


Research Article

The Impact of COVID-19 on US Clinical Trial Activity

Harold E. Glass and Andy Guy*

Abstract

The COVID-19 pandemic has certainly been one of the singular events of the twenty-first century. With the initial impact of COVID-19, clinical trial observers and professionals anticipated major interruptions in the conduct of clinical trial research. Many expected site start-ups to slow appreciably, patient enrolment and treatment to drop significantly, and the search for scarce medical staffing resources to become more daunting. The Open Payments database, a public repository mandated by US law, provides us with a more definitive answer to the question about the impact of COVID-19 on the conduct of US clinical trial activity. While a demanding database to use, the Open Payments data demonstrate that there was surprisingly little disruption in the US clinical trial landscape in 2020-2021. There were few changes in who conducted studies, or where these studies occurred. Most critically, overall US clinical trial activity continued to increase, even when COVID-19 related studies are separated from the total payment numbers. Similarly, clinical trial activity trends among the major therapeutic areas continued much as they had before COVID-19. Areas such as oncology continued to grow, while others, such as cardiovascular, continued to decline. Even previously experienced clinical investigators conducted most of the COVID-19 studies. Open Payments contains only US data for commercially sponsored clinical trials. It may be that the results are different for NIH sponsored studies or sites outside the United States.

Keywords: COVID-19; Clinical Trial Activity; Open Payments.

Introduction

The global impact of the COVID-19 pandemic has been devastating on a number of social, healths, medical, and economic fronts. The United States was not spared. The social disruption was extensive, bringing about major changes in the way people work and live. The US is estimated to have experienced over 1 million excess deaths due to COVID-19. Important medical treatments across a wide variety of indications were handicapped. The economy tumbled, resulting in a massive loss of jobs and even major educational slowdowns. Throughout this pandemic the conduct of US clinical trials had to undergo significant changes as people faced challenges as simple as accessing public areas. Social distancing became routine behavior. Pharmaceutical industry sponsored clinical trials were certainly not able to continue routine operations in an unchanged manner. But a question emerges about the extent to which the volume of US clinical trial activity itself changed. To what degree was this activity level affected by the pandemic? There are at least two ways that COVID-19 may have impacted the conduct of US industry sponsored clinical trials. This paper tests these possible effects by examining relevant data from the Open Payments databases.

Affiliation:

1100 Ludlow St 7th Floor Philadelphia, PA 19107, USA

***Corresponding author:**

Andy Guy, MBA, 1100 Ludlow St 7th Floor Philadelphia, PA 19107, USA

Citation: Harold E. Glass, Andy Guy. The Impact of COVID-19 on US Clinical Trial Activity. Archives of Clinical and Biomedical Research. 8 (2024): 196-203.

Received: April 23, 2024

Accepted: May 02, 2024

Published: May 16, 2024

First, COVID-19 studies may have taken resources from other studies, thereby slowing activity on these other studies. The United States federal government committed huge financial resources to COVID-19 clinical trials in hopes of getting critical COVID-19 vaccines approved, and into the hands of relevant medical professionals as quickly and safely as possible. Within a remarkably short time, the trial vaccines were administered to record numbers of patients. The entire COVID-19 clinical trial process moved at rates rarely, if ever, experienced before. At the same time, this absolute jolt to industry sponsored clinical trial activity may very well have taken financial, staffing and operational resources from clinical trials in other therapeutic areas. COVID-19 may have affected industry clinical trial activity in another critical fashion, the standard ways clinical trials had been done before the pandemic. Entire methods of medical treatment changed though as the introduction of social precautions affected virtually everyone, across a wide range of settings. Central portions of cities emptied out. The COVID-19 threat, along with public responses such as social distancing, discouraged people from going to dinner, the movies, outdoor events, schools and even to see their medical professionals. It is certainly difficult to conduct a traditional clinical trial when patients may have been reluctant to present in person for diagnosis and treatment.

Several key conclusions arise from a review of relevant literature. First, during the early days of the pandemic many expected to see major reductions in clinical trial start-ups and enrollments. This was true for countries around the world. For example, both industry observers and participants shared concerns about the expected slowdown in clinical trial activity [1-6]. Many studies and individual sites simply expected to see slowed patient recruitment and enrollment. This covered a range of countries and indications. Second, patient enrollment data were largely anecdotal, or case based. The various authors used a range of methodologies from site surveys, to case studies, to on-line publication and citation reviews, individual analyses across a range of therapeutic areas and geographies did report initially slower enrollments [7-17]. However, there was not systematic use of very large data sets to come to conclusions about enrollment progress. Often the case studies were simply reported in isolation or linked together in narratives as multiple cases. Third, clinical trial professionals quickly recognized that COVID-19 would require fundamental reconceptualization of clinical trial conduct. This might range from requiring participating patients in all clinical trials to test for COVID-19 and wear masks. A number of authors saw major new ethical questions and challenges. However, throughout many of these reports, the clinical trial professionals also reported changes introduced to maintain study enrollment, keep both patients and employees safe, change the way they conducted clinical

research and even how the people running the trials might analyze datasets with increasing amounts of missing data [18-32]. Open Payments database provides comprehensive public data about the level of virtually all US clinical trial activity. These data, and supporting ClinicalTrials.gov data, indicate that COVID-19 had virtually no negative impact on the overall level of US clinical trial activity, even when COVID-19 related studies are separated from all others. COVID-19 spending certainly started to appear in any significant way in 2019, and then soar in 2020. However, non-COVID-19 related study activity continued apace during that time, and even increased. Moreover, the long-term activity pattern of major non-COVID-19 therapeutic areas continued their long-term activity trends. Major therapeutic areas experiencing longer term growth, continued to grow. Major therapeutic areas, which had been declining in study activity, continued to decline. Of the active pool of US investigators during the two years of the most intense pandemic, relatively few participated in COVID-19 trials. Fewer than 6% of these investigators participated in COVID-19 studies. Moreover, most of these investigators worked on non-COVID-19 studies during the same time period.

Materials and Methods

The Open Payments database, far less well known than ClinicalTrials.gov was mandated by the Sunshine Act. Data collection began in the third quarter of 2013, continuing uninterrupted since then [33]. Pharmaceutical and medical device companies with at least one marketed product eligible for reimbursement from several federal patient support programs are covered by the law and must report all payments to physicians and related medical professionals in the year they are made. Companies may withhold publication of the payments on a selected basis for up to four years or until the compound becomes a marketed product, whichever happens first. A comparison of ClinicalTrials.gov and Open Payments estimates that ClinicalTrials.gov has about 3% more pharmaceutical industry sites than does Open Payments, with most of these sites found in earlier phase studies from the smallest pharmaceutical companies. (See Appendix A for more detail). Open Payments though has far more detailed site level activity data than does ClinicalTrials.gov. ClinicalTrials.gov study information often includes a listing of individual sites associated with a specific trial. However, there is no assurance that these listed sites were the ones that actually took part in the study. In addition, there is usually little more information about a site than the site's zip code. In contrast, Open Payments indicates the individual investigator's name and address, and the total payments that investigator received to enroll and treat patients. To date, the use of Open Payments data to assist management decision-making has been limited, unlike ClinicalTrials.gov. This is largely due to how much more difficult it is to access Open

Payments data than the ClinicalTrials.gov database. Open Payments, unlike ClinicalTrials.gov, requires a substantial amount of database development resources and activity by anyone interested in using the Open Payments data for either research or operational purposes.

Open Payments

There are two types of payments in Open Payments, general and research. This paper addresses research payments for pharmaceutical companies only. Moreover, only research payments for direct clinical patient enrollment and treatment, analogous to clinical grant payments, are used in this analysis. Research payments must be associated with a specific protocol and be covered by a written agreement. Certain research related activities are reported under general payments such as protocol development, data-monitoring committee service, steering committee service, as well as meals and travel for investigators not covered in the clinical trial agreement. Research payments though include only activities related to the conduct of clinical research as covered in the clinical trial agreement. Research payment data provide the date and amount of the payment to the clinical investigator. Even teaching hospitals receiving payments must indicate the physician(s) involved in the covered clinical trial. Certain investigators and, where relevant, teaching hospital data are specified with each payment such as: study name, sponsor company, investigator name and address, medical specialty, as well as the name and address of any institution associated with the payment. There certainly are operational challenges and limitations working with these data. First, the research payments data cover only US investigators. Second, extensive coding and data linking is necessary, particularly when connecting the individual physician’s research payment to the correct study and pharmaceutical company. Each investigator does have a unique identification number. Yet, there is usually very limited information in Open Payments about the individual study on which an investigator is working. There is commonly only an idiosyncratic study identification name and sponsor company name. From time to time there may be an NCT number, but even then, this number may not be correct. The Open Payments study name may be the same as that found in ClinicalTrials.gov, but this is infrequently the case. The Open Payments study name may be a limited descriptive phrase, or something as simple as an internal company identifier, which may consist of only a set of letters and numbers. In addition, the study name may be somewhat altered, or even spelled differently in a subsequent year. The pharmaceutical company name may also vary from year to year. One time it might be the US operating company, the next year another unit of the same parent company. Extensive computer aided reconciliation, along with substantial manual

oversight, were necessary to successfully associate the various study names, company sponsor names and individual investigator payments.

Throughout the paper we report descriptive statistics. We do not report measures of statistical significance because we are not dealing with samples, but rather a virtual census of a specific population. Particular effort was made to ensure that we were using comparable measures when analyzing comparative enrollment performance. We do not know the absolute number of patients enrolled by a given investigator in a specific study. That would be easy enough to estimate this figure using one of the several industry tools used to benchmark and negotiate clinical grant costs. More critically though, for the purposes of this paper the relative total amount of payments received is just as important as the absolute number of enrolled patients. An absolute enrollment number may be very good in one study and disappointing in another. The essential issue is how well an investigator enrolls compared to other investigators in the same study. Some study designs are far more challenging than others, for instance, the inclusion and exclusion criteria may substantially vary for studies in the same indication. By comparing performance within a study, we are controlling for study design differences. It would of course be also helpful to know the total number of patients enrolled each year as an additional check. However, no such database exists.

Results

US clinical trial activity levels

Clinicaltrials.gov provides useful directional information about industry sponsored clinical trials. There may be very little site-specific descriptive information and virtually no consistent enrollment performance information. Yet the database provides good directional data on the number of new studies opened for any study included in the database. Table One data show virtually no change in the number of phase 2 and 3 commercially funded studies, with at least one US site, started each year between 2017 and 2020. There is actually an increase in 2021. Similarly, the number of initiated US sites remains constant, increasing in 2021. However, the number of opened sites may not be a complete measure of site enrollment activity. Sites may open, but enrollment activity may lag.

Table 1: Number of Phase 2 and Phase 3 US Sites Opened 2017 - 2021

	2017	2018	2019	2020	2021
Studies Started With at Least One US Site	1332	1422	1292	1310	1515
New US Sites Opened	27463	28744	25977	25804	29725

ClinicalTrials.gov does not routinely provide actual enrollment activity for each of the sites in any specific study, that is, the number of patients. It may very well be that new sites are opened, but patient enrollment activity slows at these sites because of the pandemic and the subsequent effects on sponsor companies, associated medical professionals and potential clinical trial participants. Fortunately, the data in Open Payments helps address this shortcoming. By isolating those payments in the database, often labeled by clinical trials professionals as clinical grants, we have a good activity measure. Sites are often paid a small start-up fee, but most of the clinical grant payment is directly associated with patient enrollment and treatment activities. It bears restatement, that, after coding and data linking, the individual payments in this database enable us to understand which sponsor companies paid how much, to which sites, and for which study. We also know the date each payment was made. We can look at individual payments, for example, to a specific investigator;

it is often quite possible to see how much an investigator received in start-up payments. However, for the purposes of this study interested in total protocol specific research payments. The exact composition of individual studies most certainly changes from one time period to another. We have no evidence that there has been an increase during the years covered by our study in the protocol complexity and subsequent procedure costs across all the activity conducted within a given year. If such a phenomenon has indeed taken place. The Open Payments data do not show it as the individual payment level.

Total US clinical trial activity is clearly concentrated in the larger pharmaceutical companies. The concentration is somewhat greater for COVID-19 clinical trials. It should be pointed out though that Moderna, a major COVID-19 vaccine developer, was not required to report US clinical trial spending until 2021.

Table 2: Total 2020-2021 Research Payments on both COVID-19 and non-COVID-19 Studies (\$ Billions) as Categorized by a Company’s Size When Measured by that Company’s Total Research Payments

Company Size by Total Research Payments	COVID-19 Payments	Percent of all COVID-19 Payments	Non COVID-19 Payments	Percent of all Non Covid-19 Payments	Total Payments
1 – 10 largest	\$1.1	63%	\$6.2	60%	\$7.3
11 – 25 largest	\$0.47	27%	\$2.1	20%	\$2.6
All others	\$0.17	10%	\$2.1	20%	\$2.3
Total	\$1.7	100%	\$10.4	100%	

As we might expect, US COVID-19 activity is more often found in private practices than in institutions.

Table 3: Study Location COVID-19 and non-COVID-19 Compared (\$ Billions)

	COVID-19 \$	COVID-19 %	Non COVID-19 \$	Non Covid-19 %	Total
Teaching Hospital	\$0.21	12	\$2.5	24	\$2.7
Private Practice	\$1.5	88	\$8.0	76	\$9.5

Figure one data show a constant, if undramatic, increase in US clinical trial spending between 2017 and 2021, a trend dating back to 2013 when the database first began. We do not adjust for any measure of US medical cost inflation. (See Appendix B for the issue of late released payments.) Even if we were to remove COVID-19 related spending from the 2020 and 2021 activity, there would be no decline in non-COVID related study spending. Moreover, the total increase strongly rebounded in 2021. The COVID-19 pandemic did not reduce overall US pharmaceutically funded clinical trial activity. Through Open Payments though we can know nothing about ex-US clinical trial activity.

The impact of COVID-19 has been limited on the total

level of US clinical trial activity. Moreover, COVID-19 does not appear to have upset longer term activity levels for major therapeutic areas, as illustrated by the four largest therapeutic areas. Oncology for example has experienced continued increases in activity levels, both before and during the COVID-19 pandemic. Given the nature of the medical condition, cancer patients may have been particularly likely to remain with treatment during COVID-19. But the longer-term oncology spending pattern began before the onset of COVID-19 and oncology patient participant levels probably did not change. Neurology has remained constant. At the other end of the continuum, cardiovascular levels continued to decrease in relation to total US clinical trial spending both before and after the onset of COVID-19.

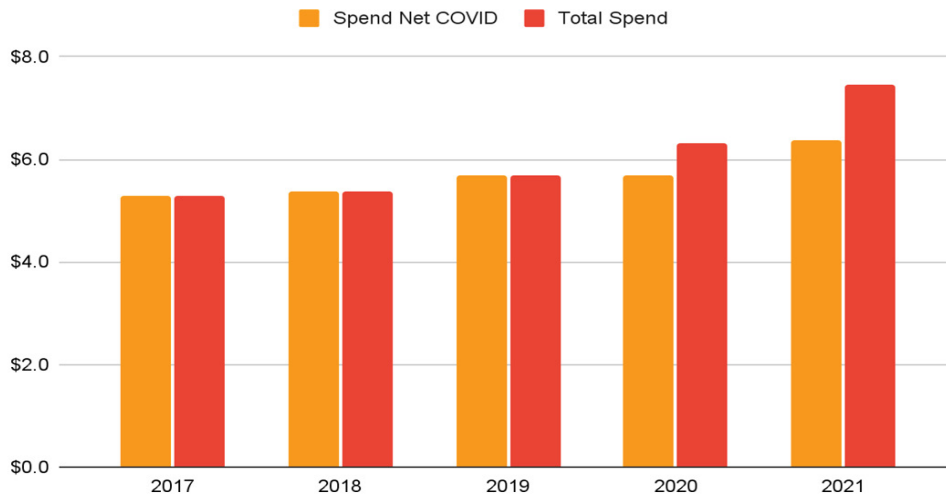


Figure 1: Total Clinical Grant Spending (\$ Billions) 2017 - 2021

Gastroenterology shows no clear direction over the covered time period.

US clinical trial investigator participation

During the two years of the COVID-19 pandemic at its most virulent, less than 6 percent of active investigators took part in COVID-19 related clinical trials. Those who only ever participated in COVID-19 related studies were distinctly less experienced. It may well have been the case that sponsor pharmaceutical companies conducting COVID-19 studies were heavily reliant on experienced investigators who could conduct both COVID-19 and non-COVID-19 studies at the same time.

Discussions

ClinicalTrials.gov data indicate that study site openings continued at rates commensurate with earlier year activity

levels, despite some concerns initially raised by industry observers and participants. COVID-19 was highly disruptive in many ways to US studies sponsored by the pharmaceutical industry. However, COVID-19 does not seem to have been as disruptive to the overall US clinical trial activity levels as may have at first been feared. Larger pharmaceutical companies represent a very large proportion of all US clinical trial activity; this is also the case for COVID-19 related studies. The large majority of US clinical trials are conducted in private practice settings. This is not always the case in other countries. COVID-19 related studies were, however, even more likely to be conducted in private practice. Most critically though, the level of clinical trial activity did not decrease following the advent of COVID-19 at pandemic levels. The total level of US clinical trial activity increased, even when COVID-19 related study activity is subtracted from the total. It is possible that vast sums were spent on non-

Table 4: Open Payments for the Five Largest Physician Specialties (\$ Billions)

	2017	2018	2019	2020	2021	Total	% of Grand Total
Oncology	\$1.5	\$1.8	\$1.8	\$2.0	\$2.1	\$9.2	33.11%
Neurology	\$0.36	\$0.33	\$0.37	\$0.30	\$0.36	\$1.7	6.17%
Cardiology	\$0.28	\$0.25	\$0.23	\$0.21	\$0.17	\$1.1	4.10%
Psychiatry	\$0.25	\$0.23	\$0.19	\$0.18	\$0.15	\$1.0	3.58%
Gastroenterology	\$0.18	\$0.14	\$0.18	\$0.17	\$0.15	\$0.82	2.93%

Table 5: Investigator Experience and Enrollment Performance Score 2020-2021

	Conducted Only COVID-19 Trials	Conducted Both COVID-19 and Non-COVID-19 Trials	Conducted Only Non-COVID-19 Trials
Number of Investigators	675	1256	30,675
Mean Number of Studies Conducted by Investigator	1.5	11.4	3.7

productive activity, although there is no published evidence of that. However, clinical investigators and their sites almost always are predominantly paid on the number of patients they enroll, treat and complete. So, it is probably likely that, even with some loss of initial productivity, patient enrollment and treatment continued. When we examine spending patterns of the largest 20 therapeutic areas, as illustrated by the five largest, there appears to have been little operational disruption. This is not to say that herculean efforts may have been necessary at times to minimize this operational disruption. A review of the investigators used to conduct clinical trials in 2021 shows that several hundred new investigators were called upon to conduct clinical trials with no experience outside of COVID-19. But few of these did more than one COVID-19 study. Most of the investigators conducting COVID-19 studies were, in fact, experienced. Operational continuity in the face of historic challenges though characterizes the US clinical trial arena in the years 2020-21.

Conclusions

Other areas exist for further research. Most importantly, did this clinical trial activity level prove similar for studies conducted in other geographies, or by public institutions such as the NIH. In addition, has the overall nature of industry sponsored clinical trial activity been permanently altered as a result of changes initially introduced to deal with the COVID-19 pandemic? For example, has study design changed? Is the pool of available investigators substantially different now than the years before COVID-19? Two major substantive conclusions emerge, the first one operational. Clinical operations professionals now have access to a major source of empirical detail about the US clinical trial arena, a data source which, until now for a number of reasons, has been largely overlooked. The Open Payments database constitutes a valuable tool for improving both longer term planning; Open Payments data are capable of demonstrating major trends in the US clinical trial landscape, including details about the clinical investigators who make up a major component of that landscape. For example, clinical trial operations professionals can substantially improve their longer-term planning by examining spending patterns and trends about clinical investigator availability. With the Open Payments it is possible to establish exact clinical trial spending trends by indication and therapeutic level, for all the participating companies in Open Payments. This is also true for each company submitting data. And, of course, companies in Open Payments constitute the vast majority of all US clinical trial activity. In addition, it is now possible to understand the exact pool of current investigators as part of a longer-term trend. For instance, how many US oncologists are active and how is this number trending? Or, have there been important changes in the locations of clinical trials, and how that varied by indication. There is

a shorter-term operational value as well. The database's detail offers a potential clinical operations management tool, for instance, investigator identification based upon actual clinical trial experience and comparative enrollment performance. Clinical operations professionals selecting US investigators and managing clinical trials can make far more informed decisions. The clinical trial experience and comparative enrollment performance of almost every active US investigator is now readily available to anyone interested in accessing, and working with, the data. Clinical operations professionals may currently have only access to information about investigators with whom they have worked, and then only for studies their company has sponsored. Some industry data consortia do exist. These, however, are only available to the participants. Moreover, these consortia data are not complete or up to date. In contrast, Open Payments mandates that all qualifying companies must update their data at the end of each year.

A second, substantive, conclusion comes from the use of Open Payments. Answers to many clinical operations issues can now be addressed on a more empirically grounded basis. A simple case in the number of US clinical investigators who actually never do a second clinical trial. An analysis of Open Payments data conclusively demonstrates that the percentage is 20.3%.

A more substantive issue is the impact of COVID-19 on the conduct of industry sponsored clinical trials involving US investigators. The COVID-19 pandemic brought about tremendous economic, educational, and health consequences. Certainly, many observers expected a highly deleterious effect on the conduct of industry sponsored clinical trials. Literature about the impact of COVID -19 on US clinical trial activity has been largely anecdotal, based on proprietary data, and limited in coverage. The publicly available data in ClinicalTrials.gov and Open Payments presents a more definitive picture: there was almost no negative impact in the overall volume of clinical trial activity, even for non-COVID-19 studies. Study director after study director may have anticipated tremendous disruption to their own clinical trials. Many reported such concerns. But, almost without exception, they also emphasized the many ways, often quite new and ingenious, to deal with the pandemic related study conduct challenges. It would appear that clinical trial professionals working during the COVID-19 pandemic were able to overcome many of the challenges which could have slowed the conduct of industry sponsored clinical trials. No other industry operates under the time constraints imposed by the patent. Many brands in other industries can last for many years, even many decades. Successful products in most industries experience growth, and often a long decline. Consumer brands for example may have very long lives, in direct contrast to the pharmaceutical industry. Certainly,

companies of all types seek to develop new products and extend product life for as long as possible. However, many products in other industries have a natural life cycle. If successful, the product grows, prospers and eventually declines. In the pharmaceutical industry the business model is entirely different, most drugs go off patent at the height of their sales. The patent and not usually individual product attributes or market demand, determines a branded drug's life cycle. This has a pronounced effect on pharmaceutical new product development. Throughout the pandemic the patent clock continued to tick for the pharmaceutical industry. COVID threatened to consume an even larger portion of a compound's patent life in the R&D stage. This critical link between necessity and invention has most certainly been understood for millennia. Necessity may not lead inexorably to invention. But as Plato in the Republic observes, "our need will be the real creator" [34].

Funding Statement

No outside funding or sponsorship was involved with the work of this manuscript.

Conflict of interest statement

The authors of this manuscript are co-owners of SunshineMD LLC.

Author contributions

Dr. Glass contributed to the conceptualization and design of the manuscript's central theme, the drafting of the copy, interpretation of the data and final approval of the manuscript.

Mr. Guy contributed to the conceptualization of the manuscript's theme, the acquisition and analysis of the data and final approval of the manuscript.

References

- Kaplan GA, Weaver R, Cloud B. The Effect of COVID-19 on Clinical Trials: Insights from the Inside. *Applied Clinical Trials* (2020).
- Alsumidaie M. Clinical Trials Feel the Coronavirus Crunch. *Applied Clinical Trials* (2020).
- Lee J. Lilly to halt enrollment in clinical trials as a result of COVID-19 (2020): 03-23.
- Fidler B, Sumida N. A guide to clinical trials disrupted by the coronavirus pandemic [Internet]. *BioPharma Dive*. Pharma pivots to face Covid-19 threat. *Sunday Times* (London, England) (2020).
- Mitchell EJ, Ahmed K, Breeman S, et al. It is unprecedented: trial management during the COVID-19 pandemic and beyond. *Trials* 21 (2020): 1-7.
- Riccaboni M, Verginer L. The impact of the COVID-19 pandemic on scientific research in the life sciences. Naudet F, editor. *PLOS ONE* 17 (2022): e0263001.
- Ebeid FE. COVID-19 effect on clinical research: Single-site risk management experience. *Perspectives in Clinical Research* 11 (2020): 106.
- Chirinos JD, Turco I, Di Fenza R, et al. Patient hesitancy in perioperative clinical trial enrollment during the COVID-19 pandemic 18 (2023): e0279643.
- Upadhaya S, Yu JX, Hodge J, et al. COVID-19 impact on oncology clinical trials: a 1-year analysis. *Nature Reviews Drug Discovery [Internet]* 20 (2021): 415.
- Chlan LL, Tracy MF, Ask J, et al. The impact of the COVID-19 pandemic on ICU clinical trials: a description of one research team's experience. *Trials* 24 (2023): 321.
- McDonald K, Seltzer E, Lu M, et al. quantifying the impact of the COVID-19 pandemic on clinical trial screening rates over time in 37 countries. *Trials* 24 (2023): 254.
- Volkers N, Wiebe S, Asadi-Pooya AA, et al. The initial impact of the SARS-CoV-2 pandemic on epilepsy research. *Epilepsia Open* 6 (2021): 255-265.
- Upadhaya S, Yu JX, Oliva C, et al. Impact of COVID-19 on oncology clinical trials. *Nature Reviews Drug Discovery [Internet]* 19 (2020): 376-377.
- Shiely F, Foley J, Stone A, et al. Managing clinical trials during COVID-19: experience from a clinical research facility. *Trials* 22 (2021): 62.
- Liu HH, Ezekowitz MD, Columbo M, et al. The future is now: our experience starting a remote clinical trial during the beginning of the COVID-19 pandemic. *Trials* 22 (2021): 603.
- Lara Gongora A, Jardim D, Assed Bastos D. Oncology Clinical Trials During the COVID-19 Pandemic. *ONCOLOGY* (2020): 265-269.
- Suman A, van Es J, Gardarsdottir H, et al. A cross-sectional survey on the early impact of COVID-19 on the uptake of decentralised trial methods in the conduct of clinical trials. *Trials* 23 (2022): 856.
- Neuer A. COVID-Sparked Practices Driving New Patient-Centric Behaviors. *Applied Clinical Trials [Internet]* 29 (2020).
- O'Brien EC, Sugarman J, Weinfurt KP, et al. The impact of COVID-19 on pragmatic clinical trials: lessons learned from the NIH Health Care Systems Research Collaboratory. *Trials [Internet]* 23 (2022): 424.
- BRIEF-Galectin Therapeutics Update On The Impact Of Covid-19. *Reuters [Internet]* (2020).

21. Cro S, Morris TP, Kahan BC, et al. A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic. *BMC Medical Research Methodology* 20 (2020): 208.
22. Davis S, Pai S. Challenges and opportunities for sponsors in conducting clinical trials during a pandemic. *Perspectives in Clinical Research* 11 (2020): 115.
23. Horgan R. Improving Drug Development for Rare Patients Post-COVID. *Applied Clinical Trials* [Internet] 30 (2021).
24. Bhutkar R, Collins JC, O'Reilly CL, et al. Guidance on the Conduct of Clinical Research within OECD Countries during the Early Stages of the COVID-19 Pandemic: A Systematic Review. *Pharmacy* 11 (2023): 15.
25. Bhatt A. Clinical trials during the COVID-19 pandemic: Challenges of putting scientific and ethical principles into practice. *Perspectives in Clinical Research* 11 (2020): 59.
26. Goothy K, Sailesh S. Conducting human research during and after covid-19 pandemic: The need of the hour. *MRIMS Journal of Health Sciences* [Internet] 10 (2022): 56.
27. O'Brien EC, Sugarman J, Weinfurt KP, et al. The impact of COVID-19 on pragmatic clinical trials: lessons learned from the NIH Health Care Systems Research Collaboratory. *Trials* [Internet] 23 (2022): 424.
28. Mahalmani VM, Ankita Semwal, Kaur H, et al. Pattern of clinical research in the era of COVID-19 pandemic: A new learning experience for the present as well as future. *Indian Journal of Pharmacology* 52 (2020): 249-253.
29. Robison L, Cho Y, Viecelli AK, et al. Conducting clinical trials during the COVID-19 pandemic—a collaborative trial network response. *Trials* 22 (2021): 278.
30. Chlan LL, Mary Fran Tracy, Ask J, et al. The impact of the COVID-19 pandemic on ICU clinical trials: a description of one research team's experience. *Trials* 24 (2023): 321.
31. Lorenc A, Rooshenas L, Conefrey C, et al. Non-COVID-19 UK clinical trials and the COVID-19 pandemic: impact, challenges and possible solutions. *Trials* 24 (2023): 424.
32. Open Payments Dataset Downloads | CMS [Internet].
33. Plato, Jowett B. Republic. London: Chartwell Books (2019).