Impact of COVID-19 on Clinical Research in Malaysia

Abstract
The novel coronavirus disease (COVID-19) pandemic has impacted global economies. These disruptions, also experienced by the global industry-sponsored research (ISR) industry, required new guidelines and standard operating procedures to be put in place to protect both staff and patients involved in clinical research. Clinical Research Malaysia (CRM), a site management organisation and a one-stop centre for ISR in the country quickly put in place various practices to navigate the conduct of clinical research during this pandemic. This narrative review details the impact of the COVID-19 pandemic and the actions put in place by CRM in managing ISRs in Malaysia.

Introduction

The catchphrases marking 2020 have been "Stay at home" and "Flatten the curve". The novel coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in an unprecedented upheaval for global citizens. Governments across the world have had to battle this surging infectious disease while contending with public health and economic repercussions.

On 25 January 2020, Malaysia recorded its first cases of the novel coronavirus disease (COVID-19).[1,2] Up to 13 March, the numbers of COVID-19 infections within the country steadily increased until the day after, when there was a spike in numbers.[2] Four days later, the Malaysian Government through its National Security Council and under advisement from the Ministry of Health announced the implementation of the Movement Control Order (MCO).[2,3] The objective of the MCO was to curb the spread of COVID-19 as much as possible, preventing the country's healthcare system from crashing under its burden. Enacted under the Prevention and Control of Infectious Disease Act (Act 342) the first phase of MCO only allowed essential services to stay open whilst effectively shutting the rest of the country down.

Impact of COVID-19 on Global Industry-sponsored Research

Global economies and healthcare sectors are still being greatly impacted due to the COVID-19 pandemic. This tremendous strain has also extended to the clinical trial industry. Multiple reports[4–9] agree that the current pandemic has negatively impacted planned and ongoing clinical trials (and research). The major impediments in conducting these studies stem from the challenges posed in managing and assuring the safety of investigators, staff and patients, and managing the sudden diversion of resources towards containment and treatment of the disease.[4–8] Though the United States Food and Drug Administration (USFDA)10 and European Medicines Agency (EMA)11 developed guidance to support sponsors, investigators and clinical trial management entities during this global public health crisis, various components of ISRs were impacted including poorer patient recruitments, protocol deviations and challenges with monitoring patients in these studies. Table 1 lists some of these challenges in greater detail.

Reduced prioritisation of ISRs at clinics and hospitals serving as clinical trial sites.
Diversion of resources (clinical staff, investigators, space, equipment) at clinical trial sites located in treatment centres (clinics and hospitals).
Non-viable or complete discontinuation of recruitment campaigns.
Increased missed visits due to fear of COVID-19, quarantine measures and travel disruptions causing protocol deviations.
Sudden increase of reportable adverse events (of flu-like symptoms) by patients of ongoing clinical trials.
Non-clinical research staff requiring to work from home.
Stay at home orders impacting monitoring of study patients, administration of treatments and data collection.
Possible interruptions to supply of investigational product either from the supplier or to the patients.

Table 1: How COVID-19 impacts ISRs[4,6,8,9]

In a survey of 363 clinical trial sites across the globe (including the Asia-Pacific region), 36% were awaiting activation of studies due to the sponsor postponing initiation of recruitment whilst 48% actively enrolling patients faced issues with getting patients in for site visits. Due to this, 34% of these enrolling sites decided to stop seeing patients or moved to virtual visits.[6] Of approximately 1000 clinical trial sites being tracked,[5] even as some countries loosen their MCOs, there is still delay in initiation of studies and slow enrolment (up by 10% and 13.9% respectively over a three-week period from June 11 to July 9 2020). However, studies that suspended enrolment during the more intensive phases of MCO have shown improvement by a 10% increase. In a larger study by Medidata[12] involving enrolment data from >4500 studies and >182,000 sites globally, in March 2020, there was a 65% decrease in new patient enrolment vs. the previous year. The United States of America had a reduction of 67% vs. Japan with a 43% reduction and India with an 84% reduction.

Malaysia's Industry-sponsored Research Experience During COVID-19

In recent years, owing to the multiple benefits of developing

Malaysia into a clinical trial hub, the Malaysian Government has invested significantly in growing the country's clinical trial capabilities and resources.[13,14] One of its initiatives was the establishment of Clinical Research Malaysia (CRM). One of the many benefits that CRM affords to the robustness of the Malaysian clinical trial ecosystem[13–15] is as an entity under the Ministry of Health. CRM therefore facilitates ISRs in the country by being a single point of contact between sponsors, CROs, various government agencies and, most importantly, the 36 major clinical research centres nationwide.

The COVID-19 pandemic significantly impacted the conduct of ISRs in Malaysia, akin to the impact experienced globally. With the implementation of MCO on 18 March and the rising number of cases, most principal investigators decided to withhold patient recruitment and non-essential patient visits. In addition, with the focus on safety of staff and patients in mind, most sponsors and contract research organisations (CROs) either withheld or converted to remote modalities for site start-up visits and monitoring activities which were in line with the USFDA10 and EMA guidance.11 Being the single point of contact, CRM greatly facilitated effective communications between all stakeholders, ensuring that all parties were up to date with the latest in the operational status of individual CRM-managed trials.

Feasibility Studies

One of CRM's key core services is its complimentary feasibility studies.[13] During the MCO period, the company decided to withhold outreach of feasibility studies requiring site approaches, except for studies specifically relating to COVID-19. This naturally resulted in a decline in the number of feasibility studies accepted in March 2020 by 46% vs. the previous month. Due to the cordon sanitaire, 14 ongoing feasibility studies recorded during the MCO were put on hold. Understandably, all other ongoing studies had timelines extended until the MCO eased into the Conditional MCO (CMCO) and Recovery MCO (RMCO) beginning June 2020. Table 1 shows the number of full feasibility studies from January to June 2020.

CRM's decision to put on hold the feasibility assessments requiring site-level information was due to several reasons. Firstly, the Ministry of Health had started building surge capacity in hospitals and as such, some hospitals were specifically designated into COVID-19 treating hospitals, with non-COVID-19 cases being transferred to other nearby hospitals. Secondly, the temporary halt in CRM's feasibility approach was to provide more capacity for clinicians to focus on treating COVID-19 cases that had seen a rise in its number during the MCO in March and April. Thirdly, some of the clinician investigators were deployed to COVID-19 centres to fill the insufficiency of manpower at these sites. Finally, with the restriction of movement being in place, most CRM study coordinators (SCs) worked from home and thus were not able to collect feasibility feedback from the investigators.

	January (Pre-MCO)	February (Pre-MCO)	March (MCO)	April (MCO)	May (CMCO)	Jun (RMCO)
Full Feasibility	14	13	7	4	13	13

MCO: movement control order; CMCO: conditional MCO; RMCO: recovery MCO. MCO was initiated on 18 March 2020 in Malaysia.

Table 1: Number of full feasibility studies from January–June 2020

The Impact of COVID-19 on Patient Recruitment, Protocol Deviations, Patient Visits and Investigational Product Management

A survey conducted from 18 March to 23 April 2020 was carried out at all clinical trial sites supported by CRM's SCs across 44 hospitals and institutes to determine the impact of COVID-19 on patient recruitment, protocol deviations, patient visits and IP management. In total, there are 480 active clinical trial sites whereby each trial site may conduct similar study protocol.

Patient Recruitment

Medidata (2020) conducted an electronic survey in April 2020 at investigator sites in the United States and Asia. It was reported that 63% of them halted new patient recruitment for ongoing trials[16]. In a follow-up survey done in August 2020, there was a decrease in the number of trials in which patient recruitment was halted (39%)[18]. Another study conducted by the DIA China Digital Health Community (DIA China 2020) in February 2020 among 176 responders, 67% experienced suspension of subject recruitment[17]. Similarly, in Malaysia, most of the clinical trial sites located within the Ministry of Health hospitals were closed and research staff including SCs were required to work from home during the MCO. The impact on patient recruitment is seen in Figure 1. Of the trials managed by CRM, 66% put patient recruitment on hold while 21% maintained active recruitment and 13% had successfully achieved their targets. By June, with the MCO transitioning to CMCO and then to RMCO, patient recruitment resumed. Trials that withheld recruitment reduced by 13% (from 66% to 53%) and active recruitment increased by 14% (from 21% to 35%). As per another survey conducted from 1 July, the percentage of active recruitment increased to 74%, with only 16% of trials still withholding recruitment. These numbers are encouraging, and it shows the recovery in Malaysia is extremely fast. This could be associated with the decreasing numbers of COVID-19 cases in the country, the development and implementation of industry-specific standard operating procedures (SOPs) and a centralised agency such as CRM effectively bridging communications amongst various stakeholders.

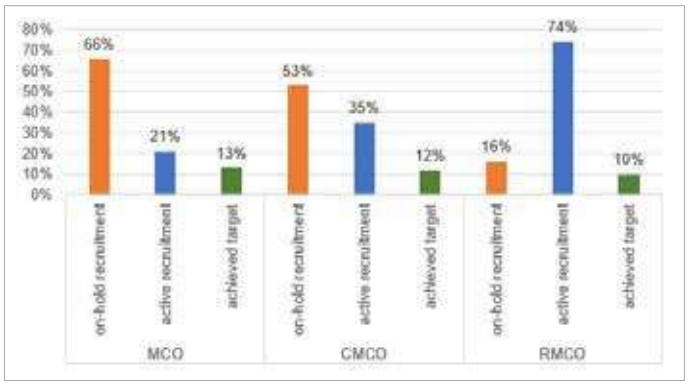

Figure 1: Impact of Patient Recruitment

Protocol Deviations

As experienced with clinical studies globally, CRM-managed ISRs were faced with protocol deviations (14%). The reasons for protocol deviations are shown in Figure 2, while reasons for protocol deviations classified as "Others" are listed in Table 2. Of the nine protocol deviations classified as "Others", five were related to the COVID-19 pandemic.

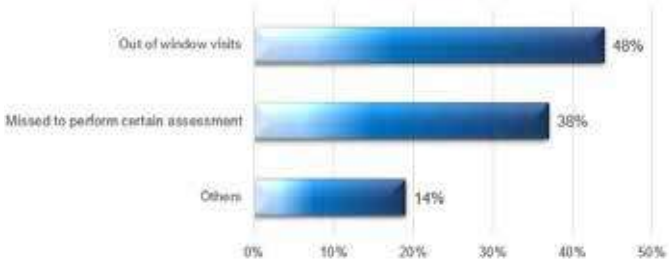

Figure 2: Reasons for protocol deviations in clinical studies during MCO

Related to COVID-19/MCO	– Collected samples unable to be shipped out on the day of visit as per protocol requirement. – Delay in receipt of IP at site before end of patient visit window period. – Patient visit to site was changed to phone call visits.
Not related to COVID-19/MCO	– IP compliance not within protocol range. – Expired kit was used. – Temperature excursion of IP storage – Procedures were not performed as per protocol.

Protocol deviations occurring in CRM-managed clinical trials during the MCO period and classified as "Others". Some deviations may have occurred more than once during the survey. Of the total CRM-managed studies, protocol deviations occurred in 14%. MCO: movement control order; IP: investigational product.

Table 2: Protocol deviations classified as "Others"

Patient Visits to Trial Sites

During the survey period between 18 March to 23 April 2020 involving 480 trail studies, 52% (n=247) continued patient visits as per schedule, 39% (n=188) had no active patient visits and 9% (n=45) postponed patient visits. Sixty per cent of the 188 trial sites had completed all patient visits before MCO, whilst 33% had no patient enrolled yet. Of the 45 trial sites that postponed patient visits, 42% were based on investigator discretion, 23% on sponsor/CRO discretion and 35% due to unwillingness of patient. Throughout the period of March to July, a total of 58 patient visits were reported as cancelled.

Eighty-seven per cent of patient visits were done on-site while the remaining 13% of follow-up visits were done through telephone/video calls. As patient and staff safety were paramount, SOPs developed by the Ministry of Health were strictly adhered to during on-site patient visits. All patients who presented for on-site visits were screened for influenza-like illness symptoms and signs prior to entering the clinics. A specific COVID-19 declaration form was used, which also included travel history.

Investigational Product (IP) Management

Six per cent of trial sites had IP supply withheld from the sponsor. These involved studies in nephrology, cardiology, infectious disease, paediatrics, and rheumatology. As for sites that continued to dispense IPs to the patients during the MCO, 68% were dispensed at the sites and if patients couldn't be present on site per the scheduled visit, the IP was either given in advance in bulk (8%) or was delivered directly to the patient's home (7%). Three per cent of IPs were "put on hold" for various reasons including safety concerns based on the principal investigator's discretion, IPs which required laboratory results prior to being dispensed and the patient could not be present for these tests, and patient refusing to receive the IP for one month due to suspicion of another disease. No concerns have been reported by site staff and there have not been any reports of adverse effects of withholding the IP in patients. The methods of dispensing the IP in studies are seen in Figure 3.

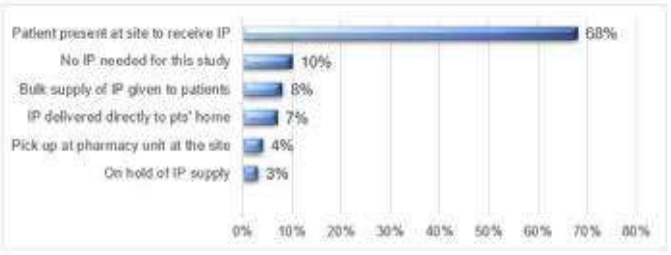

Figure 3: Methods of IP dispensing in studies during MCO

IP: investigational product; pt's: patients. No IP needed = no IP involved in studies (e.g. observational or biomarker studies) or patients have already completed IP prior to MCO.

IPs delivered to the patients' homes used locally available courier services. The clinical research associates (CRAs) arranged for courier pick-up at the site. Protocols were set in place for IPs requiring temperature control wherein the courier company prepared and sent reports to the SC. In cases of temperature excursions, these were reported to the CRA to confirm if the IP could still be used. The SC also confirmed directly with the patients if the IPs were received in good condition and at the right quantity.

Site Monitoring Visits

A survey was also done on arrangements of site monitoring visits by the sponsors/CROs. The findings showed that 54% had monitoring visits postponed, 44% had off-site or remote monitoring and the remaining 2% had no monitoring visits during the MCO period. The majority of sites on off-site or remote monitoring did so via sending scanned documents through email with redacted patient identifiers (80%) and 19% were monitored by tele/video conferencing methods.

Site Start-ups

Of 69 trials slotted to start-up, 17% were delayed and 83% continued as planned. Management of site start-ups was done remotely in 58% while 42% had on-site visits. CRM worked together with the hospitals, sponsors and CROs involved in these instances to disseminate correct information to stakeholders in a timely manner to ensure adherence to SOPs that had been developed with specific guidelines and arrangements by individual hospitals. These allowed for planned site selection visits and site initiation visits to be conducted smoothly.

Conclusion

Even with the impact of COVID-19 on ISRs, the Malaysian experience allowed many of the essential clinical studies to carry on with adaptation of processes and few protocol deviations. These

included, where possible, converting trial procedures and visits to be performed remotely or online. However, a large proportion of studies still followed the traditional route, but did so safely, ensuring that on-site visits were done under strict SOP guidelines with collaboration between the hospital administration, investigators, sponsors and CROs. Though patient recruitment was impacted, our experience showed a fast recovery post-MCO. There was also no major disruption of IP supply to patients and the majority were able to visit the site for the IP, largely due to implementation of SOPs.

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