)
<b>Phase number</b>		
Phase 1	353 (13%)	168 (14%)
Phase 2	399 (15%)	158 (14%)
Phase 3	171 (7%)	84 (7%)
Phase 4	186 (7%)	67 (6%)

**Table 2.** Impact of COVID-19 on new patients entering trials. (From *Reference 22*)

		<b>YoY difference (%) March 2020 vs March 2019</b>	<b>YoY difference (%) April 2020 vs April 2019</b>
	All	-65%	-79%
Asia	China	-68%	-33%
	India	-84%	-97%
	Japan	-44%	-69%
	South Korea	-61%	-42%
Europe	France	-68%	-81%
	Germany	-33%	-77%
	Italy	-53%	-49%
	Spain	-68%	-82%
	United Kingdom	-80%	-95%
North America	United states	-66%	-83%
Therapeutic Area	Cardiovascular	-69%	-95%
	CNS	-68%	-76%
	Dermatology	-64%	-91%
	Endocrine	-81%	-88%
	ID/Anti-Infectives	-47%	-66%
	Oncology	-48%	-60%
	Respiratory	-34%	-86%