

The Impact of COVID-19 on the Initiation of Clinical Trials in Europe and the United States

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The coronavirus disease 2019 (COVID-19) pandemic has a major impact not only on public health and daily living, but also on clinical trials worldwide. To investigate the potential impact of the COVID-19 pandemic on the initiation of clinical trials, we have descriptively analyzed the longitudinal change in phase II and III interventional clinical trials initiated in Europe and in the United States. Based on the public clinical trial register EU Clinical Trials Register and clinicaltrials.gov, we conducted (i) a yearly comparison of the number of initiated trials from 2010 to 2020 and (ii) a monthly comparison from January 2020 to February 2021 of the number of initiated trials. The analyses indicate that the COVID-19 pandemic affected both the initiation of clinical trials overall and the initiation of non-COVID-19 trials. An increase in the overall numbers of clinical trials could be observed both in Europe and the United States in 2020 as compared with 2019. However, the number of non-COVID-19 trials initiated is reduced as compared with the previous decade, with a slightly larger relative decrease in the United States as compared to Europe. Additionally, the monthly trend for the initiation of non-COVID-19 trials differs between regions. In the United States, after a sharp decrease in April 2020, trial numbers reached the levels of 2019 from June 2020 onward. In Europe, the decrease was less pronounced, but trial numbers mainly remained below the 2019 average until February 2021.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The coronavirus disease 2019 (COVID-19) pandemic impacts the conduct of clinical trials and challenges clinical trial sponsors.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What is the impact of the COVID-19 pandemic on the initiation of phase II and III clinical trials, both overall and for non-COVID-19 related trials, in Europe and the United States?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study indicates that the COVID-19 pandemic affected the initiation of clinical trials overall and of non-COVID-19

trials. Although an increase in the overall numbers of clinical trials could be observed both in Europe and the United States, the number of initiated non-COVID-19 trials is reduced, with a slightly larger relative decrease in the United States. Short-term trends are also described.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The investigation and findings are a starting point to understand the impact of the COVID-19 pandemic on clinical trial initiation. The analysis allows to be rerun to capture more recent developments during and after the pandemic.

The outbreak of coronavirus disease 2019 (COVID-19) has a major impact not only on public health and daily living, but also on clinical trials worldwide. Trial sites have been under pressure as healthcare resources were redirected on the response to the public health emergency, and social distancing measures issued by local governments together with efforts of healthcare providers to protect patient and healthcare personnel impacted clinical research conduct. It has been shown that patient enrollment of ongoing clinical trials, protocol adherence, clinical trials operations, and

data collection were negatively affected.¹⁻⁵ Informed consent changes, protocol amendments, revised statistical analysis plans, and increased risk of bias are also raising great concern for sponsors and sites in terms of data integrity.^{6,7} In addition, academic and industry-sponsored research has shifted focus to address COVID-19.^{8,9} Medicines regulatory agencies issued guidance on how to address potential impact of the COVID-19 pandemic on ongoing clinical trials. In the United States of America, the US Food and Drug Administration (FDA) has published general

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guidance for industry, investigators, and institutional review boards on the conduct of clinical trials of medical products during the COVID-19 public health emergency¹⁰ and on master-protocols evaluating drugs and biological products for treatment and prevention of COVID-19.¹¹ In Europe, the Clinical Trials Expert Group (CTEG) of the European Commission (EC), the European Medicines Agency (EMA), Good Clinical Practice Inspectors Working Group (GCP IWG), and the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agencies (HMA) have also published general guidance on the management of clinical trials during the COVID-19 pandemic.¹² Statistical guidance was also published by the FDA on “Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency.”¹³ Likewise, the EMA Biostatistics Working Party (BSWP) issued a points-to-consider document on the implications of COVID-19 on methodological aspects of ongoing clinical trials.¹⁴ At the same time, biostatistical research was conducted on the impact of COVID-19 on the power of ongoing trials using simulation studies,¹⁵ on appropriate estimands, and analysis methods for affected trials,^{16–19} and on the role of adaptive designs to handle the impact of the pandemic.²⁰

In an effort to understand the organizational modifications in response to the pandemic, Le Breton *et al.*²¹ interviewed clinical operations professionals at 25 pharmaceutical companies in the United States from June to early August 2020. The majority of organizations (23/25) reported a high or moderate level of impact on ongoing trials. In order to mitigate the impact of the COVID-19 pandemic on clinical trials’ operation, a wide range of novel remote monitoring technologies and decentralized approaches were implemented, including telemedicine and electronic consent.²² Ongoing research shows that the disruption in ongoing clinical trials also varies by therapeutic area, with oncology showing the highest proportion of disrupted trials.^{23,24}

The effects of the pandemic on ongoing research also led to consequences on the initiation of new clinical trials. In a survey conducted by Medidata distributed to over 7,000 sites during the first week of August 2020, sites were asked to assess the impact of COVID-19 on their ability to initiate new trials.¹ Among the 734 responders, almost half of them claimed that the pandemic has had a significant impact on the initiation of new clinical studies, whereas one third claimed that the pandemic had little to no impact on their ability to initiate new research.¹ Taking a more direct approach, Xue *et al.*²⁴ have analyzed the number of non-COVID-19 clinical trials registered on clinicaltrials.gov by month from January 2020 to June 2020 and showed that the trial numbers follow a U-curve: starting in January, the trial numbers decreased until April and increased until they reached the January level again in June. From this, Xue *et al.* concluded a recovery from the disruption of the initiation of new trials. This is in line with the findings of Upadhaya *et al.*, who showed that the impact of the pandemic on ongoing oncology trials lessened from June 2020.²⁵ Along the same lines, Unger and Xiao investigated trial data for interventional and observational oncology, cardiovascular, and mental health studies from January 2015 through September 2020 based on clinicaltrials.gov for the United States and globally, and concluded that for these indications the COVID-19 outbreak was associated with a

decrease in new clinical trial activations.²⁶ Similarly, the analysis by Lamont *et al.*²⁷ demonstrates a decrease in trials initiated in oncology. This study uses the Medidata Enterprise Data Store, which only includes trials from adhering sponsors, and has a limited coverage of the pandemic, with an observation period up to May 2020.

Although these analyses focus on the global trial numbers, they do not allow any conclusions for specific regions. This was partly addressed by an analysis by Hawila and Berg,²⁸ who compared the number of clinical trial submissions at clinicaltrials.gov also stratified by global region. A comparison of the number of initiated clinical trials between April and October of 2020 with those in the same time frame in 2019 showed that the overall number of non-COVID-19 clinical trials submissions decreased by 10% globally. For the United States, they showed a decrease of 14.3%, for Europe, a decrease of 19.6%, and, for Asia, an increase of 5.1%. However, an important caveat still applies to these analyses, as also noted by the authors. For the global analyses and regional analyses not focusing on the United States alone, the clinicaltrials.gov database includes only a selection of all initiated trials, as registration is voluntary in most countries except the United States. Additionally, voluntary registration behavior might have changed over time and during the pandemic. Taken together, this selection/voluntary registration potentially confounds the analysis of the impact of the COVID-19 pandemic. An analysis of trial initiation in Europe based on a complete register has not been conducted, yet.

To overcome these limitations of the data sources of the above outlined analyses and add to the understanding of the impact of the COVID-19 pandemic on trial initiation, this article investigates trial initiation in Europe and the United States based on data sources that are complete for the respective region.

The objective of this article is to investigate the impact of the COVID-19 pandemic on the initiation of phase II and III interventional clinical trials, both overall and non-COVID-19 related, for therapies in the United States and Europe, first from a broad perspective conducting a yearly comparison from 2010 to 2020. Second, we investigate the time since the start of the pandemic on a monthly basis to gain insights into short-term trends. By repeating the analyses separately for study phases II and III, we gain further insights into the impact of the COVID-19 pandemic on trial initiation.

METHODS

We investigate the potential impact of the COVID-19 pandemic on the initiation of interventional clinical phase II and III trials (i) by a yearly comparison of the number of initiated trials from 2010 to 2020 and (ii) by a monthly comparison starting in January 2020 of the number of initiated trials. This was done by (i) taking into account all clinical trials, irrespective of whether they were COVID-19 related (all trials), and (ii) for all trials that were not investigating COVID-19 as an indication (non-COVID-19 trials). For the comparison year on year, we derive the monthly average numbers of initiated trials separately for each year from 2010 to 2020. The relative changes from 2019 to 2020 in Europe and the United States are the main focus of the analysis. An analysis for the global numbers based on clinicaltrials.gov without restricting the variable country is included in the **Supplementary Information**. To investigate the short-term pattern in trial initiation, we derive the monthly numbers of initiated trials in 2020 and 2021. These analyses are conducted separately for Europe and the United States and are based on public clinical trial

registers. We define Europe as the European Union (EU) together with the European Economic Area (EEA), including the United Kingdom (UK) until December 31, 2020. Although the official leave date of the United Kingdom from the European Union is January 31, 2020, the United Kingdom uploaded and updated clinical trial information until December 31, 2020, in the EudraCT data base, because the EU legislation on clinical trials was applicable to UK trials until this date. The *EU Clinical Trials Register* (EUCTR), which is based on the EudraCT database and the *clinicaltrials.gov* register are used for a systematic search of interventional non-COVID-19 phase II and phase III clinical trials in Europe and the United States. For the United States, the registration of phase II and phase III trials in *clinicaltrials.gov* is mandatory, making the clinical trial register complete for the United States. In particular, *clinicaltrials.gov* includes all interventional studies of FDA-regulated drugs, biologics, or devices that has one or more sites in the United States.²⁹ For the European Union and the EEA, the national competent authorities (NCAs) register all authorized trials in EudraCT and the EUCTR provides public access.³⁰ Based on trials included in the registers, we calculate the average monthly number of initiated trials within the time frame of interest for each year. For identification of FDA-regulated trials, the *clinicaltrials.gov* data base includes the variable *isFDARegulated* since 2017.^{31,32} However, for previous time frames, no direct identification of FDA-regulated trials is possible. As an approximation for all treatments regulated by the FDA, we specified the type of treatment to be “Biologic,” “Drug,” “Combination,” “Vaccination,” or “Genetic” for the years from 2010 to 2016. In the years from 2017 to 2020, where the approximation can be used as well as the variable *isFDARegulated*, the relative difference between the true number of FDA-regulated trials (as defined by *isFDARegulated*) and the estimated number of FDA-regulated trials (defined by the above approximation), calculated as $(\#isFDARegulated - \#approximation) / \#isFDARegulated$, are 2.6%, -0.2%, -0.3%, and 0.3% for the years from 2017 to 2020, respectively. Whereas this does not impact the comparison between 2019 and 2020 in our main analyses, trial numbers before 2017 cannot directly be compared with trial numbers starting in 2017 without further considerations.

For each calendar year from 2010 to 2020, we calculate the monthly average number of initiated interventional clinical trials from January 1 to December 31. Using the monthly average numbers instead of yearly absolute numbers allows direct comparison to the monthly numbers in the subsequent analysis that is based on the same scale. The time frame of interest was chosen to start in January, as done in Lamont *et al.*²⁷ (in contrast to starting later, e.g., only after the World Health Organization (WHO) declared COVID-19 a pandemic in March) to capture also clinical trial sponsor decisions taken in anticipation of the subsequent declaration of a pandemic and to facilitate interpretation and comparison with previous years. For example, the WHO declared COVID-19 “a public health emergency of international concern” already on January 31, 2020, which could have impacted sponsor decisions.

The number of initiated clinical trials regulated by the FDA that are registered in *clinicaltrials.gov* for the respective search settings and time frames were extracted from the registers using the function *ctrLoadQueryIntoDb* with the `only.count=TRUE` option from the R package *ctrdata*.³³ The search was restricted to interventional phase II and phase III clinical trials, with country specified as “United States” and the time frame was restricted to the year or month of interest. COVID-19 related trials were identified using the search term “(COVID-19 OR COVID19 OR SARS-CoV2 OR SARS-CoV-2 OR COVID).” The search strategies (with direct links) we used for identifying all trials for 2020 and 2016 and COVID-19 trials for 2020 are listed in the **Supplementary Material** (search strategies 1, 2, and 3, respectively).

These search terms go beyond the recommended search terms of the EUCTR and *clinicaltrials.gov* of using only “COVID-19,” and were used to increase sensitivity of the search as a pilot search identified COVID-19 related trials that could not be identified using the recommended search terms alone. To derive the number of initiated trials for the European Union,

we downloaded all phase II and III trials authorized by any NCA in the EU/EEA between 2010 and 2020 using the *ctrdata* package. Trial phase was included in the search query as “phase=phase-two&phase=phase-three” and the country was required to be any EU or EEA country (e.g., adding to the query “&country=NL” for the Netherlands). For identifying all COVID-19 related trials, we downloaded all phase II and III trials authorized by any NCA in Europe identified via the search term “(COVID-19 OR COVID19 OR SARS-CoV2 OR SARS-CoV-2 OR COVID).” As the search for keywords in the EUCTR is conducted on all data fields, false positive “COVID-19” trials might be included in the search results. For example, a false-positive trial would occur if a trial had an exclusion criterium related to COVID-19 but would not address the indication of COVID-19. Hence, to filter out false-positive trials, the trial title and indication were checked to include one phrase from the list of COVID-19-related search terms. Additionally, identified “COVID-19” trials with a trial authorization date before November 1, 2019, have been deleted from the dataset as false-positive trials. These strategies are listed in the **Supplementary Material**, with direct links (search strategies 4 and 5).

The number of non-COVID-19 clinical trials is calculated as the difference among all trials registered within the respective time frame and the COVID-19 related trials registered within the same time frame. Data extraction took place at mid October 2021 from both registers. For the analysis of the short-term trends, this allowed for a delayed data entry by NCAs in Europe into the EUCTR and of registration by clinical trial sponsors in *clinicaltrials.gov* in the United States of 7 months.

The time frame of interest for the monthly analysis in 2020 and 2021 includes December 31, 2020, the date from which information about trials in the United Kingdom could no longer be uploaded or updated in the EUCTR. From this date onward, the United Kingdom no longer registers authorized clinical trials in the EUCTR, which introduces heterogeneity into the data collection. The trial numbers for January and February 2021 reflect the European Union and the EEA excluding the United Kingdom, whereas trial numbers before reflect the European Union including the United Kingdom. This could lead to a decrease in the derived trial numbers from January 2021 onward as trials solely conducted in the United Kingdom or first authorized in the United Kingdom and not authorized in the same month by any EU or EEA country, are not included.

Due to the structure of the regulatory system in the European Union, where a trial needs to be authorized separately in every member state where it is conducted, the same trial could be listed multiple times in the EUCTR with different dates of ethics committee approval and trial authorization from the NCA. For our analysis, we downloaded all phase II and III trials with a trial authorization from any NCA after January 1, 2010, using the function *ctrLoadQueryIntoDb* from the R package *ctrdata*³³ and identify trials by their unique EUDRA-CT number. To avoid a selection bias by time, we did not restrict the trial status in the search. As older trials have a higher chance of being “temporarily halted” or “restarted,” excluding these trials from the analysis would produce a downward bias for early time frames. For each trial, we use the “first past the post” approach and define the starting date as the earliest date at which both an NCA authorization and a favorable ethics committee opinion is recorded in one EU member state. Practically, we first calculated the latest between date of favorable ethics committee opinion and date of positive NCA decision within each member state in which the trial is conducted. Subsequently, we calculated the earliest of these dates over all member states where the NCA decision was and the ethics committee opinion was favorable. This approach ensures that each trial identified by its EudraCT number is associated with a unique starting date and double counting of trials in different time frames is avoided.

To assess the impact on phase II and phase III separately, we recorded the trial phase from the EUCTR and included study phase in the search term for *clinicaltrials.gov*. In our analysis, we categorize hybrid phase II/III trials (trials registered as both phase II and phase III in the trial registers) as phase III trials to take into account the confirmatory purpose.

Limitations

To interpret the numbers of initiated clinical trials, differences between clinicaltrials.gov and EUCTR need to be considered. First and foremost, the regulatory systems differ between the European Union and the United States, with different modes and rules of trial authorization by the regulatory agencies. Consequently, absolute trial numbers cannot directly be compared between both regions. To make relative changes over time as comparable as possible, we only considered trials of the FDA regulated drugs for the U with the caveat described above that the variable *isFDARegulated* is only available from 2017 and an approximation had to be used for earlier trials. This approach does not impact the comparison between 2019 and 2020, but trial numbers prior to 2017 cannot directly be compared with trial numbers starting in 2017.

Additionally, clinicaltrials.gov lists the start date of the clinical trial as the date when the first patient is enrolled into the trial for already recruiting trials, and an estimated start date for not yet recruiting trials. In contrast, the EUCTR lists the date of authorization by the national competent authority and the date of a (favorable) ethics committee decision without information on trial enrollment. Therefore, for the same trial, the date registered in clinicaltrials.gov would always be posterior to the respective date registered in EUCTR, with the exact amount depending on the time from trial authorization to actual study start. This systematic difference could lead to trends manifesting earlier in the EUCTR. In contrast, the EUCTR does not provide information on the actual recruitment status.

Whereas, in principle, the EudraCT and clinicaltrials.gov should include all interventional phase II and III trials started in the EU/EEA and the United States, respectively, different factors might contribute to a delay/omission in registration and could result in an incomplete sample.³⁴ In Europe, a delayed trial registration by the responsible NCA could either lead to an underestimation of trials (if the trial is not included at all) or a bias toward later dates of authorization (if the entry for the first authorization is delayed). In the United States, the potential bias might vary according to the strength of the incentives and norms for reporting studies with certain characteristics.³⁴ In particular, the trial sponsor registers the trial in clinicaltrials.gov whereas in the EudraCT database the NCA of the respective EU/EEA member state where the trial is conducted is responsible for data entry. Both clinical trial sponsor and NCAs might be faced with increased workloads due to the COVID-19 pandemic. Importantly, this impact could be differential, for example, because clinical trial sponsors might more easily shift/increase resources. We include monthly numbers of initiated trials up to February 2021, which allowed for a 7-month registration period between the end of the time frame of interest and the date of data extraction. Notwithstanding this registration period, a reporting bias for the most recent time frames cannot be fully excluded and monthly numbers need to be interpreted with caution. Therefore, the same analysis will be repeated in the future to allow for updated trial registrations in the databases.

The analysis by year and month is a simplification to ease readability of the figures, but information on the exact starting date is lost and the choice of categories includes an arbitrary element. For example, whereas calendar year is an intuitive time frame, COVID-19 was not declared a pandemic on January 1, 2020, and the effect of COVID-19 might have increased gradually with time, therefore a comparison between 2019 and 2020 might underestimate the impact of the COVID-19 pandemic on trial initiation.

Another potential source of bias is the (potentially) inconsistent categorization of trials as “phase I,” which would prevent publication of the trial in the EUCTR and results in voluntary publication via clinicaltrials.gov.^{34,35} Taken together, both the EUCTR and clinicaltrials.gov are similar, but due to the inherent differences, no direct comparison of absolute trial numbers is possible without further considerations. Therefore, in this article, we focus primarily on within-region effects of the pandemic on the initiation of clinical trials, avoiding any comparison of absolute trial numbers and time points.

In summary, we selected two databases for clinical trial registration for which legal requirements exist for sponsors / NCAs to register clinical

trials to ensure that the basis for the analysis is as complete as possible. However, in line with the above considerations, some epistemic uncertainty remains and needs to be considered for the interpretation of our results.

RESULTS

Long-term trend 2010 to 2020

Taking into account all phase II and phase III interventional clinical trials (COVID-19 and non-COVID-19 related trials), the investigation of trial initiation from 2010 to 2020 by year shows a small increase in the trial numbers in 2020 in Europe and in the United States as compared with 2019. Although, in the United States, the increase in overall trial number is about 3%, in the European Union, the trial number increased 10% in 2020 as compared with 2019 (see **Table 1**). This finding is consistent among development phases. However, whereas in the European Union the number of phase III trials has increased more than the number of phase II trials (11.8% vs. 8.4% increase; see **Table 1**), in the United States, the number of phase III trials has increased less than the number of phase II trials (1.6% vs. 3.9% increase; see **Table 1**). In contrast, the number of phase II and phase III clinical trials initiated in Europe and the United States in 2020 that are not directly related to COVID-19 falls below the level of the previous years (see **Figure 1**). In particular, the number of non-COVID-19 clinical trials initiated in Europe during 2020 marks a 10-year low. As compared with 2019, in Europe, the number of initiated non-COVID-19 clinical trials decreased by 11.1%. The decrease in initiated non-COVID-19 clinical trials in the United States shows a relative decrease in 2020 as compared with 2019 of 13.2% (see **Table 1**).

These findings suggest that the COVID-19 pandemic affected the initiation of non-COVID-19 clinical trials both in the United States and in Europe.

The degree of the decline according to phase of development appears slightly different between the United States and Europe, as depicted in **Figure 1**. For phase II trials alone, **Table 1** shows that in Europe and the United States, on average, 9.0 and 15.7 fewer non-COVID-19 clinical trials have been initiated per month in 2020 as compared with 2019. This corresponds to relative declines of 11.4% in Europe and 11.9% in the United States. In contrast, the same cannot be observed for phase III trials alone. As compared with 2019, 10.8% fewer non-COVID-19 clinical trials have been initiated in Europe and 16.1 fewer non-COVID-19 clinical trials in the United States, respectively.

To investigate the magnitude of the impact of the COVID-19 pandemic on trial initiation in the United States and Europe in more detail, we analyzed the initiation of clinical trials from January 2020 to February 2021 by months.

Short-term trend 2020 to 2021

The short-term trend of monthly numbers of all clinical trials and non-COVID-19 clinical trials from January 2020 to February 2021 is shown in **Figure 2** and show the different patterns of trial initiation in Europe and the United States.

For all trial numbers, in Europe, a large increase 70% in April 2020 can be observed as compared with the 2019 average,

Table 1 Comparison of all trials and non-COVID-19 clinical trial initiation between 2019 and 2020

Trial type	Phase	Region	2019 monthly average ^a	2020 monthly average ^a	Absolute difference ^c	Relative difference ^c
All trials	II + III	US	190.9	196.9	6.0	3.14%
		EU	134.2	147.3	13.2	9.81%
	II alone ^b	US	131.8	136.8	5.1	3.86%
		EU	79.2	85.8	6.7	8.42%
	III alone ^b	US	59.2	60.1	0.9	1.55%
		EU	55.6	61.5	6.5	11.82%
Non-COVID-19 trials	II + III	US	190.7	165.5	-25.2	-13.20%
		EU	134.1	119.2	-14.9	-11.12%
	II alone ^b	US	131.6	115.9	-15.7	-11.91%
		EU	79.1	70.1	-9.0	-11.38%
	III alone ^b	US	59.1	49.6	-9.5	-16.08%
		EU	55.0	49.1	-5.9	-10.76%

COVID-19, coronavirus disease 2019; EU, European Union; US, United States.

^aThe time frame for each year is January to December.

^bTrials categorized as phase II/III in clinicaltrials.gov and the EU Clinical Trials Register (EUCTR) are counted as phase III trials.

^cAbsolute difference is calculated as the monthly average 2020 minus monthly average 2019, and the relative difference is calculated as the absolute difference divided by the monthly average 2019.

whereas in all other months no outstanding differences to the 2019 average can be detected. In contrast, in the United States, the monthly trial numbers are below the 2019 average between 11% and 39% from January 2020 to May 2020 and recover from June 2020. From June 2020 to December 2020, the monthly trial numbers in the United States exceed the 2019 average by between 13% and 37%. These patterns are consistent across development phases both in the United States and in Europe (see **Figure 2, Table 2**).

For non-COVID-19 related clinical trials, in the United States, we observe a drastic decrease in the beginning of the pandemic from March to May with a decrease of up to 69% as compared with the 2019 average in April 2020 (see **Table 2**). In turn, the number of initiated trials increased again in June 2020 and reached the levels of 2019 already in July 2020 again.

In contrast, the number of initiated non-COVID-19 clinical trials in Europe decreased less in the beginning of the pandemic, with the maximum relative decrease of 32% in

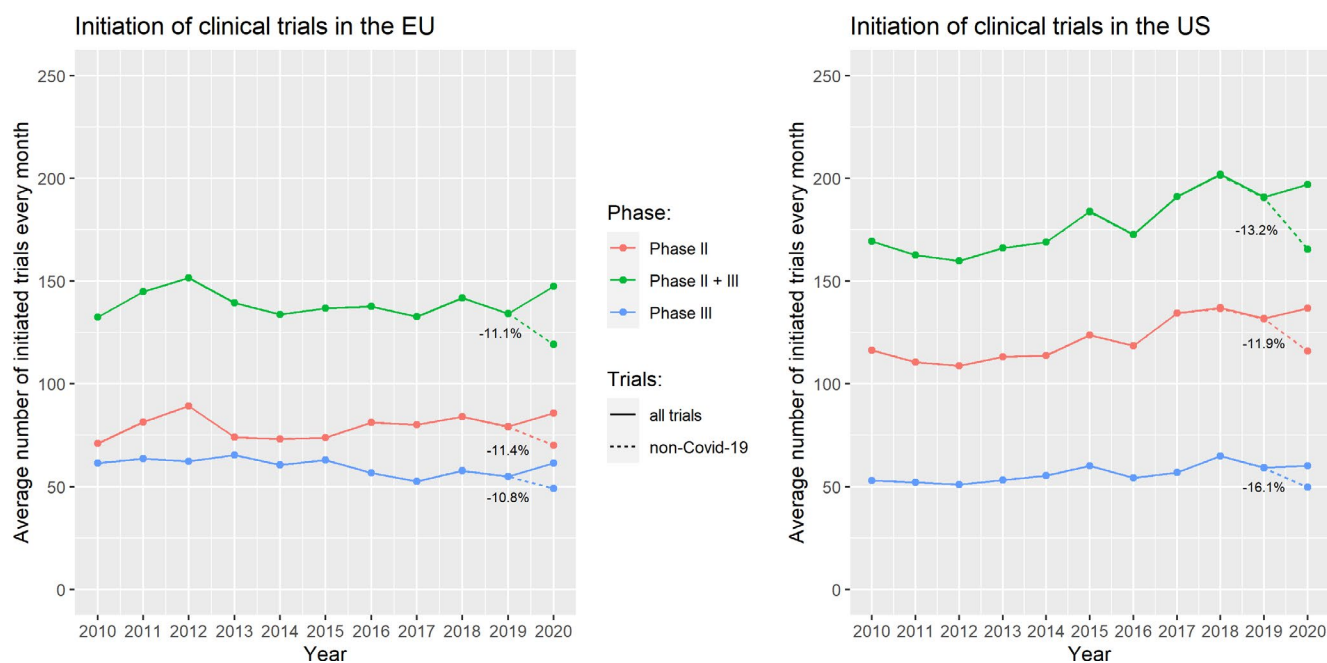


Figure 1 Trial initiation in Europe and the United States by year from 2010 to 2020. For each calendar year, the monthly average number of initiated phase II and III clinical trials is depicted for the European Union based on the EU Clinical Trials Register (EUCTR) and for the United States based on clinicaltrials.gov, relative decreases indicate the change in non-coronavirus disease 2019 (COVID)-19 trials from 2019 to 2020.

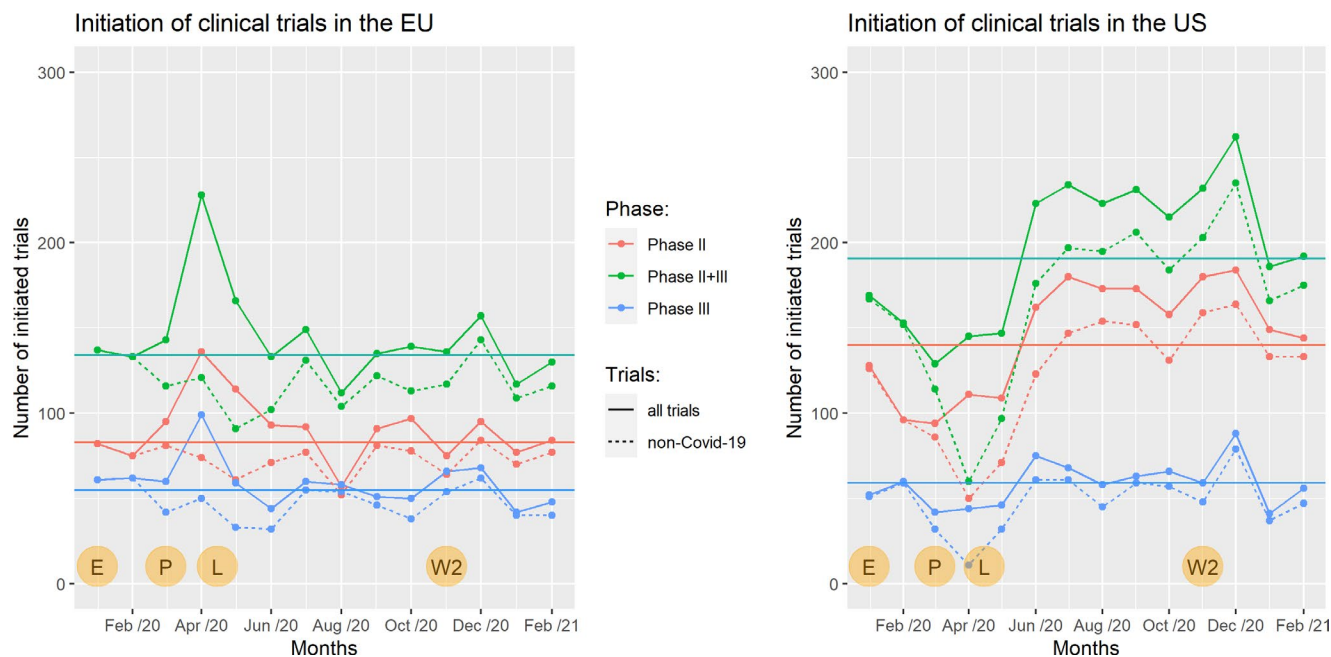


Figure 2 Trial initiation in Europe and the United States by month from January 2020 to February 2021. Horizontal lines mark the monthly average number of initiated trials in 2019 in Europe (red) and the United States (blue). Major events related to the coronavirus disease 2019 (COVID)-19 pandemic and affecting the data source are highlighted by E (the World Health Organization (WHO) declared COVID-19 a global health emergency), P (the WHO declared COVID-19 a pandemic), L (most European countries have initiated lockdowns) and wave 2 (both in Europe and the United States, a second wave materialized in November).

May 2020. Our results also allow to evaluate the outlook of a full recovery where a difference between the United States and Europe can be observed: whereas trial initiation in the United States regained 2019 levels already from July 2020 again, in Europe, there was only a rise in trial numbers until July 2020, but no full recovery to the 2019 levels can be detected. In Europe, trial numbers remain below the 2019 average until February 2021 for all months except December 2020. However, it should be noted that monthly averages may be impacted by seasonality. Hence, a comparison to the 2019 average and results related to short-term trends need to be interpreted with caution. In summary, whereas the United States seems to have recovered from the impact of the COVID-19 pandemic from June 2020 onward in term of initiation of non-COVID-19 related phase II and III clinical trials, the trial numbers in Europe remain slightly below the 2019 average as of February 2021.

Investigating clinical development phases II and III separately, **Figure 2** shows that the general patterns seen in Europe and the United States are qualitatively consistent across development phases (see **Table S4** for corresponding trial numbers, and relative changes as compared with 2019 averages). However, also for the short-term trend, the magnitude of the impact is slightly different for phase II and phase III trials. In the United States, the decrease in initiated non-COVID-19 clinical trials in April 2020 as compared with the 2019 average is 63% for phase II trials but 81% for phase III trials (see **Tables S5, S6**). A similar pattern is seen in Europe, where the decrease in initiated non-COVID-19 clinical trials in May 2020 as compared with the

2019 average is 27% for phase II trials and 40% for phase III trials.

DISCUSSION

The long-term analysis suggests that the COVID-19 pandemic affected the initiation of clinical trials both in Europe and in the United States. Overall, an increase in the number of interventional clinical trials could be observed both in Europe and in the United States in 2020 as compared with 2019. In the United States, the relative increase in phase II trials was larger than in phase III trials, whereas, in Europe, the relative increase in phase III trials was slightly larger than the relative increase in phase II trials. However, although overall an increase in phase II and phase III clinical trial numbers is observed, the number of non-COVID-19 phase II and phase III clinical trials initiated both in Europe and in the United States in 2020 is reduced as compared with the yearly trial numbers in the previous decade. Both phase II and phase III non-COVID-19 trials are affected in the United States and in Europe, in equal proportion in Europe, whereas phase II trials are being relatively less affected than phase III trials in the United States.

In addition to differences in impact on yearly numbers of initiated non-COVID-19 trials, the short-term time pattern of impact also appears to differ, as seen in our monthly analysis of trial initiation from January 2020 to February 2021. In the United States, a sharp decrease could be observed in April 2020 followed by a quick recovery that persisted throughout 2020. Particularly, the trial numbers in 2020 exceed the 2019 average from June 2020 onward again. In contrast, the largest decrease in the European Union as compared with the 2019 average can be observed for

Table 2 Comparison of all trial and non-COVID-19 clinical trial initiation by month in 2020

Trial type	Months	EU			US		
		Absolute number of initiated trials	Absolute difference to 2019 average ^a	Relative difference to 2019 average ^a	Absolute number of initiated trials	Absolute difference to 2019 average ^a	Relative difference to 2019 average ^a
All trials	January 1, 2020	137	2.8	2.11%	169	-21.9	-11.48%
	February 1, 2020	133	-1.2	-0.87%	153	-37.9	-19.86%
	March 1, 2020	143	8.8	6.58%	129	-61.9	-32.43%
	April 1, 2020	228	93.8	69.94%	145	-45.9	-24.05%
	May 1, 2020	166	31.8	23.73%	147	-43.9	-23.00%
	June 1, 2020	133	-1.2	-0.87%	223	32.1	16.80%
	July 1, 2020	149	14.8	11.06%	234	43.1	22.57%
	August 1, 2020	112	-22.2	-16.52%	223	32.1	16.80%
	September 1, 2020	135	0.8	0.62%	231	40.1	21.00%
	October 1, 2020	139	4.8	3.60%	215	24.1	12.61%
	November 1, 2020	136	1.8	1.37%	232	41.1	21.52%
	December 1, 2020	157	22.8	17.02%	262	71.1	37.23%
Non-COVID-19 trials	January 1, 2021	117	-17.2	-12.80%	186	-4.9	-2.58%
	February 1, 2021	130	-4.2	-3.11%	192	1.1	0.57%
	January 1, 2020	137	2.9	2.18%	167	-23.7	-12.41%
	February 1, 2020	133	-1.1	-0.81%	152	-38.7	-20.28%
	March 1, 2020	116	-18.1	-13.49%	114	-76.7	-40.21%
	April 1, 2020	121	-13.1	-9.76%	60	-130.7	-68.53%
	May 1, 2020	91	-43.1	-32.13%	97	-93.7	-49.13%
	June 1, 2020	102	-32.1	-23.93%	176	-14.7	-7.69%
	July 1, 2020	131	-3.1	-2.30%	197	6.3	3.32%
	August 1, 2020	104	-30.1	-22.44%	195	4.3	2.27%
	September 1, 2020	122	-12.1	-9.01%	206	15.3	8.04%
	October 1, 2020	113	-21.1	-15.72%	184	-6.7	-3.50%
November 1, 2020	117	-17.1	-12.74%	203	12.3	6.47%	
December 1, 2020	143	8.9	6.65%	235	44.3	23.25%	
January 1, 2021	109	-25.1	-18.71%	166	-24.7	-12.94%	
February 1, 2021	116	-18.1	-13.49%	175	-15.7	-8.22%	

COVID-19, coronavirus disease 2019; EU, European Union; US, United States.

^aAbsolute difference is calculated as the monthly average 2020 minus monthly average 2019, relative difference is calculated as the absolute difference divided by the monthly average 2019.

May, June, and August 2020. Overall, the initial decrease in the European Union was smaller than in the United States, but trial numbers mainly remained below the 2019 average throughout 2020. A sharp decrease and recovery in the United States forming a “v” and a smaller but more prolonged decrease and recovery in the European Union forming a shallow “u” appear to have impacted non-COVID-19 trials. With minor variations, these patterns could be found with different magnitudes for both phase II and phase III trials separately.

Harper *et al.* argue that “research staff and resources have been purposely and purposefully prioritized to COVID-19 activities above all else,”³ which could partly explain the decrease in non-COVID-19 clinical trial initiations. Our findings support this view, as the overall number of initiated trials, including COVID-19 and non-COVID-19 clinical trials, in 2020 slightly increased compared with 2019. **Figure 1** suggests that the overall capacity for conducting phase II and III clinical trials has not changed substantially in the last 10 years. Consequently, high priorities for COVID-19 related research and the conduct of many COVID-19 related trials in 2020 could lead to lower priorities for and a decrease in non-COVID-19 clinical trials (“resource shift” hypothesis). The pattern of resource shift toward COVID-19 between February and May 2020 is similar between the European Union and the United States, supporting our original hypothesis that there would be a short-term adaptation to the pandemic. Given the measures implemented and the burden on healthcare systems, with resources shifted from research- to care-related activities, it is remarkable that the overall capacity did not seem to decrease, but the overall number of trials actually increased in 2020 as compared with 2019. However, although this rationale supports a decrease in non-COVID-19 trials for a short period, it does not explain the regional differences between Europe and the United States in terms of both (i) development phases being affected differently and (ii) marked differences in the dynamics of the impact as seen in the analysis of the short-term trend. Other factors need to be considered to explain these patterns and additional research is needed.³⁶ The higher financial risk associated with a (failed) phase III trial could be another contributing factor of the higher decrease in phase III trials as compared with phase II trials observed in the United States. However, with development phases affected equally in Europe, this can only be part of an explanation. In the future, a different factor could play a role for the initiation of phase III trials: as many ongoing phase II trials are affected by the pandemic, both a delayed completion and a more complex analyses^{4,11} could lead to delays in development programs, which would translate into decreasing numbers of initiated phase III trials.

Follow-up questions

Although our findings describe the evolution of trial initiation in Europe and the United States and gives direction for subsequent investigation, it does not allow to unambiguously attribute the many causes and factors impacting observed trends. Follow-up research in collaboration with the pharmaceutical industry and clinical trial sponsors is needed to investigate potential causes of

the differential impact of the COVID-19 pandemic in Europe and the United States in depth. Additionally, as indicated by Xue *et al.*, research in different clinical indications might be affected differently, and flexibility in trial conduct might vary between indications.²⁴ Here, a more granular investigation of different indications could help to indicate where additional scientific, procedural, or financial support by regulatory agencies or funding bodies are needed to prevent a continuing decrease or halt in the development of medicines. Importantly, the pandemic is still ongoing and public health measures keep changing. The implementation of large-scale vaccination both in Europe and the United States might affect the capability and willingness to conduct clinical trials. Our analysis will need to be rerun to capture recent developments and delayed registration and data entry by clinical trial sponsors and NCAs.

In addition to trial initiation, other dimensions need to be considered to understand the impact of COVID-19 on medical research more comprehensively. Importantly, the enrollment progress of the trials initiated before and during the pandemic needs to be considered. Clinicaltrials.gov and the EUCTR provide information on the initiation of clinical trials, but no information on the actual recruitment, and therefore on the likelihood of the trial to be completed, is included. This is of particular relevance for multicenter trials, as the trial initiation is agnostic to the successful initiation and pace of recruitment in all planned centers. Beyond information on the recruitment, also information on the collection of primary, key-secondary, and important safety end points would be helpful to comprehensively understand the likelihood of initiated trials to provide the intended evidence.

Although the focus of our analysis was on phase II and phase III clinical trials, as phase I clinical trials are exempt from registration in the EUCTR (except pediatric trials) and clinicaltrials.gov, early phase clinical research might have also been impacted by COVID-19, leading to downstream consequences for/potentially delaying later phase clinical research in the future.

CONCLUSION

The COVID-19 pandemic affected the initiation of non-COVID-19 clinical trials both in the United States and in Europe. On the one hand, an increase in overall numbers of phase II and III clinical trials could be observed both in Europe and the United States in 2020 as compared with 2019. This highlights the ability of the clinical research environment—both in Europe and in the United States—to increase capacity in presence of a health emergency.

On the other hand, the number of non-COVID-19 phase II and phase III clinical trials initiated both in Europe and in the United States in 2020 is reduced as compared with the previous decade, with a slightly larger relative decrease in the United States. Additionally, the short-term trend differs between Europe and the United States. In the United States, after a sharp decrease in April 2020, the number of initiated non-COVID-19 clinical trials reached the levels of 2019 from June 2020 again. In Europe, the decrease in the number of initiated non-COVID-19 clinical trials was less pronounced, but trial numbers mainly remained below the

2019 average until February 2021. Follow-up research is needed to understand the contributing factors.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

F.L., E.E.P., R.H., A.M., L.G., F.P., and A.S. wrote the manuscript. F.L. and A.S. designed the research. F.L., E.E.P., R.H., A.M., L.G., F.P., and A.S. performed the research. F.L. and R.H. analyzed the data.

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