Received: 23 June 2020 | Accepted: 7 October 2020 | Published on: 27 January 2021

DOI: 10.1111/ajco.13510

ORIGINAL ARTICLE

WILEY

Overcoming the impact of the COVID-19 pandemic on oncology early phase trials and drug development in Asia—Experiences and perspectives of the Asian Oncology Early Phase 1 Consortium

Toshio Shimizu[1] | Dong-Wan Kim[2] | Herbert H. Loong[3,4] | Chia-Chi Lin[5] | Matthew CH Ng[6] | Noboru Yamamoto[1] | Brigette Ma[3,4] | Daniel SW Tan[6]

[1] Early Phase 1 Drug Development Service, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

[2] Department of Internal Medicine, Clinical Trials Center, Seoul National University Hospital, Seoul, South Korea

[3] Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Hong Kong SAR, China

[4] Department of Clinical Oncology, State Key Laboratory of Translational Oncology, The Chinese University of Hong Kong, Hong Kong SAR, China

[5] Phase 1 Center, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

[6] Experimental Cancer Therapeutics Unit, Division of Medical Oncology, National Cancer Centre Singapore, Singapore

Correspondence
Toshio Shimizu, M.D., PhD., Early Phase 1 Drug Development Service, Department of Experimental Therapeutics, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-City, Tokyo 1040045, Japan.
Email: tosshimi@ncc.go.jp

Abstract

Aim: The significance and prioritization of early phase oncology trial continuation during a global pandemic is unknown. This study reported the outcomes, multiple challenges, and broad recommendations associated with the impact of the novel coronavirus disease 2019 (COVID-19) on oncology early phase 1 trials—and on drug development in Asia—based on the experiences and perspectives of Asian oncology phase 1 centers.

Methods: Between March and April 2020 during the initial period of outbreak, the impact of COVID-19 across oncology phase 1 sites in five Asian countries—China (Hong Kong), Japan, South Korea, Taiwan, and Singapore—was retrospectively analyzed.

Results: There was no trial termination or treatment discontinuation in all five countries. Although the most common impact was new patient enrollment being placed on hold, which was based on pharmaceutical sponsors' decision-making, the situation varied per site. Most sites had no restrictions in place that would limit their ability to fully comply with the requirements of conducting the early phase studies. The number of protocol deviations during the pandemic was largely dependent on domestic transportation status during the outbreak rather than the ability of the clinical trial centers.

Conclusion: Determining the risk to benefits ratio of patients with cancer who are enrolled in early phase 1 clinical trials under the unusual circumstances of a global

pandemic is important. Specific guidance or guidelines on the conduct of early phase 1 clinical trials during public health emergencies that are based on the recent lessons learned is urgently required.

KEYWORDS
Asia, clinical trial, COVID-19, pandemic, phase 1

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been rapidly spreading worldwide and was first identified as a public health emergency of major international concern and later declared a pandemic by the World Health Organization. December 2019 witnessed an outbreak of acute respiratory disease caused by COVID-19, and it has now spread to more than 180 countries. The causative virus was named severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), and it is phylogenetically similar to SARS-CoV-3, which caused the SARS pandemic in 2002.

The challenges due to the impact of the COVID-19 pandemic and the unprecedented public health crisis are severely affecting oncology clinical trials and early phase drug development. There has been a decrease in the numbers of new trial initiations, site activations, and patient enrollments, as well as negative impacts upon on-site monitoring, protocol compliance/deviations, and safety assurance for patients with cancer participating in early phase 1 clinical trials. Further, clinical trials may be affected by the spread of COVID-19 owing to the implementation of extreme measures, such as local hospital and patient treatment facility closures, travel restrictions, and delays in the shipment of study treatment and trial supplies. This has been reported in many affected countries, including those in Asia. Currently, all pharmaceutical sponsors are supporting the safety and well-being of clinical trial patients, and investigator sites such as communities, hospitals, and government agencies are striving to regain control over public health and taking proactive steps to ensure regulatory compliance and the scientific integrity of trial data.[1–8]

Similar to those in the United States and the European Union, all early phase 1 oncology clinical trial sites in Asia are currently facing the challenges raised by this unprecedented event. The Asian Early Phase 1 Oncology Drug Development Consortium (AsiaOne) was formed under an agreement concluded on September 14, 2017 by the early phase new drug development institutions (key oncology phase 1 centers) in China (Hong Kong), Japan, South Korea, Singapore, and Taiwan. AsiaOne formed the Asian Oncology Early Phase 1 Consortium, which conducts international collaborative phase 1 clinical trials across Asia to determine what novel early phase oncology drugs will benefit the region.

AsiaOne sites have several common pandemic-related characteristics, including the quarantining of confirmed COVID-19 cases, universal imposition of face mask use, and dedicated local operation by clinical trial staff for the safety of both patients and staff through intensive cooperation and communication with pharmaceutical sponsors. These measures are based on past experiences with SARS and the 2015 Middle East respiratory syndrome coronavirus in Asia. This report describes the current situation of, and multiple challenges associated with, the impact of COVID-19 on oncology early phase 1 trials and drug development in Asia, through the experiences and perspectives of key oncology phase 1 centers in Asia.

2 | METHODS

Between March and April 2020, the impact of COVID-19 on oncology early phase trials was retrospectively analyzed across oncology phase 1 sites in five Asian countries: Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong Special Administrative Region (HKSAR; China); National Cancer Center Hospital (NCCH; Japan); Seoul National University Hospital (SNUH; Republic of Korea); National Cancer Centre Singapore (NCCS; Singapore); and National Taiwan University Hospital (NTUH; Taiwan).

Key measurements and data collection were focused on the impact of COVID-19 on the number of trials required for holding new patient enrollment or trial termination, number of trials delayed for new trial activation, number of institutional review board (IRB)-submitted phase 1 protocol deviations, and details concerning new patient enrollment being put on hold. Data were collected under cooperation with principal investigators, clinical trials offices, and IRBs across the noted oncology phase 1 sites.

3 | RESULTS

There was no phase 1 trial termination or treatment discontinuation in all five Asian countries. Most sites had no restrictions in place that would limit their ability to fully comply with the requirements needed to conduct the early phase studies. Although the most common impact was new patient enrollment being placed on hold, which was based on pharmaceutical sponsors' decision-making, the situation varied per site. Japan had most IRB-submitted phase 1 protocol deviations compared to other Asian countries. This was likely owing to the affected domestic transportation system, including the canceling of domestic flights during the state of emergency (from April 7–May 25, 2020; Tables 1 and 2).

TABLE 1 The impact of COVID-19 on phase 1 trials during the initial period of the pandemic across five phase 1 centers in Asia

	China (Hong Kong)	Japan	South Korea	Singapore	Taiwan
Numbers of IRB-submitted phase 1 protocol deviations [†]					
March 2020	0	83	1	21	0
April 2020	0	87	1	26	0
Number of trials for which new patient enrollment was held or trial termination [‡]					
March 2020	0	6	3	6	3
April 2020	1	10	5	19	4
Number of trials delayed for new trial activation [§]					
March 2020	0	1	0	1	0
April 2020	1	1	0	0	0
Number of treatment discontinuations for ongoing patients					
March 2020	0	0	0	0	0
April 2020	0	0	0	0	0

[†]These protocol deviations consisted of both execution of examinations and imaging procedures, and delay or shipment of planned treatments. For all deviations, the safety of patients was the priority to minimize the avoidable risks of COVID-19. The reason Japan had a large number of deviations compared to other countries was owing to domestic transportation issues including the cancellation of domestic flights under the state of emergency (from April 7 until May 25, 2020). Similarly, in Singapore, the majority of protocol deviations were due to travel restrictions imposed on overseas patients during the "circuit breaker" period from April 7 to June 1, 2020.
[‡]There was no trial termination in all five Asian countries. The numbers represent new patient enrollment in ongoing studies, which were placed on hold based on pharmaceutical sponsors' direction, or due to local measures implemented.
[§]Numbers of new site activations for new studies was placed on hold.

3.1 | Actions taken by Asian oncology phase 1 sites during the COVID-19 pandemic

3.1.1 | Hong Kong, HKSAR China

The first case of COVID-19 in Hong Kong was diagnosed on January 23, 2020—a 39-year-old male traveler from Mainland China. Despite a steady rise in confirmed cases over the past few months, most cases diagnosed in Hong Kong were either imported from foreign countries or transmitted through close contacts of people who had recently traveled to the country who were confirmed COVID-19 cases themselves. Several specific local clusters, without anyone having a travel history, have also been identified. Fortunately, owing to Hong Kong's prior experience with SARS in 2003 and the high vigilance regarding universal mask wearing, hand hygiene, and social distancing enforced in the region since mid-January, Hong Kong has managed to keep the number of confirmed COVID-19 cases under control to date. The implementation of progressively aggressive and decisive measures, including the closure of schools and universities after the Chinese New Year holidays in late January, advocating work from home for both the members of the civil service and employees of private enterprises, and the closure of various leisure facilities and a ban on public gatherings of over four persons since April 2020 have all contributed to successful containment. As of May 31, 2020, there are 1085 confirmed COVID-19 cases and four deaths in a densely populated city of over 7.5 million inhabitants in Hong Kong.

Throughout this period, there has been no significant effect on clinical oncology service provision within the territory in the public sector. Clinics and inpatient wards continue to function at full capacity. Although some surgical colleagues have reduced their elective non-oncology operation lists to conserve personal protective equipment (PPE), as well as reserving intensive care beds for possible patients with COVID-19, there have also been no changes in the staffing and labor allocation to clinical oncology services. The non-interruption of public transport services during this period and the small geographical footprint of Hong Kong facilitated continual in-person consultations, rather than the implementation of a telemedicine approach.

Oncology clinical trials that were actively recruiting patients before the onset of the COVID-19 pandemic are continuing without interruptions. During the pandemic, participants who had already consented to participate and even started participating in clinical trials were being cared for at the same intervals and frequencies as outlined earlier, and protocol deviations from scheduling issues have been kept to a minimum. New patient enrollment rate of phase 1 study during March/April 2020 had no change compared with that during March/April 2019 (ie, the number of enrolled patients in 2020 was same of that in 2019) at CUHK. In response to the Hong Kong Government's COVID-19 Responsiveness Plan and the Hong Kong Hospital Authority's "Emergency Response Level," which has banned all individuals, except patients themselves (and one accompanying family member), from visiting public hospitals, technically feasible clinical trial monitoring and site auditing have been performed remotely

TABLE 2 Details of new patient enrollment being placed on hold owing to COVID-19 across five phase 1 centers in Asia during the initial period of pandemic

	China (Hong Kong)	Japan	South Korea	Singapore	Taiwan
Impacted trials	**n = 1**	**n = 10**	**n = 5**	**n = 19**	**n = 4**
Sponsors' decision	1/1 (100%)	10/10 (100%)	5/5 (100%)	1/19 (5.2%)	4/4 (100%)
Site/institute policy	0/1 (0%)	0/10 (0%)	0/5 (0%)	18/19 (94.7%)	0/4 (0%)
Government statement	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)
Delay of study material shipment	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)
Other	0/1 (0%)	0/10 (0%)	0/5 (0%)	0/19 (0%)	0/4(0%)

wherever acceptable to the study sponsor and/or clinical research organization (CRO). Further, new studies scheduled to start in the coming months have had their site initiation visits performed remotely through teleconferencing facilities. This continued functioning of oncology clinical trial activities is very different from the approach adopted by the non-oncology healthy volunteers' phase 1 studies that have been postponed by our Phase 1 Clinical Trial Centre.

3.1.2 | Japan

In Japan, on April 7, 2020, the government declared a state of emergency in response to the rapidly increasing numbers of COVID-19 positive cases in major cities of the Tokyo metropolitan area and three surrounding prefectures (as well as Osaka, Hyogo, and Fukuoka); although, people cannot legally be forced to stay home or businesses be forced to close in the country. At the time of the enforcement of the state of emergency, Japan reported 4,257 COVID-19 positive cases and 81 COVID-19 deaths (as of May 31, 2020, 16 851 infected cases and 891 deaths).

Even in this situation, the oncology clinical trials, including early phase 1 trials, at the NCCH have been functioning virtually normally, except for several temporary limitations, such as site monitoring problems and protocol deviations for emergency and patient safety assurance. To prioritize patient safety, the site IRB and ethics committees defined a process to report protocol deviations, particularly those that might affect the safety of trial participants during the pandemic period. Further, the NCCH's principal investigators extensively communicated with pharmaceutical sponsors (to capture specific information in the form that explains the reasons for missing data—changes to study visit schedules, missed visits, etc.—and include the prefix COVID-19 to indicate relationships) according to the prevalent healthcare authority guidance on COVID-19 precautions and clinical trials. Regarding the non-availability of normal site monitoring, all the mechanisms and alternative functions that were in contact with pharmaceutical sponsors were utilized to ensure regulatory compliance and the scientific integrity of trial data. The NCCH uses a hybrid monitoring style that uses both remote monitoring and on-site monitoring approaches with restrictions on data review for ongoing trial patients (ie, through teleconferencing/videoconferencing); however, this can potentially affect the quality of study. The number of phase 1 trials for which the recruitment of new trial participants has been interrupted owing to the impact of COVID-19; in accordance with pharmaceutical sponsors' directions these have been gradually increasing since April 2020.

Concerning the domestic transportation infrastructure for patients with cancer in Japan during March and May 2020, a large reduction in the number of both domestic flights and bullet trains from all local cities to Tokyo impacted patients' visits to oncology clinical study sites in Tokyo; this was despite most public transportation services, including subways, railways, and buses being available without restriction. The patient enrollments rate was slightly impacted by the pandemic: the rate of early phase 1 trials, including first-in-human (FIH) phase 1 trials (which includes the entire process from obtaining study consent, the full screening process, and C1D1 dosing) increased by 35–60% during March–April 2020, compared to the rates for the same period in 2019. This increased enrollment rate in Japan was potentially caused by an immediate increase of slot allocations as some oncology phase 1 sites in both the United States and some European countries could not enroll new patients in multiregional phase 1 trials during the initial period of the pandemic.

Some noteworthy points are as follows: several first-patient doses for the study cohort level-1 were successfully administered immediately after study initiation in several global FIH phase 1 trials—jointly conducted by NCCH Japan and US/EU phase 1 sites—despite the pandemic situation; and research biopsies (ie, serial tumor biopsies for required phase 1 trial protocols and optional procedures) have been conducted by the interventional radiology department using a specific standard operation procedure to maximize patient safety assurance against the increased pandemic risk. Further, earlier experiences of other Asian sites (Hong Kong China, South Korea, Singapore, and Taiwan) significantly contributed to the exemplary operation of clinical trials in Japan.

3.1.3 | Republic of Korea

On May 31, 2020, the cumulative number of COVID-19 positive cases reached 11 468 and 270 deaths in the Republic of Korea. Based on the data available to date, the daily number of newly diagnosed patients peaked on February 29, 2020 at 909; however, this number has been decreasing gradually and reached less than 35 a day by early May 2020.

The government implemented preventive strategies, such as ensuring active polymerase chain reaction (PCR) testing of suspicious cases; social distancing, including the wearing of face masks; closing schools and implementing tele-education; canceling or delaying social events; and mandating self-isolation for two weeks in high-risk situations. The SNUH implemented a series of preventive measures as well. Currently, all SNUH visitors have a brief history taking, including details on fever, cough, throat pain, dyspnea, and body temperature measurement. All admitted patients should have a negative COVID-19 PCR result in tests conducted not earlier than 48 h before admission. Additionally, the SNUH has special wards and intensive care units (ICUs) dedicated to patients who tested positive for COVID-19.

With such preventive measures in place, the SNUH's oncology clinic and cancer clinical trials center are operating normally. The SNUH's subject visit schedules are well-maintained since domestic transportation facilities are working normally. The current daily number of trial participant visits is virtually the same as that of past year. However, COVID-19 has changed some aspects of clinical trials. To comply with the social distancing strategy, the teleconferencing platform is being used for site evaluation and/or initiation visits. The frequency of on-site monitoring has decreased and been replaced by remote monitoring through teleconferencing or phone calls. Some trials operated by global pharmaceutical companies have stopped recruiting new patients owing to global logistic issues. New patient enrollment rate of phase

1 study decreased by 63.5% during March/April 2020 compared with March/April 2019 period at SNUH. Further, the SNUH is carefully monitoring possible further effects of COVID-19 on clinical trials.

3.1.4 | Singapore

In Singapore, the first COVID-19 case was diagnosed on January 23, 2020 in a Chinese national from Wuhan who had traveled to Singapore three days earlier. The necessity of developing a multipronged strategy to address this emerging pandemic was identified, and a multi-ministry taskforce co-chaired by the Japanese Minister of Health and Minister of National Development was formed. The key principles of the strategy were the reduction of imported cases by implementing travel restrictions and ringfencing of returning travelers; also containment through social distancing, promotion of good handwashing practices, and use of PPE (masks), and implementation of rigorous contact tracing and quarantine practices. Anonymized profiles of individual cases were transparently and rapidly communicated to the public, along with evolving case definitions and adjustments to the extent and coverage of travel restrictions.

Once community spread was confirmed, risk assessment was raised to the Disease Outbreak Response System Condition Orange on February 7, 2020, which necessitated more stringent measures, including temperature screening at workplaces, cancellation of large-scale events, and progressive restrictions on sizes of social gatherings. These measures were calibrated in accordance with the community prevalence (from both imported and local cases) of COVID-19. From a medical support perspective, the National Centre of Infectious Disease spearheaded case screening, assessment, and isolation; further, all public- and private-sector institutions were engaged in disease mitigation, and an expanded pool of healthcare workers was mobilized to ensure the continuum of care required by patients with COVID-19, including community screening, intensive care, and management of the convalescent phase. As of May 31, 2020, Singapore has had 34 884 cases and 23 reported deaths.

At the NCCS, inpatient and outpatient medical oncology teams were segregated, which enabled the streamlining and continuation of specialist cancer services, albeit with some clinical workflow modifications. All patients and accompanying caregivers were instructed to wear surgical masks and complete a screening questionnaire on travel history and respiratory symptoms. A dedicated outpatient clinic and workflow was set up to assess patients with COVID-19 symptoms/suspicion. Among inpatients, patients with pneumonia or respiratory symptoms (cough, sore throat, runny nose, anosmia) with close contact or positive travel history were admitted to isolation wards; and they were transferred to general wards only after two negative COVID-19 PCR swabs.

From the phase 1 trial unit perspective, the NCCS encountered several major challenges. First, owing to the travel restriction in China and evolution of policy for stay-home notices, many patients who were on trials could no longer be observed in the usual clinic setting. Under these circumstances, open communication with trial sponsors, regulatory authorities, and the IRB enabled solutions based on adherence to ongoing clinical and safety assessments (both local and through virtual consultations) and the continued supply of the investigational product, for example, delivery to overseas patients. Although most patients could consult a local oncologist for assistance in physical follow-up assessments, there were instances where stringent restrictions in movement curtailed access to medical services, which made remote consultations particularly critical. Second, owing to the fluidity of the public health emergency, uncertainty in labor exigencies, and evolution of knowledge on COVID-19 transmission, research-related activities were temporarily halted. To optimize resource utilization, clinical trials were triaged, and factors such as the level of evidence of clinical benefit, trial-related evaluations that may contravene institutional containment measures, and resource availability were considered. Finally, with additional national measures that further restricted travel and reduced overall workforce on April 7, 2020, the enrolment of new patients was put on hold, and an evaluation of the risk–benefit ratio for each clinical and protocol-specified visit was made for ongoing patients to balance the need for continued treatment, patient safety, and risk of COVID-19 transmission. New patient recruitment of phase 1 study during March/April in 2020 was 18% of 2019 (i.e. an 82% reduction in patient recruitment) at NCCS. In parallel, efforts are ongoing to increase and broaden COVID-19 testing to screen for asymptomatic carriers, as well as leveraging the use of digital tools, for example, the TraceTogether smartphone app, to facilitate contact tracing.

3.1.5 | Taiwan

The Taiwanese government's efforts to contain the global COVID-19 pandemic are based on its experience with the 2003 SARS epidemic. On January 20, 2020, the Taiwan Centers for Disease Control officially activated the Central Epidemic Command Center—a response mechanism that enables rapid actions during public health crises—for COVID-19, with the Minister of Health and Welfare as the designated commander. As of May 31, 2020, Taiwan reported 442 COVID-19 positive cases and seven deaths in a population of 23,000,000. The NTUH implemented several preventive measures, including obligatory travel, occupation, contact, and cluster history taking and symptom questionnaires for every patient; mandatory surgical mask use by every patient and companion; and dedicated inpatient services and ICUs for patients with COVID-19. Currently, NTUH does not universally screen all its patients. It screens only those with fever, cough, dyspnea, rhinorrhea, diarrhea, and dysgeusia at the emergency room or a dedicated COVID-19 screening clinic using in-house PCR. New patient enrollment rate of phase 1 study during March/April 2020 decreased by 42% compared with that during March/April 2019 at NTUH. To date, the COVID-19 situation has not significantly affected the oncology phase I trials conducted at NTUH. Site initiation/closeout, patient visits, investigational agent administration, trial-specific procedures, and on-site monitoring/auditing/inspection take place as usual, with the latter being conducted at the discretion of relevant CROs/sponsors/regulatory authorities.

4 | DISCUSSION

As the repercussions of the COVID-19 pandemic are increasing worldwide and its effects are becoming increasingly relevant to the oncology clinical trials being conducted in the United States and Europe, oncology early phase 1 sites in Asia experienced various limitations and hurdles. Concerning practical considerations of the impact on oncology early phase 1 trials, diverse problems and challenges were considered, including national policies, patient referrals, leeway for pharmaceutical sponsors in terms of protocol deviations, activation of new studies, approval timelines, and issues with logistics. Particularly, logistics issues include shipment delays, concerning both inbound items—study drugs and laboratory kits—and outbound items—laboratory specimens and other associated biomaterials. This is probably the result of a significant global reduction in commercial aviation. Clinical trial sites shall be closely monitoring this situation and may elect to schedule research participants' follow-up visits to dates and times that are more convenient in arranging subsequent shipping arrangements. Holding continuous discussions with specific study sponsors to check the feasibility of performing some of the central laboratory biochemical tests in-house during this exceptional period is also important.

To our knowledge, this investigation across five Asian oncology early phase 1 sites is the first report of the impact of COVID-19 on oncology early phase trials during the initial period of pandemic and the multiple challenges faced by sites across the countries. During the initial period of the COVID-19 outbreak, a vast majority of both pharmaceutical companies and clinical trial sites did not have enough know-how and metrics for conducting both appropriate clinical research operations and standard enrollment metrics. Uncertainties about the investigational new drugs supply chain, reallocation of medical resources in clinical trial sites, and restrictions of study site monitoring and patient travel raised critical initial challenges about the short- and medium-term implications for clinical trial sites and pharmaceutical sponsors. Since we especially focused on the impact of the COVID-19 pandemic on oncology phase 1 trials during the initial period of COVID-19 outbreak, March and April 2020 were selected as the study period for our investigation.

It is important to point out several limitations of this study. In Korea, the first wave of the COVID-19 pandemic was almost controlled by March 2020, while in both Japan and Singapore, the disease did not surface until early April 2020. In Singapore, the 2020 Singapore circuit breaker (lockdown) measures were introduced by the government of Singapore during April 7, 2020 (2020-04-07)–June 1, 2020. In Japan, on April 7, 2020, the government announced a one-month state of emergency for Tokyo and the prefectures of Kanagawa, Saitama, Chiba, Osaka, Hyogo, and Fukuoka. On April 16, 2020, the declaration was extended to the rest of the country for an indefinite period. The state of emergency was lifted in several prefectures during May, extending to the whole country by May 25, 2020. According to these differing pandemic backgrounds and variable timing of the peaks, impact on clinical trials in these countries is not strictly comparable and we consider this is one limitation of our study.

A recent survey in Korea to investigate the impact on major milestones of clinical trials revealed that only 9% of FPI (first patient in) of clinical trials was affected as a specific milestone during February/March 2020 in Korea.[9] In terms of new patient enrollment rate during COVID-19 outbreak, a recent prospectively tracked study at the academic cancer center in the United States also showed the new patient enrollments number of medical oncology interventional studies fell dramatically by 42.0% between March and May 2020, compared with the period of January 2018 to February 2020, before beginning to recover in June 2020. The enactment of COVID-19-related policies at several academic cancer centers in the United States also resulted in a statistically significant reduction in the monthly infusion of investigational agents, a collection of biopsies for research purposes, and blood collection for research purposes.[10,11] In our study, the difference of patient enrollment rates during the same period (March/April) between 2020 and 2019 across all five sites was investigated (-82%~+60%) but these percentages tend to be influenced by various kinds of elements and causes.

Generally, most sites had no restrictions that limited their ability to fully comply with the requirements in place to conduct early phase studies. Hong Kong (China), South Korea, and Taiwan sites mostly did not have any protocol deviations, including visit delays, missing visits, and an inability to perform scheduled laboratory/radiographic tests or medications. Japan had more deviations compared to other Asian countries owing to their domestic transportation issues, including the canceling of domestic flights from April 7 to May 25, 2020. It seems that the number of protocol deviations was largely dependent on domestic transportation status during the outbreak rather than the ability of clinical trial centers. It is also important to consider that this experience across the five Asian oncology phase 1 centers might not reflect the situation at all cancer centers around the world, since backgrounds, policies, and resources differ by clinical trial sites and countries.

All efforts to minimize the impact of COVID-19 on phase 1 trial integrity and document the reasons for protocol deviations are vital. Robust efforts are expected on the part of research sponsors, investigators, and IRBs in maintaining trial participant safety and study data integrity, and such efforts should be documented. Protocol modifications may be required on a case-by-case basis, which includes unavoidable protocol deviations owing to COVID-19 infection and/or control measures. To initiate clinical trial sites or resume enrollment if a hold was in place, established requirements to continue recruitment of new patients into ongoing studies as an approach to oncology early phase 1 trials during pandemic will be required for all of the described conditions to be met (Table 3).

Finally, specific guidelines on the conduct of early phase 1 clinical trials during public health emergencies that are based on the recent lessons learned are strongly advocated in the near future. Although the significance and prioritization of early phase oncology trials continuation during a global pandemic is known, determining the risk to benefits ratio of patients with cancer who are enrolled in early phase 1 clinical trials under the unusual circumstances of a global pandemic is critical.

TABLE 3 Approach to oncology early phase 1 trials during the global pandemic and established requirements to continue recruitment of new patients into ongoing studies

Assess impact to local health system	• Establish population prevalence • Risk to patients • Risk to healthcare workers • Impact on local resources (systems level) • May require triaging of trials (e.g., if potentially life-saving)
Stakeholder engagement	Close communication with industry, sponsors, ethics, and health authorities
Site capability during pandemic	Site has no restrictions in place that would limit ability to fully comply with the requirements of the conduct of the study. In particular, this would include site capability for participants enrolled to have all study-mandated procedures performed on-site including physical exams, tumor assessments, adverse event assessments, processing of biomarker and pharmacokinetic materials, as well as laboratory assessment and administration of trial product
Safely monitoring for the conducting trial activities	• Remote access to electronic medical records • Tele-communication/video-communication across local study coordinator and monitors of sponsors especially in the timing at eligibility criteria check for new patient enrolment, occurrence of severe adverse events, etc.
Patient communication	• Explain local situation to patients and provide regular updates • Provide open and transparent communication channels to reassure patients • Assess and discuss risk–benefit ratio of continued trial participation/alternatives
Manpower preservation	• Ensuring safety of medical and trial staff • Trial coordinators as "essential" workers • Re-organization of specialty services (depending on standalone cancer center vs part of internal medicine; eg, deployment to support pandemic response
Containment (public health measures)	• Minimize travel/non-essential visits • Deferment of trial-related procedures unrelated to patient safety • Halting of new patient enrolment
Remote visits (for patients)	• Tele-consultation/video-consultation • Drug delivery to patients (local and overseas) • Employ local laboratory services • Liaise with local physicians (where feasible)
Risk management	• Pre-visit check in (by trial team) • Screening questionnaire of travel and contact history • Technology enabled contact tracing • Mandatory wearing of surgical masks • Prospective COVID-19 screening in patients
Guidance/policy	• Guidance/policy in place that describes preventive measures against pandemic and required screening or clearances for safe participant visits to clinical trial sites. • Guidance/policy in place that describes the care for participants exposed to or infected with pathogen, after enrolment
Benefits to participants	Determine that the benefits to the participant of enrolling in the clinical trial exceed the risks of trial participation in the unusual circumstances of pandemic

ACKNOWLEDGEMENTS

We thank Ms. Harumi Maruno, Ms. Miki Ito, Ms. Yoshiko Kanazu and Ms. Nobuko Ushirozawa at Clinical Trials Office, NCCH Japan, for data collection support.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the conception and design of the work; acquisition, analysis, and interpretation of data; drafting the work and revising it critically for important intellectual content; and provided approval of the final version to be published.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Toshio Shimizu https://orcid.org/0000-0001-6632-0638
Matthew CH Ng https://orcid.org/0000-0003-3170-4126

REFERENCES

1. U.S. Food & Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 public health emergency.

Guidance for industry, investigators, and institutional review boards. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency Accessed April 16, 2020.
2. European Medicines Agency. EMA guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf#search=%27EMA,guidance,clinical,trial,COVID19%27. Version 3.0. Accessed April 28, 2020.
3. Tan AC, Ashley DM, Khasraw M. Adapting to a pandemic—conducting oncology trials during the SARS-CoV-2 pandemic. *Clin Cancer Res*. 2020. https://doi.org/10.1158/1078-0432.CCR-20-1364.
4. Tarantino P, Trapani D, Curigliano G. Conducting phase 1 cancer clinical trials during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease pandemic. *Eur J Cancer*. 2020;132:8-10.
5. Hollander JE, Carr BG. Virtually perfect? Telemedicine for COVID-19. *N Engl J Med*. 2020. https://doi.org/10.1056/NEJMp2003539NEJMp.2003539.
6. Cortiula F, Pettke A, Helleday T, et al. Managing COVID-19 in the oncology clinic and avoiding the distraction effect. *Ann Oncol*. 2020;31:553-555.
7. Ngoi N, Lim J, Jeyasekharan AD, et al. A segregated-team model to maintain cancer care during the COVID-19 outbreak at an academic center in Singapore. *Ann Oncol*. 2020. https://doi.org/10.1016/j.annonc.2020.03.306.
8. Segelov E, Prenen H, Toh HC, et al. Impact of the COVID-19 epidemic on a Pan-Asian academic oncology clinical trial. *JCO Glob Oncol*. 2020;6:585-588.
9. Jeon JuYeun, Kim Hyeikyoung, Yu KyungSang. The impact of COVID-19 on the conduct of clinical trials for medical products in Korea. *J Korean Med Sci*. 2020;35(36):e329. 14.
10. Tolaney SM, Lydon CA, Li T, et al. The impact of COVID-19 on clinical trial execution at the dana-farber cancer institute. *J Natl Cancer Inst*. 2020:djaa144. Sep 22.
11. Waterhouse DM, Harvey RD, Hurley P, et al. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology Survey. *JCO Oncol Pract*. 2020;16(7):417-421.

AUTHOR BIOGRAPHIES

Toshio Shimizu has a consultancy/advisory role for Takeda Oncology, and received research funding to his institution (outside the submitted work) from Novartis, Eli Lilly, AbbVie, Pfizer, AstraZeneca, Eisai, Millenium-Takeda, Bristol-Myers Squibb, Incyte, Astellas Pharma, Symbio Pharmaceuticals, 3D-Medicine, Chordia Therapeutics, Five Prime, PharmaMar, and Daiichi Sankyo. He acts as a Scientific Committee Member for Phase 1 Trials in Hong Kong under the Consortium on Harmonization of Institutional Requirements for Clinical Research, Hong Kong, HKSAR China.

Dong-Wan Kim received research funding to his institution (outside the submitted work) from Alpha Biopharma, Astrazeneca/Medimmune, Boehringer Ingelheim, Hanmi, Janssen, Merus, Mirati Therapeutics, MSD, Novartis, ONO Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan. He received travel and accommodation support for advisory board meeting attendance from Amgen and Daiichi Sankyo.

Herbert. H. Loong has consultancy/advisory roles for Boehringer Ingelheim, Celgene, Eli Lilly, Illumina, Novartis, Merck Sereno, and Takeda. He has received honorarium for speakers' bureau for AbbVie, Bayer, Eisai, Eli Lilly, Guardant Health, and Novartis. He has received research funding to his institution from MSD, Mundipharma, and Novartis.

Chia-Chi Lin has consultancy/advisory roles for Blueprint Medicines, Daiichi Sankyo, Novartis, and Takeda; received honorarium (outside the submitted work) from Bristol-Myers Squibb, Daiichi Sankyo, Novartis, and Roche; and received travel grants from BeiGene and Eli Lilly.

Matthew CH Ng has consultancy/advisory roles for MSD, BMS, Novartis, and ASLAN. He also received honorarium for speakers' bureau for Eli Lilly, MSD, and Taiho, and received research funding from ASLAN.

Noboru Yamamoto has consultancy/advisory roles for Eisai, Takeda, Otsuka, Boehringer Ingelheim, Cimic, and Chugai; received research funding to his institution (outside the submitted work) from Astellas, Chugai, Eisai, Taiho, BMS, Pfizer, Novartis, Eli Lilly, AbbVie, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO Pharmaceutical, Janssen Pharma, MSD, MERCK, GSK, and Sumitomo Dainippon; and received honoraria in a speakers bureau from BMS, Pfizer, AstraZeneca, Eli Lilly, ONO Pharmaceutical, Chugai, and Sysmex.

Brigette Ma has consultancy/advisory roles for Novartis and T-biologics; received research funding to her institution (outside the submitted work) from Novartis and Boehringer Ingelheim; received speaker honoraria from MSD, BMS, and Roche; and received travel support for advisory board meeting attendance from Taiho and Merck Serono.

Daniel SW Tan has consultancy/advisory roles for Novartis, Merck, Loxo Oncology, AstraZeneca, Roche, and Pfizer; received research funding to his institution (outside the submitted work) from Novartis, GlaxoSmithKline, and AstraZeneca; and received honoraria from Bristol-Myers Squibb, Takeda Pharmaceuticals, Novartis, Roche. and Pfizer.

How to cite this article: Shimizu T, Kim D-W, Loong HH, et al. Overcoming the impact of the COVID-19 pandemic on oncology early phase trials and drug development in Asia—Experiences and perspectives of the Asian Oncology Early Phase 1 Consortium. *Asia-Pac J Clin Oncol*. 2021;17:388–395. https://doi.org/10.1111/ajco.13510