International Association for the Study of Lung Cancer (IASLC) Study of the Impact of COVID-19 on International Lung Cancer Clinical Trials

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Matthew P. Smeltzer, PhD[1], Giorgio V. Scagliotti, MD, PhD[2], Heather A. Wakelee, MD[3], Tetsuya Mitsudomi, MD[4], Upal Basu Roy, PhD, MPH[5], Russell C. Clark, JD[6], Renee Arndt, MS[6], Clayton D. Pruett, BS*[6], Karen L. Kelly MD[7], Peter Ujhazy, MD, PhD[8], Melissa L. Johnson MD[9], Yesim Eralp MD[10], Carlos H. Barrios MD[11], Fabrice Barlesi MD,PhD[12,13], Fred R. Hirsch, MD, PhD[14], Paul A. Bunn, MD[15]

For the IASLC COVID-19 and Clinical Trials Steering Committee

1. Division of Epidemiology, Biostatistics, and Environmental Health School of Public Health, University of Memphis, Memphis, TN
2. A.O.U. San Luigi Gonzaga Hospital, University of Torino, Orbassano, Italy
3. Stanford University, Palo Alto, CA
4. Kindai University Faculty of Medicine, Osaka-Sayama, Japan
5. LUNGevity Foundation, Bethesda, MD
6. Cancer Technology Applications, LLC, San Diego, CA
7. University of California, Davis Heath, Sacramento, CA
8. Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville, MD
9. Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN.
10. Acibadem University, Maslak Acibadem Hospital, Istanbul, Turkey
11. Latin American Cooperative Oncology Group, LACOG Oncoclínicas Group, Porto Alegre, Brazil
12. Gustave Roussy, Medical Oncology, Villejuif, France
13. Aix Marseille University, INSERM, CNRS, CRCM, Marseille, France
14. Icahn School of Medicine at Mount Sinai, Center for Thoracic Oncology/Tisch Cancer Institute, New York, NY
15. University of Colorado School of Medicine, Aurora, CO

Corresponding author:

Matthew P. Smeltzer, PhD, MStat
Division of Epidemiology, Biostatistics, and Environmental Health
School of Public Health, University of Memphis
222 Robison Hall
Memphis, TN 38152
(901) 678-3702
msmltzer@memphis.edu

*Clayton D. Pruett passed away on July 24, 2021

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Abstract

Introduction

To determine the effects of the global COVID-19 pandemic on lung cancer trials, we surveyed investigators and collected aggregate enrollment data for lung cancer trials across the world before and during the pandemic.

Methods

A Data Collection Survey collected aggregate monthly enrollment numbers from 294 global lung cancer trials for 2019-2020. A 64-question Action Survey assessed the impact of COVID-19 on clinical trials and identified mitigation strategies implemented.

Results

Clinical trial enrollment declined from 2019 to 2020 by 14% globally. Most reductions in enrollment occurred in April-June where we found significant decreases in individual site enrollment (p=0.0309). Enrollment was not significantly different in October-December of 2019 versus 2020 (p=0.25).

The most frequent challenges identified by the Action Survey (N=173) were fewer eligible patients (63%), decrease in protocol compliance (56%), and suspension of trials (54%). Patient-specific challenges included access to trial site (49%), ability to travel (54%), and willingness to visit site (59%).

The most frequent mitigation strategies included modified monitoring requirements (47%), telehealth visits (45%), modified required visits (25%), mail-order medications (25%), and laboratory (27%) and radiology (21%) tests at non-study facilities. Sites felt the most effective mitigation strategies were telehealth visits (85%), remote patient reported symptom collection (85%), off-site procedures (85%), and remote consenting (89%).

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Conclusion

The COVID-19 pandemic created many challenges for lung cancer clinical trials conduct and enrollment. Mitigation strategies were employed and, although the pandemic worsened, trial enrollment improved. A more flexible approach may improve enrollment and access to clinical trials, even beyond the pandemic.

Introduction

Lung cancer remains the leading world-wide cause of cancer deaths with over 1.8 million deaths annually.[1,2] We recently observed a reversal of the trend in lung cancer specific mortality as a consequence of major advances in lung cancer early detection and extensive use of targeted therapies and immunotherapy leading to increased survival.[3,4] These improvements are the end result of a multitude of clinical trials.

Lung cancer patients have been adversely affected by the COVID-19 pandemic in several important ways. First, the severity of the disease and the mortality rates following COVID-19 infection in lung cancer patients have been quite high in nearly all reports.[5-11] Mortality rates have averaged over 30% in most of these studies. Patients have experienced delays in diagnostic procedures and initiation, continuation of treatment.[11] Further, the pandemic led to a decrease in lung cancer screening rates, a critical area as screening has been shown to increase cure rates and save lives.[11] Despite the availability of several highly effective vaccines that induce neutralizing antibody levels in the majority of cancer patients, some reports suggest a small but significant minority fail to mount normal antibody responses making them susceptible to COVID-19 infection.[12-16]

The worldwide COVID-19 pandemic produced a major decline in accrual to clinical trials.[13,17,18] As an example, during the pandemic, actual enrollments to SWOG clinical trials in 2020 were 77.3% of expected enrollments overall and 54.0% of expected enrollments for Cancer Prevention and Control trials.[13] Several sponsors of clinical trials have documented the magnitude of the decline in trial accruals and others have documented the effectiveness of some measures taken to mitigate the declines.[19-21] There have been recent reports urging regulatory bodies to incorporate some of the mitigation strategies into permanent changes as a means to overcome low accrual rates.[22]

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The International Association for the Study of Lung Cancer (IASLC) is the largest international organization dedicated to reducing the worldwide burden of lung cancer. The IASLC undertook a worldwide survey of lung cancer specific clinical trials to understand the effects of the COVID-19 pandemic on accrual to lung cancer trials and document strategies that might be adopted to permanently increase future clinical trial participation. The data presented in this report indicate that the decline in clinical trial enrollment was international in scope and that many of the mitigation strategies were adopted on a worldwide scale. Nonetheless, clinical trial accrual has still not reached pre-pandemic levels. Data from this report emphasize the potential effectiveness of numerous mitigation strategies which could be carried forward beyond the pandemic.

Methods

In accomplishing its mission, IASLC conducted surveys to determine the impact of the COVID-19 pandemic on enrollment to worldwide lung cancer clinical trials and to determine if any mitigation strategies were effective in improving clinical trial enrollment. An *ad hoc* executive committee was established and met 2 to 4 times per month from September 2020 until March of 2021 (Supplemental Data 1).The executive committee identified key global leaders and sites conducting lung cancer clinical trials and created surveys to quantitate trials enrollment and identify mitigation strategies. We implemented a two-pronged approach with a trial enrollment survey and an action mitigation survey to evaluate the experiences of clinical trial sites across the world.

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Data Collection Survey

The Data Collection Survey looked at aggregate clinical trial enrollment data, per trial, for each month of 2020, the first year of the pandemic, with 2019, the year before the pandemic, as a control. Data sources included government or regulatory agencies, industry sponsors, and study principal investigators). We included all lung cancer trials open to enrollment at any time in 2019 or 2020, with trial site as the unit of analysis. For multi-site and multi-national clinical trials, we used site level data when available and grouped based on country of enrolling site. In some cases, only multiple site trial data were available. Therefore, we stratified results based on single versus multiple site trial data (based on data availability, not the trial design) when comparing quarterly enrollment between 2019 and 2020. We collected the start date and stop date for each trial, and in per trial analyses, trials did not contribute to the denominator in periods before the start date or after the stop date.

A custom REDCap database was developed to house the data from this project at the University of Memphis. Clinical sites had two options to provide data for this project. First, a link was provided to upload data directly to the REDCap database via secure hypertext transfer protocol (https). Second, sites have the option to provide data in an excel spreadsheet or csv file, using a standardized template uploaded via a custom secure File Transfer Protocol (FTP) site. Data were collected in accordance with the (IASLC Privacy Policy: https://www.iaslc.org/privacy-policy) with oversight from the University of Memphis Institutional Review Board.

We estimated the number of COVID-19 cases diagnosed each month in 2020 using data downloaded from Our World Data (Global Change Data Lab, Our World in Data). Countries were categorized by IASLC region (Asia, Europe, Latin America, North America, and the Rest of the World).

Action Mitigation Survey

The Action Survey included 64 questions designed to assess the impact of COVID-19 on the conduct of clinical trials in 2020, and identify mitigation strategies used to combat these impacts. The target respondents were lung cancer clinical trial sites across the world, with site as the unit of analysis (one response per site). The sampling frame for the Action Survey was constructed using a multi-stage referral process from the Executive Committee and an *ad hoc* Steering Committee that was comprised of an additional 21 leaders around the world (Supplemental Data 1). After identification of key site investigators worldwide, we evaluated the list to ensure adequate representation across global regions and expanded as necessary. In total, we identified and contacted 429 potential sites from the Executive and Steering Committee recommendation and 804 principal investigators identified by industry partners. We distributed the survey (Supplemental Data 2) via email, with personal reminders approximately every 2 weeks during the data collection period. This purposive sampling strategy allows for representation from a diverse group of individuals and institutions globally. Survey results were collected by the IASLC using Survey Monkey.

Statistical Analysis

Data are summarized overall and by region of the world with means and standard deviation or frequencies and percentages. Some analyses collapse categories from a 5-point or 6-point scale to a binary variable (as described in the results). Statistical comparisons across regions used Chi-Square tests. We evaluated monthly trial enrollment data and compared differences in average quarterly enrollment by year using the Kruskal-Wallis test due to the distribution of the data. Analyses were conducted with SAS Version 9.4 (Cary, NC) and the threshold for statistical significance was set at 0.05.

Results

We evaluated study enrollment data from 294 lung cancer trials across 26 countries. This included 114 (39%) from North America, 55 (19%) from Asia, 26 (9%) from Latin America, 79 (27%) from Europe, 20 (7%) from the rest of the world. These 294 trials enrolled a total of 4,163 patients in 2019 compared to 3,590 in 2020, a 14% decrease. We evaluated per trial enrollment (Figure 1A) and total number of patients enrolled (Figure 1B) per month between 2019 and 2020. Quarterly enrollment per trial was compared between 2019 and 2020 within single institution trial data (Figure 1C) and within multiple institution trial data (Figure 1D). Most reductions in enrollment occurred in quarter 2 (April to June) where we found significant decreases from 2019 to 2020 in single site trial data (p=0.0309, Figure 1C) and marginally significant differences in multiple site trial data (p=0.0541, Figure 1D). Enrollment in multiple site trials were also lower in the first quarter (January to March) of 2020 compared to 2019 (p=0.0185, Figure 1D). However, there was no meaningful difference in enrollment between 2019 and 2020 in quarter 4 (October to December) in single site trial data (p=0.25, Figure 1C) or multiple site trial data (p=0.37, Figure 1D). Despite the apparent rebounding of trial enrollment numbers in the last quarter of 2020, we observed increasing numbers of COVID-19 cases throughout 2020. Specifically, the total numbers of COVID-19 cases diagnosed per month around the world increased consistently from approximately 2,000,000 in February to over 35,000,000 in December of 2020 (p-value for trend < 0.0001, Figure 1A).

Differences in total enrollment from 2019 to 2020 varied significantly across global regions (p<0.0001). Based on the trials available in our study we found a 35% decrease in total number of patients enrolled in 2019 compared to 2020 in Europe (from 217 to 142), 10% decrease in Asia (from 177 to 160), 13% decrease in North America (from 3,658 to 3,195), 88% decrease in Latin America (from 26 to 3), and a 5% increase in the Rest of the World (from 85 to 89).

Quarterly enrollment patterns for each region varied based on the numbers of trials available, and are shown in Supplemental Data 3.

Action Survey

We received responses to our Action Survey from 173 clinical sites across 45 counties. This included 35 (21%) from North America, 35 (21%) from Asia, 19 (11%) from Latin America, 50 (30%) from Europe, 27 (16%) from the rest of the world, and 6 with missing information. The primary respondents were 94% (N=159) physician investigators, 2% (N=3) research nurses, 2% (N=4) research coordinators, with the remainder as other or unspecified. 117 (68%) of the responses were from academic research centers, 27 (16%) from non-academic practice or network, 20 (12%) from community practice or health systems, and 7 (4%) other.

Challenges

A total of 90 sites provided information in the Action Survey on the greatest challenges their lung cancer clinical trials program faced from the pandemic (Figure 2). We evaluated the proportion of sites that considered each challenge to be moderate, significant, or critical. The most frequent institutional challenges (% moderate or greater) identified were fewer eligible patients (63%), protocol compliance (56%), and suspension of trials (54%, Figure 2). When asked which months the challenges were first apparent, March (60%), April (82%), and May (77%) of 2020 were the most frequent answers.

Critical institutional barriers in Europe (N=21 sites) were fewer eligible patients (81%), sponsors suspending or placing recruiting on hold (65%), and difficulty complying with protocols (62%). These were also critical in the North America (N=20), with fewer eligible patients (81%), sponsors suspending or placing recruiting on hold (75%), and difficulty complying with protocols (80%). Compared with Europe and North America, sites from Asia (N=20) reported institutional barriers less frequently, with the fewer eligible patients 40% (p=0.0475), sponsors suspending

or placing recruiting on hold 35% (p=0.0615), and difficulty complying with protocols 45% (p=0.0596). The most frequent institutional barriers from the Rest of the World fewer eligible patients (71%), difficulty complying with protocols (47%), and sponsors suspending or placing recruiting on hold (41%); Data on institutional barriers (N=8) from Latin America were too sparse for regional comparisons.

Overall 24% of sites reported disruptions from trial participants COVID-19 infection and 40% from exposure-related quarantine. Patient-specific challenges included access to trial site (49%), ability to travel (54%), and willingness to visit site (59%, Figure 2). Additionally, patient-specific concerns included fear of COVID-19 infection (83%), securing transportation (38%), travel restrictions (50%), and lab/radiology access (16%).

Patient willingness to visit the site was a consistent barrier reported across Europe, North America, and Asia. In North America patient ability to visit the site was seen as less of a barrier, though not significantly different (p=0.1366). Specifically, in Europe patients' willingness to visit the site (62%), patients' ability to visit the site (62%) were recognized as major barriers while in North America they were patients' willingness to visit the site (70%), patients' ability to visit the site (35%), in Asia patients' willingness to visit the site (65%), patients' ability to visit the site (50%) and finally in the Rest of the World patients' willingness to visit the site (59%), patients' ability to visit the site (76%). Data on patient specific barriers from Latin America were too sparse (N=8) to make regional comparisons. International travel restrictions were a barrier for patient participation in sites that recruited patients from other countries (22% of sites surveyed, Supplemental Data 4).

The impact on lung cancer trials was substantial, with more than 50% of sites experiencing moderate or greater impacts across Phase I to Phase III trials, most frequently impacting chemotherapy (52% of sites), immunotherapy (51% of sites) and targeted therapy trials (38% of

sites). As anticipated, trials with investigational agents that required infusion appear to be more effected than those with targeted therapies (Supplemental Data 4). We found little impact from COVID-19 vaccine trials, with 80% of sites enrolling no lung cancer patients and 80% reporting the vaccine trials had no impact on lung cancer trial enrollment. Only 33% of sites planned to discuss the choice of COVID-19 vaccine with lung cancer clinical trial patients.

Mitigation Strategies

Sites implemented mitigation strategies to battle the barriers to clinical trial enrollment they faced from the pandemic. Mitigation strategies that sites implemented, by the percent employing at least half, most, or all the time, were modified monitoring requirements (47%), telehealth visits (45%), phone visits (42%), and mail-order medications (25%, Figure 3). Some sites allowed laboratory (27%) and radiology (21%) tests at non-study facilities and a few implemented altered (10%) or electronic (11%) consent processes (Figure 3).

Telehealth (38%-50%) and phone visits (39%-50%) were among the top mitigation strategies in North America, Europe, and Asia. Mailed oral medications were more frequent in Europe compared to Asia or North America, though this was not statistically significant (39% vs. 25% / 17%, p-value=0.47). In the North America modified monitoring requirement were more frequent than in Europe or Asia (76% vs. 39% / 24%, p-value=0.0171). Sites in Asia were significantly more likely to use electronic consent (28% vs. 6% / 0%, p-value=0.0182) and may have allowed delayed or skipped visits more frequently (33% vs. 17% / 11%, p-value=0.27) than Europe or North America. Percentages of sites implementing mitigation strategies from Latin America and the Rest of the World were generally similar to global percentages, although not compared statistically.

We asked sites to identify the most effective mitigation strategies employed to fight the impact of the pandemic on clinical trials. Eighty percent of sites who employed telehealth visits reported it

was an effective strategy, 85% reported remote collection of patient-reported symptoms was effective, and 85% reported off-site diagnostic or monitoring procedures (clinical evaluations, blood draws, imaging) was an effective strategy (Figure 4). Additionally 89% felt remote consenting and 81% felt electronic signatures were effective when utilized. Delayed assessments (81%), institutional review board (IRB) changes (89%), and the use of liquid biopsy in lieu of tissue biopsy (83%) were also considered effective when implemented. We also asked sites if they would like to continue any of the adjustments to the lung cancer clinical trial processes after the pandemic. Telehealth visits (52%) were considered the most frequent adjustment sites would like to continue, followed by remote monitoring (49%), electronic signature (47%), and remote patient reported symptom collection (35%).

Discussion

The IASLC international survey found significant declines in enrollment in lung cancer clinical trials across the world in the beginning of the COVID-19 pandemic. The magnitude of the declines varied across the globe with 13% decline in North America, 35% decline in Europe, 10% decline in Asia, and an apparent 88% decline in Latin America, although the sample size was smaller. Although the pandemic worsened throughout 2020, most enrollment declines were in the early months of the pandemic with few differences in enrollment in the last three months of 2020, likely due to mitigation strategies.

The challenges at the institutional level centered on the ability to keep sites open, keep staff available, and keep staff and patients safe. This affected the delivery of standard care for patients with lung cancer.[21,23-27] Lung cancer patients had decreased utilization of outpatient services, hospital admissions, and surgical procedures during the first months of the pandemic.[27] A large allocation of health resources towards caring for patients sick with COVID-19 made it more difficult for many institutions to maintain standard care.[27] These strains on the

system made allocation of time and resources for rigorous clinical trial monitoring, and ultimately, recruiting new patients to clinical trials less feasible. Previously described deficits in clinical trial screening processes for eligible patients were likely magnified at some sites due to the reported staffing issues in this study.[28] An overall reduction in screening and diagnoses may partially explain why sites in this study reported fewer identified patients who may have been trial eligible. We found no evidence that COVID-19 vaccine trials interfered with lung cancer trials, and two-thirds of respondents did not plan to discuss vaccination with lung cancer patients. Ensuring access to COVID-19 vaccination for patients and providers involved with lung cancer trials could provide additional mitigation against some of the barriers identified.

Patient level challenges and concerns included COVID-19 infection or quarantine, fear of exposure to SARS-CoV-2, transportation to sites, and willingness to travel. While some of these issues are specific to a time of crisis, transportation and the time it takes to fulfill study visits is a well-established barrier to optimal trial enrollment.[29] Even before the pandemic, efforts have been underway to provide equitable access to lung cancer clinical trials.[30-32] Less than 5% of adults with cancer currently participate in clinical trials across the world, with noted disparities in enrollment by demographic factors.[33]

Across the world, the impact of the pandemic on healthcare delivery was influenced by differences in hospital capacity, ICU capacity, national public health policies, and patient-level factors such as transportation modality and availability.[34,35] However, we found that many of the challenges faced from the COVID-19 pandemic were similar for different geographic regions. Although the magnitude of these challenges varied somewhat by region, the barriers we have discussed were typically faced by 40% or more of sites in each region. We found some mitigation strategies were employed in similar proportions across regions such as telehealth and phone visits, while the employment of others like modified monitoring requirements and electronic consent were variable by region. Observed differences could reflect variability in the

challenges faced, opportunities available based on specific regulatory requirements, or could be an artifact of regional response patterns to our survey. Overall, these data suggest that we face many of the same issues across the world, some solutions may be broadly applicable across regions, and others may benefit from tailoring to the population and setting.

The mitigation strategies that sites identified as most effective in reducing the impact of the COVID-19 pandemic were focused on greater flexibility. Sites used technology to provide more flexibility in "place" by implementing telehealth visits, remote monitoring, and remote diagnostics. Although not novel strategies per se, these were not frequently implemented before the pandemic. Telehealth was a top migration strategy, in both utilization and perceived effectiveness, across global regions. Historically, symptoms and toxicity data have been collected at in-person visits by physicians and research staff. Shifting interactions to an electronic format became a need that could be continued in places where it has been successfully implemented. The capacity to obtain consent remotely also appeared effective where implemented. Telehealth was adopted early in the COVID-19 crisis, and has been strongly supported by the European Society for Medical Oncology recommendations for the management of lung cancer and the American Society for Clinical Oncology, among others.[36,37] There is growing consensus across medical disciplines that the increased utilization of telehealth is here to stay.[38] However, reimbursement barriers that impede clinicians' ability to conduct Telehealth are still in place in some countries, and should be addressed at the policy level.

Collection of laboratory and imaging data was a major challenge met during the pandemic with loosening of regulations allowing for use of local laboratories and imaging centers. This strategy could be continued in future trials, including home collection of blood tests. Certification and

billing at remote sites are global issues that will require future attention. Re-assessment of the need for the extensive laboratory and imaging endpoints built into many trials may also be considered to improve trial feasibility.

Allowing mail-order medications was also identified as an effective strategy for oral therapies, which was employed most frequently at sites in Europe. This may explain why infusion-related trials were more affected as such trials require travel to the trial site. Additionally, mitigation strategies that provided more flexibility in "time", including delaying study visits and assessments, were seen as highly effective. These strategies leveraged modern technology to address barriers to healthcare delivery, highlighting the need for continual modernization of processes of care delivery. Electronic health records and standardized electronic treatment plans were used to reduce research staff time and reduce paper records. Digital health technology such as remote vital sign monitoring, EKG monitoring and pulse oximetry monitoring was used in some institutions. The pandemic era has highlighted the need to improve our utilization of technologic solutions to improve healthcare.

Agencies including the NCI Cancer Therapy Evaluation Program (CTEP), US Food and Drug Administration (FDA), The European Commission, the European Medicines Agency (EMA) and national Head of Medicines Agencies (HMA), among others, have provided continued guidance on the management of clinical trials during the pandemic.[39-41] Moving forward, the American Association for Cancer Research (AACR) has called for better use of technology to improve clinical trials across the cancer continuum and incorporate COVID-19 guidance beyond the current crisis.[22] The barriers and mitigation strategies we identified in this survey support this call. Moving forward, they suggest a greater role for the integration of electronic medical records and electronic data collection and an overall streamlining of cancer clinical trials.[22] Our survey illustrates that these approaches are consistent with the needs of lung cancer investigators and patients across the world.

Trial sponsors, trial sites, and regulatory bodies should consider employing trials with less collection of marginally important data, more flexibility in clinical trials (such as allowing for remote monitoring for late-phase trials), while maintaining the necessary scientific rigor that is a hallmark of clinical trials. Well-applied strategies could improve flexibility and maintain scientific rigor. Some changes may be appropriate globally while others may require tailoring to the region or country. The future of lung cancer advances continues to rely on good clinical trials and we should redouble our efforts to increase accrual both during and after the pandemic.

Limitations

This study achieved many of the goals determined at the onset, but has limitations. We were not able to attain complete information from every site requested, which led to missing data in the surveys. The amount of information requested from sites, differing global regulatory standards for providing data, and clinical challenges during the pandemic likely contributed to this limitation. The purposive sample scheme was used in favor of probabilistic sampling to allow more targeted recruitment of sites in under-represented areas, while not excluding any willing participants from providing potentially useful information. However, we attained valuable quantitative and qualitative information about the impact of the pandemic from many sites representing multiple countries. To our knowledge, this is the largest study of the impact of COVID-19 on lung cancer clinical trials.

Conclusion

The COVID-19 pandemic had a substantial impact on enrollment in lung cancer clinical trials across the world. Trial sites and regulatory bodies adapted with mitigation strategies largely aimed to provide more flexibility and leverage modern technology. Despite the acceleration of COVID-19 cases in the later months of 2020, enrollment numbers in lung cancer clinical trials started to rebound. A more flexible approach to clinical trials, removing unnecessary barriers

and leveraging technology, may improve enrollment and access to clinical trials, even beyond the COVID-19 pandemic.

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Figure Legends

Figure 1. A. The average enrollment in global clinical trials by month for 2019 (the year before the pandemic) and 2020 (the first year of the pandemic). The dotted line shows the monthly COVID-19 cases diagnosed globally for each month of 2020. B. Total numbers of patients enrolled in global clinical trials by month for 2019 (the year before the pandemic) and 2020 (the first year of the pandemic). C. Quarterly enrollment per site for 240 individual sites included in this study, compared between 2019 and 2020. D. Quarterly enrollment per site for 54 multiple sites included in this study, compared between 2019 and 2020.

Figure 2. Site reported challenges to enrollment in lung cancer clinical trials by perceived severity.

Figure 3. Site reported mitigation strategies to address challenges to enrollment in lung cancer clinical trials.

Figure 4. Mitigation strategies sites identified as the most effective.

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Supplemental Data 1: IASLC COVID-19 and Clinical Trials Steering Committee (PDF)

Supplemental Data 2: Survey (PDF)

Supplemental Data 3. Quarterly enrollment patterns for each region varied based on the numbers of trials available.

Supplemental Data 4. Impact of COVID-19 on Trials by Phase, Trial Type, and Trans-Border Issues

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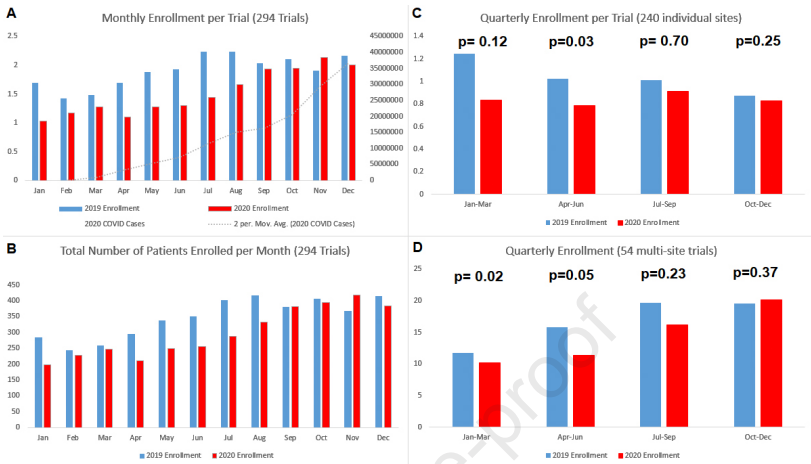

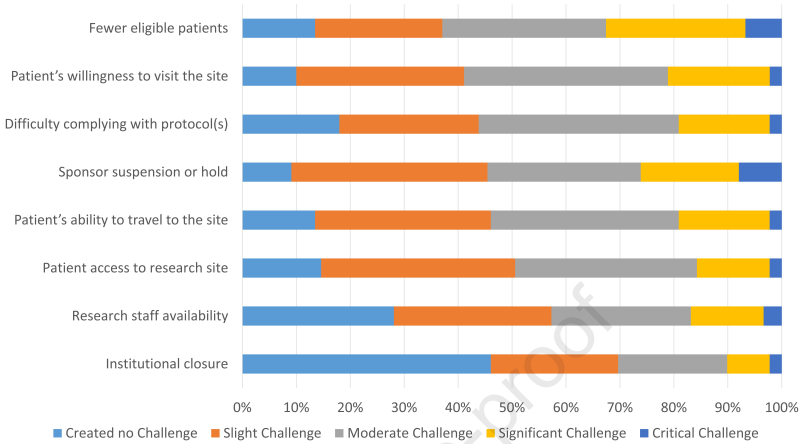

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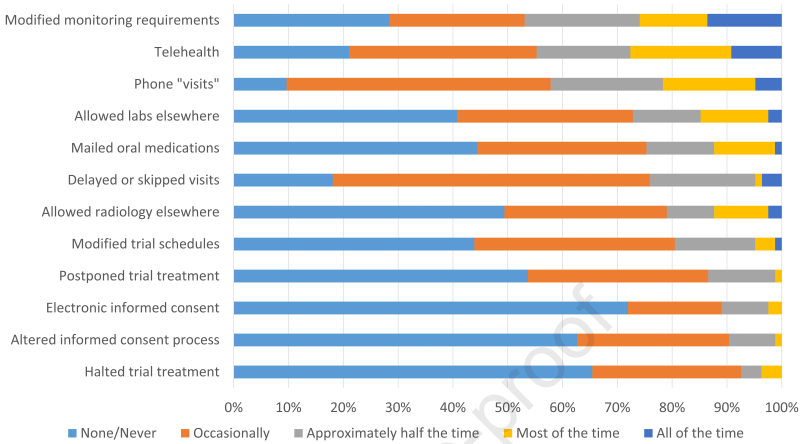

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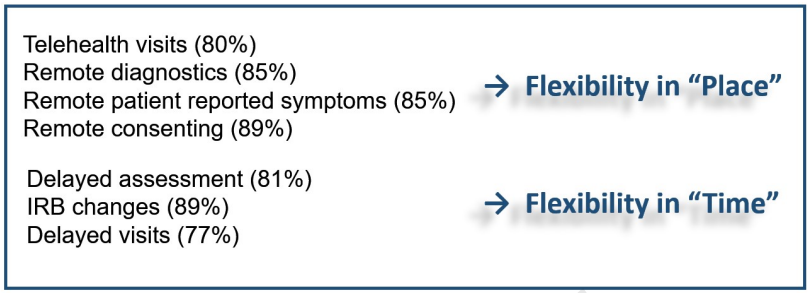

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