The impact of COVID-19 on clinical trials in the Asia-Pacific region and future implications

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Research Article

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The impact of COVID-19 on clinical trials in the Asia-Pacific region and future implications

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Abstract: The COVID-19 pandemic has affected the conduct of clinical trials in an unparalleled manner due to multiple levels of restrictions imposed to control the spread of SARS-CoV2. These restrictions have presented major challenges for clinicians, sponsors, contract research organizations and patients participating in ongoing clinical trials and have necessitated alternative solutions to ensure study and patient care continuity. In this review, we assessed the impact of the pandemic on key metrics of the commencement and continuation of clinical trials in the Asia-Pacific region and the efforts made to mitigate these challenges. Overall, newly initiated studies in 2020, outside of those directly related to COVID-19, were reduced. Access to sites and recruitment were also impacted significantly although recovery has begun in the latter half of 2020. Clinical trials consist of complex workflows across study procedures and site-patient engagements. Based on clinician and industry surveys, the impact of COVID-19 may drive an increase in interest and adoption of virtual, digital technologies and tools to help alleviate the numerous challenges for

clinical trial stakeholders. We discuss these new approaches and debate their readiness and appropriateness for widespread use. With ongoing acceleration of the pandemic and the maturation of technology, we expect increasing near-term adoption of virtual and digital methodologies in clinical trials. As a silver lining of the pandemic, these approaches may make studies more patient centric, improve clinical trial efficiency and enhance the experience and care of the patients enrolled on trials.

Keywords: Asia-Pacific; clinical trials; COVID-19; drug development; SARS-CoV-2; virtual trials

Background

COVID-19 has continued to precipitate unprecedented health and economic consequences in 2020. With the various control measures of movement restrictions, travel restrictions and lockdowns, the conduct of clinical trials has not been spared [1]. Site closures have affected not only patients, but also research staff from industry and contract research organizations (CROs) alike. In addition, site resources have been adapted to follow social distancing measures and also diverted away from research to the day-to-day care of COVID-19 patients. The transformation of clinical drug development has long been touted to reign in the astronomical and escalating costs of bringing drugs to market [2]. Consequently, there is an urgent need to improve the efficiency of clinical trial conduct with strategies aimed towards more remote and patient centric models [3,4]. A silver lining to the current pandemic may be an accelerated push to adopt these alternative models or systems [5]. In this review, we highlight the magnitude of impact on clinical trials in the Asia-Pacific region. Furthermore, we discuss adaptive changes undertaken to ensure continuity of studies, the challenges in implementing these changes and the long-term outlook for such measures to ensure studies are more robust and efficient. As the pandemic continues to wax and wane with second and later waves, it is becoming clear that temporary measures may be more permanent, driving long-lasting changes to the clinical trial ecosystem.

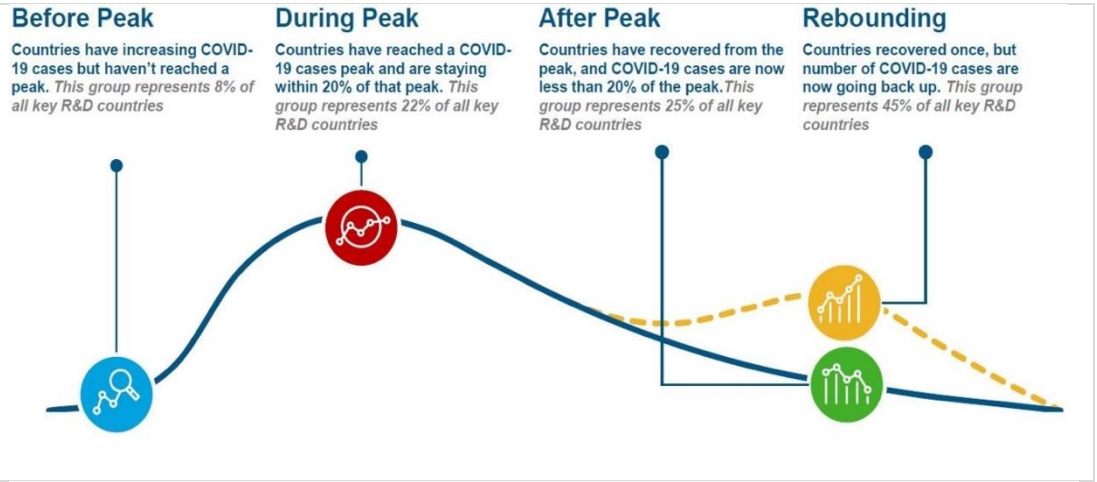
Main Text

Overview of data sources and methodology

Publicly available datasets were searched, including epidemiological data from academic institutions such as Johns Hopkins University and government agencies [6]. Key stakeholder insights were obtained from interviews conducted by IQVIA with market participants and industry executives in each of the Southeast Asia (SEA) markets. Additionally, an online survey of healthcare providers (HCP; n=350) from both public and private sectors across SEA markets on the impact of the COVID-19 pandemic on the conduct of clinical trials was performed. Insights into the management of clinical trials in the pandemic and the expected impact for the future were also obtained from an IQVIA conducted survey of Principal Investigators (n=100) across Europe and the United States. We accessed and summarized IQVIA proprietary data from February 2020, evaluating the number of ongoing clinical trials according to region, country and disease area. Data on patient recruitment were obtained from analyses conducted by Medidata throughout the course of the pandemic. Data on clinical trial startup was accessed from Trialtrove in September 2020 [7]. Finally, a single-centre case study on the impact of the COVID-19 pandemic on clinical trial enrolment and conduct was conducted using data from the Experimental Cancer Therapeutics Unit (ECRU), Division of Medical Oncology, National Cancer Centre Singapore (NCCS).

Dynamic phases during an evolving COVID-19 pandemic

A



B

Regions	Before Peak	During Peak	After Peak	Rebounding
APAC	India		China New Zealand Taiwan **South Korea**	Australia Japan
EMEA: Europe		Bulgaria Poland Romania Ukraine Russia	Italy Spain **Estonia**	**Belgium** **UK** **Denmark** Austria **Netherlands** Croatia **Germany** Slovakia **France** Czechia **Hungary** Lithuania
EMEA: Middle East Africa		**South Africa**	Turkey	Serbia Israel
LATAM	Argentina Brazil	Mexico		
US/CAN		United States	Canada	

Figure 1: Different stages of the COVID-19 pandemic (A) and selected countries categorized by stage (B) as of August 2020. Countries were categorized according to the IQVIA Institute Country Categorization from Johns Hopkins University publicly available data as of August 2020.

As the COVID-19 pandemic spread throughout the world, many countries progressed through different stages as illustrated in Figure 1. With countries progressing through stages at varying rates, there will be no immediate end to the pandemic in the medium-term. Although in some countries, vaccines are now completing the regulatory process and vaccinations have commenced

in others, it will still take time for widespread use to occur due to supply chain challenges and the logistics of vaccinating large populations. The resurgence of cases in countries such as Australia and South Korea, that had previously begun to recover in terms of clinical trial activity, is particularly pertinent. Second and third waves of COVID-19 cases and the subsequent reintroduction of localized restrictions may continue to limit further recovery in those selected regions. These challenges spark debate on the need to safeguard new clinical trials from future pandemics.

A survey of healthcare providers on the impact of COVID-19 on their clinical practice

We undertook a survey of HCPs from both public and private sectors in SEA to better understand the impact of the pandemic on their local healthcare system overall, a lead indicator to the successful running of clinical trials (Figure 2) [8]. Of 350 HCP surveyed, two out of three hospital doctors had experienced a >60% decrease in outpatient patient visits. In addition, 50% of responders expected a time period of 4 to 6 months before normal patient loads resumed from the current decrease in total patient visits. In order to manage patients more safely and reduce the risk of infection, ~25% of doctors had also doubled their standard prescription duration to reduce patient visits. With such decreases in the overall utilization of the healthcare ecosystem, it would be expected that clinical trials be impacted in a similar way.

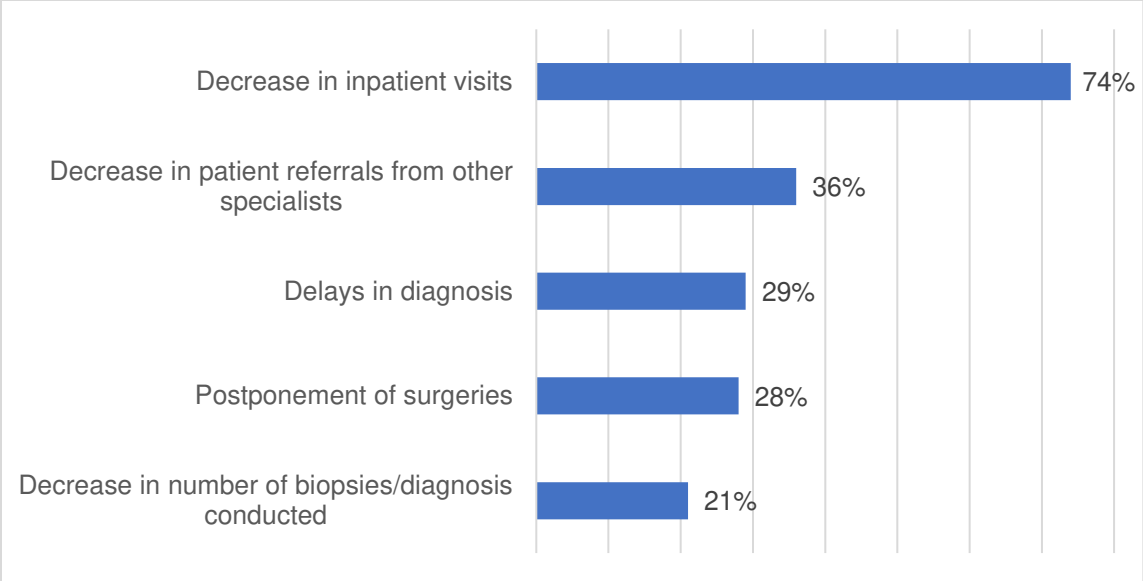


Figure 2: Survey of healthcare providers on the impact of COVID-19 on their clinical practice.

Numbers are given as percentages of respondents, n=350 [8].

Impact of COVID-19 on clinical trial activities globally and in the Asia-Pacific region

The numbers of new trials started from January to August 2020, compared to the same time period in 2019 is shown in Table 1. From the data, we observe that there is a trending decline on clinical trial activities due to the impact of COVID-19. Globally, and in all major regions including the Asia-Pacific, Europe and the Americas, the commencement of new studies declined by an average of 22.5%. The impact appeared more pronounced for phase I and IV compared to phase II and III studies. Specifically, in the therapeutic areas of oncology and non-COVID-19 infectious diseases clinical trials, similar decreases were seen (Table 2). As expected, taking into account COVID-19 clinical trials, there was a dramatic increase in infectious diseases clinical trials overall.

Table 1: Year-on-year comparison of all new clinical trials between January to August 2020.

Data obtained from Trialtrove, accessed 23 Sep 2020 [7].

	All trials														
	Jan to Aug 2019 (number of trials)					Jan to Aug 2020 (number of trials)					Year-on-year change (%)				
	Total	Phase I	Phase II	Phase III	Phase IV	Total	Phase I	Phase II	Phase III	Phase IV	Total	Phase I	Phase II	Phase III	Phase IV
Global	8779	2256	1994	1152	2023	6803	1429	2029	1008	1248	-23%	-37%	2%	-13%	-38%
APAC	4045	1156	830	668	948	3036	651	867	575	559	-25%	-44%	4%	-14%	-41%
Europe	2132	365	519	407	482	1651	244	470	309	290	-23%	-33%	-9%	-24%	-40%
Americas	3268	790	912	493	509	2631	603	871	425	309	-19%	-24%	-4%	-14%	-39%

Table 2: Year-on-year comparison of new oncology and infectious diseases clinical trials between January to August 2020. Data obtained from Trialtrove, accessed 23 Sep 2020 [7].

	Oncology			Infectious diseases (excl. COVID-19 studies)			Infectious diseases (incl. COVID-19 studies)		
	Jan to Aug 2019 (number of trials)	Jan to Aug 2020 (number of trials)	Year-on-year change (%)	Jan to Aug 2019 (number of trials)	Jan to Aug 2020 (number of trials)	Year-on-year change (%)	Jan to Aug 2019 (number of trials)	Jan to Aug 2020 (number of trials)	Year-on-year change (%)
Global	2267	1660	-27%	704	344	-51%	708	1956	176%
APAC	1194	836	-30%	378	175	-54%	381	925	143%
Europe	498	337	-32%	154	86	-44%	157	464	196%
Americas	936	781	-17%	212	111	-48%	214	642	200%

Other key measures of clinical trial activity are the ability for research staff (such as contract research associates from CROs) and patients to access sites and the recruitment of new subjects. In the first quarter of 2020, approximately 80 percent of IQVIA's clinical research sites were inaccessible due to limitations on the ability to travel to and access sites [9]. In Figure 3, recruitment is measured by the percentage of the average number of new patients entering trials per study-site by month compared to a 2019 pre-COVID baseline. Recruitment was impacted in key Asia countries by up to 98% in 2020. While we observe improvements in some countries during the

course of the year, second waves have further impacted recruitment in some countries in August [10].

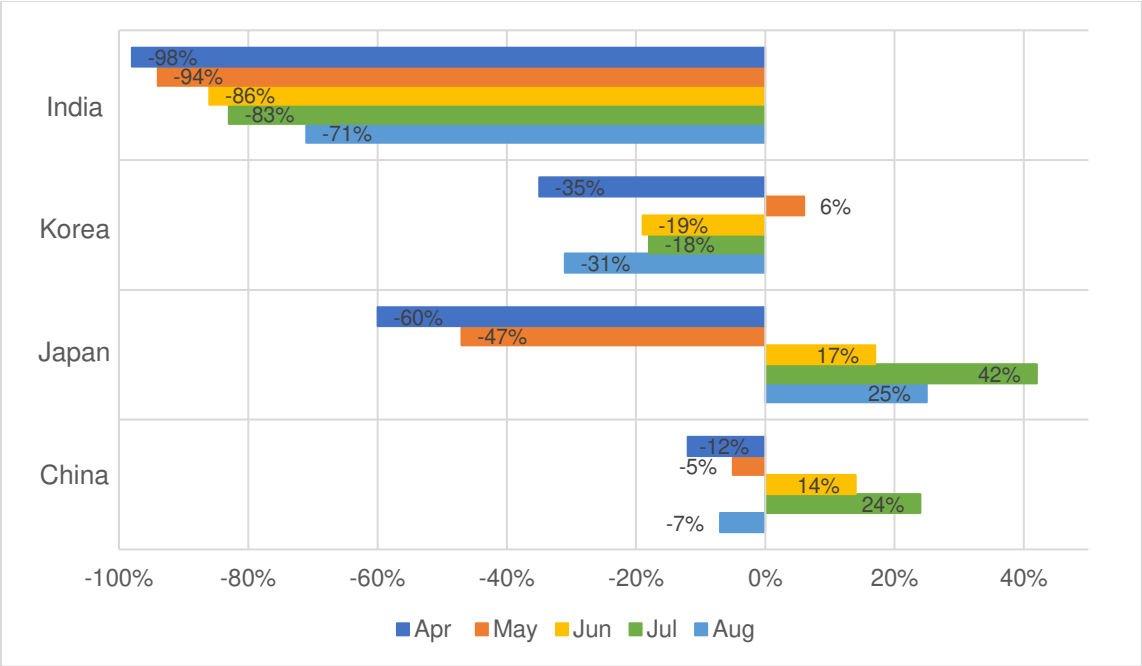


Figure 3: Change in new patients entering study sites by region. Data from Medidata COVID-19 and Clinical Trials: The Medidata Perspective Release 9.0 [10]

Avenues to adapt during the COVID-19 pandemic

Given the widespread impact of the COVID-19 pandemic, the clinical trial ecosystem has been forced to adapt to ensure continuity of ongoing studies. A number of Principal Investigators (PI; n=100) in Europe and the United States were also surveyed for the IQVIA Pharma Decision Maker Research, June 2020. Investigators were asked on the use of remote or hybrid strategies they think will be employed for clinical trials in the future as a consequence of the pandemic (Figure 4). A majority of respondents cited 'Digital Tools and Technology', 'Remote Monitoring/Data' and 'Telemedicine' as key measures that should be increasingly adopted in the future. Notably, 'Home/Telemedicine Visits' were not widely used before the COVID-19 pandemic but were considered by most as an important aspect of future clinical trials.

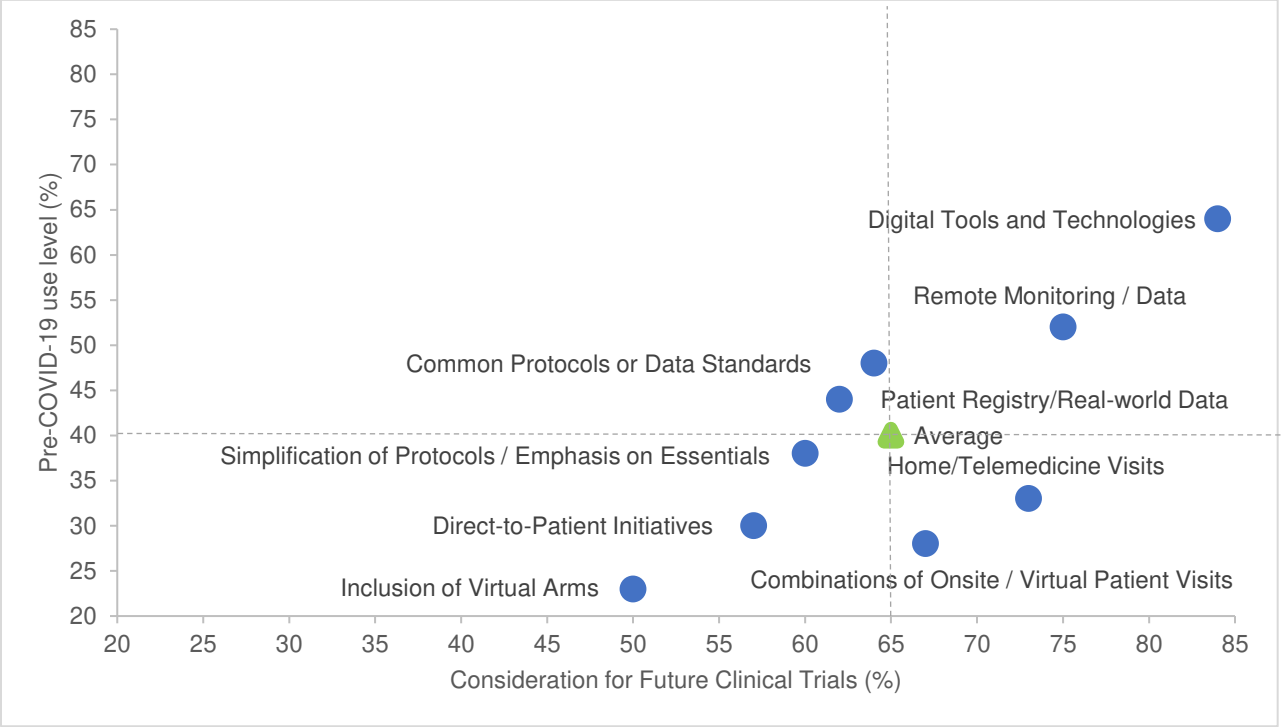


Figure 4: Pre-COVID-19 usage versus future consideration for new trials. Percent of PI respondents, n=100.

As a marker of the level of adaptation which occurred during the pandemic, Table 4 demonstrates the proportion of CRA monitoring visits conducted remotely in the Asia-Pacific region between March and August 2020. In countries such as Singapore, Malaysia, Philippines, New Zealand, and India, virtual site visits were done universally during the months of April and May 2020.

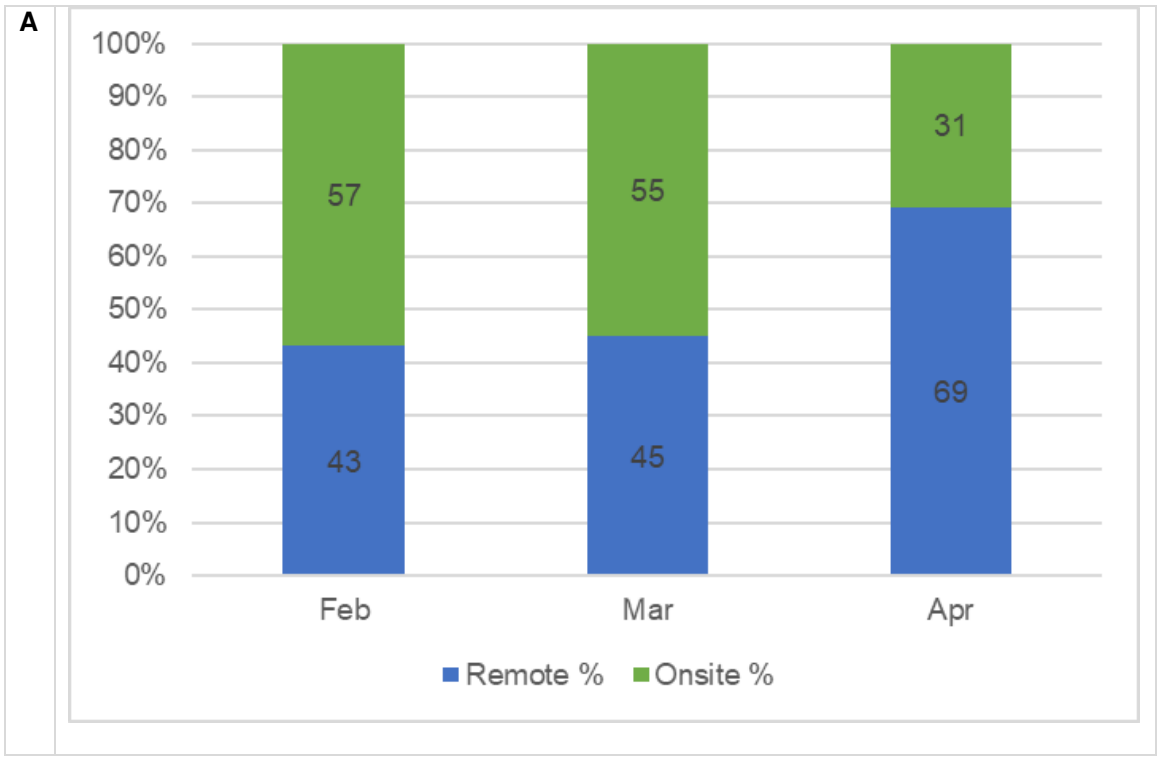
Table 4: Proportion of clinical research associate visits conducted remotely. Data from IQVIA Trial Management Data Hub; Clinical Trial Management System (CTMS) and Electronic Data Capture (EDC).

	Mar	Apr	May	Jun	Jul	Aug
Asia Pacific	23.0%	27.8%	24.5%	16.6%	11.9%	15.8%

An early phase trials unit adapting to the COVID-19 pandemic

Singapore was one of the first countries to experience local community transmission of COVID-19 in early 2020, with travel restrictions and changes to the routine clinical care of patients quickly implemented [11]. Accordingly, this necessitated adaptation to the conduct of clinical trials, particularly for ongoing patients – including patients enrolled on early phase trials at NCCS. Figure 5 shows the extended impact of the pandemic on patients residing in neighboring countries in the Asia-Pacific region. Patient visits and consultations were increasingly conducted via remote means (Figure 6). As patients were unable to attend sites as per their treatment schedules, treatment continuation was also impacted with IV treatments most severely affected but utilization of direct-to-patient (DTP) delivery where possible to mitigate the effects on oral IP. Reimbursement processes were established to allow foreign patients to have investigations performed locally and the results and images delivered to NCCS for review.

Figure 5: Countries of patients enrolled on early phase trials unable to enter Singapore due to travel restrictions



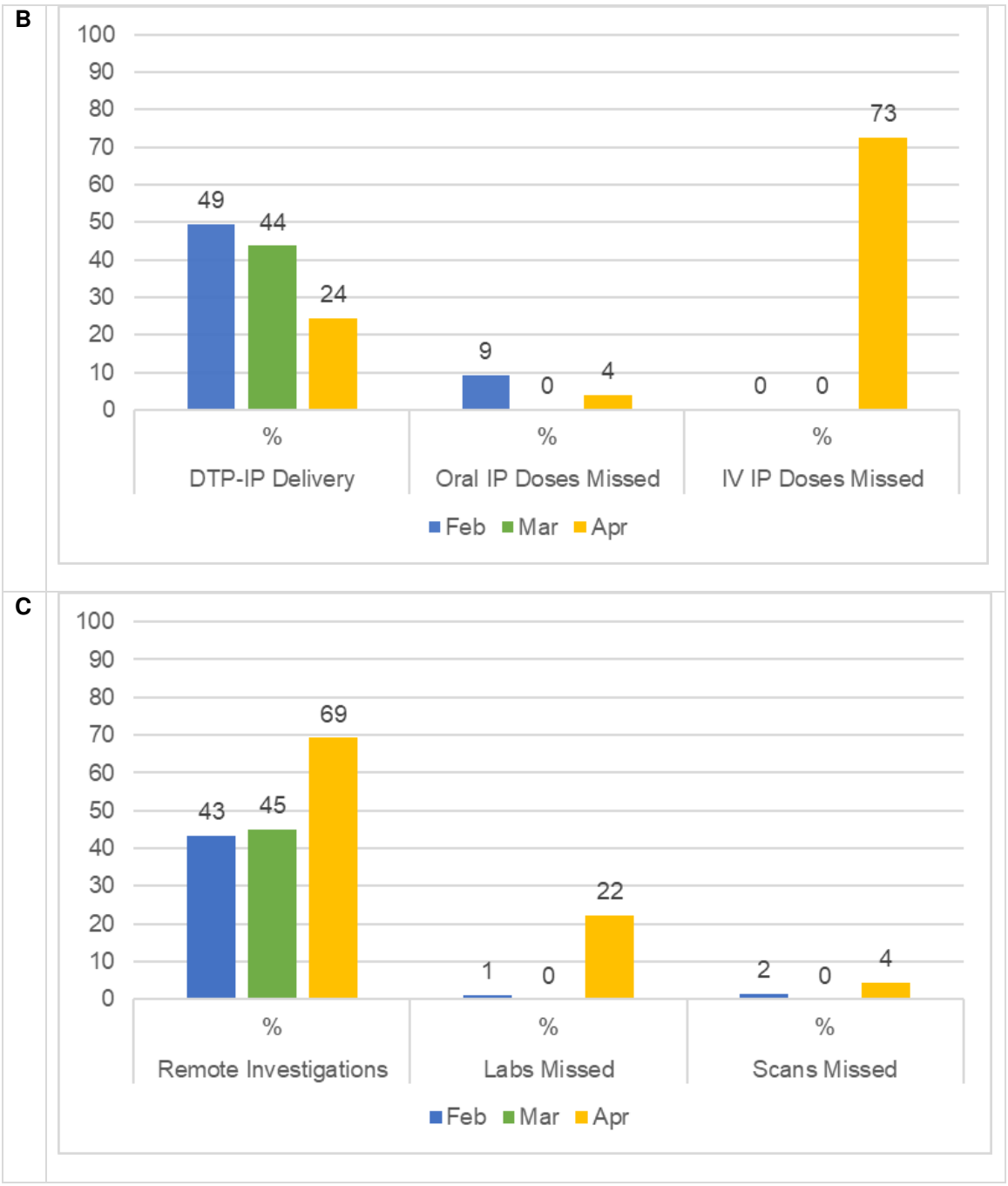


Figure 6: Effect of COVID-19 on trial procedures for ongoing early phase trial patients at the National Cancer Centre Singapore. Remote versus on-site consultations (A). Treatment continuation for ongoing trial patients (B). Safety and efficacy assessments for ongoing trial patients (C).

Discussion

COVID-19 has clearly disrupted the conduct of clinical trials, and remote visits and consultations have been increasingly adopted to ensure clinical trial continuity. However, there must be careful consideration into how we can implement these measures, even after the pandemic, to improve the efficiency and innovate the clinical trial ecosystem while maintaining patient safety [5,12]. Apart from the aforementioned remote monitoring processes, two key areas are targeted in the virtual context – study procedures and patient engagement. One of the biggest challenges of the pandemic in the current clinical trial model is that it is location-centric at the clinical research site. Site-centricity is a challenge for patients given the burden of travel and follow-up. Conducting clinical trial procedures virtually, or at partner sites locally, may ease the patient burden of traveling to sites for multiple visits and tests, and remove geographic and logistical constraints to participation.

Figure 7: Site-centric versus patient-centric clinical trial activities.

Technology is instrumental in enabling the successful conduct of virtual/decentralized research. In such trials, smart devices are used to connect all the stakeholders (e.g. patients, investigators, team members in clinical settings, local health care providers). These smart devices require a

clinical trial grade validated platform to manage study documents, collect and analyze data, facilitate study workflows and host modes of communication with stakeholders [13].

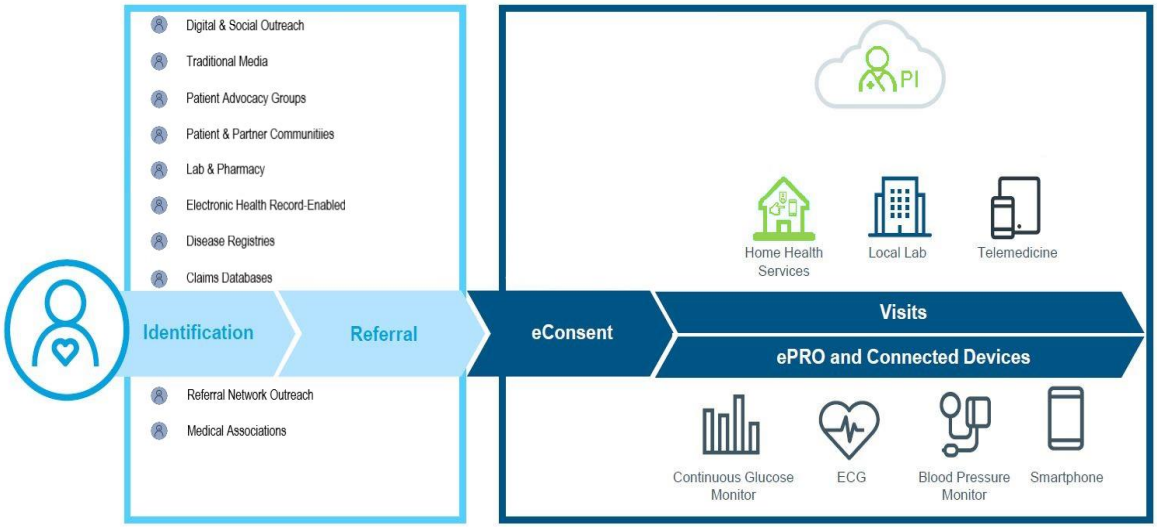


Figure 8: New study flow using digital tools and technology

Importing the clinical trial process online is a challenging task which requires complex integration of various interoperable elements as shown in Figure 8. Over the recent years, many of the technologies have matured to be configurable into a reliable and robust solution. Some examples of such developed technologies and tools include cloud computing, connected devices, advanced analytics, secure platforms – which must be harmonized to deliver an optimal user experience regardless of their background, age and comfort with technology. These technologies and virtual trial platforms are now mostly secure, robust and interface seamlessly with other systems or devices as part of an overall ecosystem – including for example trial master file (TMF) or safety databases [13,14,15]

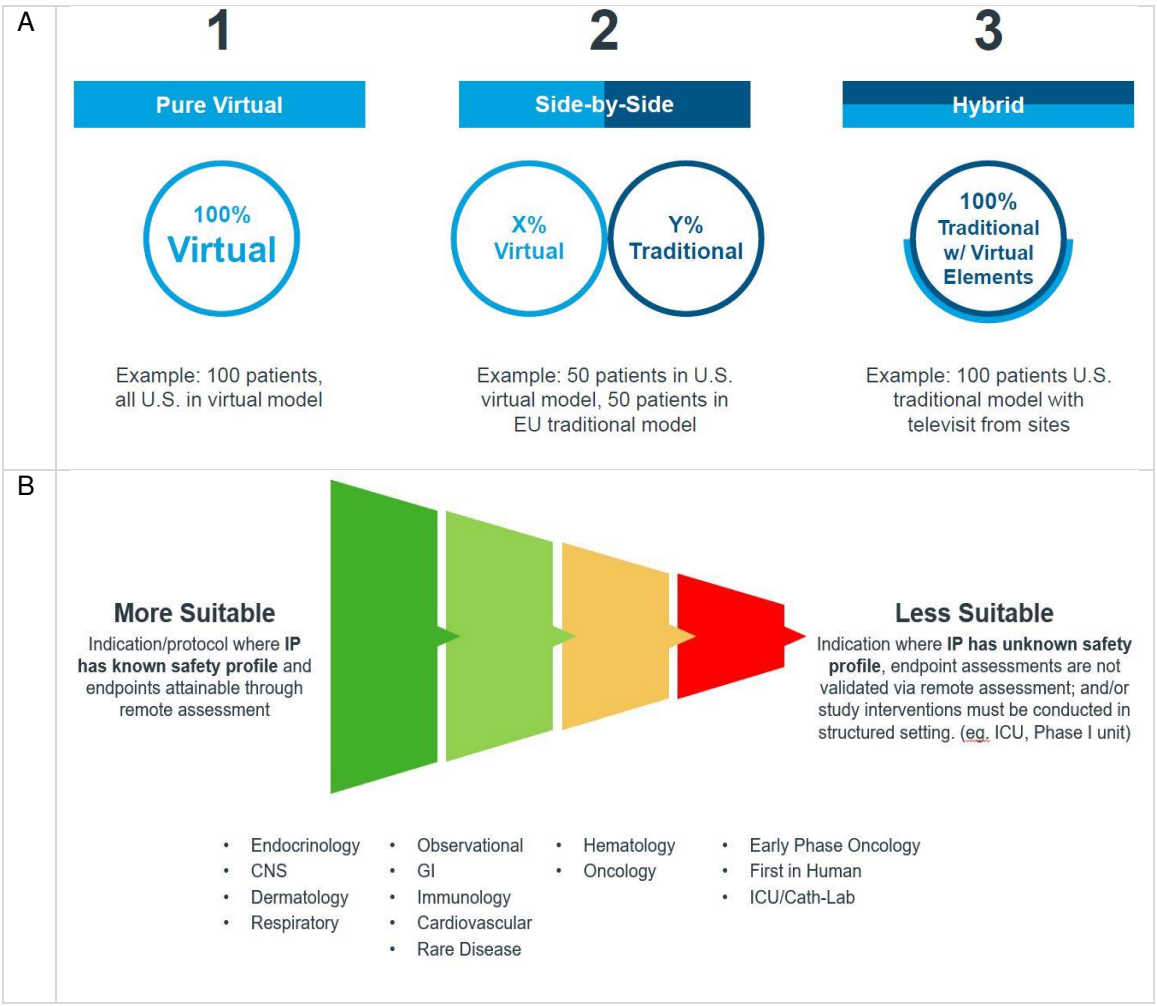


Figure 9: Evolving models of clinical trials. Current models of clinical trial conduct (A). Suitability assessment for different therapeutic areas (B)

The virtual/decentralized trials solution is still evolving, and continued growth of this approach is expected even after the pandemic. However, virtual/decentralized trials are not suitable for every study or indication and a detailed evaluation of each study is necessary to determine the right fit. We expect that virtual/decentralized and traditional studies will continue to run in parallel with other side by side or hybrid models as depicted in Figure 9 [13,15,17].

With the advances in digital technologies and tools, such as connected devices and patient-reported-outcome platforms, this model has become increasingly relevant and applicable for a broad number of treatment areas. (e.g. central nervous system (CNS), dermatology,

cardiovascular, long-term extension trials etc.) However, if a clinical trial requires complex treatment procedures, in-patient care, or acutely ill patients such as seen in early phase oncology studies, this model may not be appropriate [15,17].

Virtual/decentralized trials require a network of multiple tools, apps and software to support their clinical and data collection activities. For example, meetings via videoconference tool, 24/7 access chatbots, tablets or smart phones functioning as smart connected devices for alerts and survey responses, mobile health devices that collect a variety of health data such as blood pressure, glucose and respiratory function. This network allows the streamlined workflow of communication, data transmission and documentation [13,14,15] The ultimate aim and intention of such technology and tools are to enable a similar level of relationship and interaction between the patient and investigator virtually as compared to a face to face one.

Digital tools and technologies have also allowed better monitoring of patients and studies allowing earlier detection of issues that require corrective actions. The real time availability of continuous data feeds offers more insights and understanding of patients. For example, sensors can trigger alerts when a patient has not completed the medication requirements for the day – this enhances the patient support, safety and the data integrity by mitigating potential protocol deviations [16,17].

Conclusion

The COVID-19 pandemic has had a dramatic impact on the conduct of clinical research worldwide. The research ecosystem has evolved to cope with the road to recovery. It also needs to take the opportunity to make studies more patient centric, improving continuity and enable a second order change that will dramatically improve the efficiency of bringing new innovations to market. Thanks to the evolution of technology, these tools are now more present than ever to achieve this. Furthermore, building up a trusted network of study sites will allow continuity of some study procedures locally where the quality can be assured to mitigate against future lockdowns where movement is restricted.

Post-pandemic, there is a need for concrete actions and initiatives in order to continue driving the adoption of new digital innovations and approaches in today's clinical trials. All parties, both public and private (e.g. regulatory authorities, patients, sites, investigators, CROs) will need to accept these new approaches together and embark on a roadmap for clinical research to evolve. Clinical research is complex and multifaceted, and it requires the coordinated efforts of all stakeholders in order to change. Eventually when pre-pandemic status has resumed, the new technologies and practices that have proven to be beneficial should remain.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Some of the datasets generated and/or analysed during the current study are not publicly available due to confidentiality reasons but may be available from the author on reasonable request.

Competing interests

Lucas Lui is an employee of IQVIA. The other authors declare that they have no competing interests.

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Authors' contributions

LL helped conceptualize the paper, provided data and information from IQVIA, and was also a major contributor in writing the manuscript. AT provided and interpreted NCCS site data and was a major contributor in writing the manuscript. MN revised and edited the manuscript. PC revised and edited the manuscript. DT helped conceptualize the paper, revised, and edited the manuscript. All authors read and approved the final manuscript.

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Abbreviations: HCP, healthcare providers; SEA, Southeast Asia; WHO, world health organization; NCCS, national cancer centre of Singapore; APAC, Asia pacific; CRA, clinical research associate; CRO, contract research organization; TMF, trial master file; CNS, central nervous system; DTP, direct to patient; IP, investigational product; IV, intravenous