COMMENTARY

Revisiting Scientific Research Amidst the Unexpected COVID-19 Pandemic: Sustenance, Resumption and Recommendations

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ABSTRACT

The COVID-19 pandemic has posed an unprecedented challenge to the global scientific community including those in Malaysia. Researchers should essentially learn from the COVID-19 pandemic to become more resilient in the future. The present paper highlights our experience from sustaining research output throughout the lockdown restrictions to jump-starting and driving the newly gained momentum of research activities after the lockdown period. We also suggested some practical ways in terms of acquisition and handling of human biological samples for research and replacement of site visits with telemedicine that can drive non-COVID-19 related clinical-based research forward during the course of a pandemic. We then recommended a few measures that can be taken by research centres and institutions of higher learning as well as researchers to move their wet laboratory- or clinical-based research forward during potential outbreaks in the future.
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INTRODUCTION

Approximately three and a half years have elapsed since the first case of COVID-19 in Malaysia, which was detected on the 25th of January 2020. The first wave of the outbreak (i.e., 22 positive cases) then led to a series of lockdowns. As of 27th of May 2023, Malaysia has accumulated 5,100,249 confirmed and 5,044,652 recovered cases, respectively, with 37,087 total number of deaths (1). The entire lockdown period has been very challenging for the scientific community nationwide. As part of the research community who endured from the pandemic, we would like to revisit and share our experience from sustaining research output throughout the lockdown restrictions to jump-starting and driving the newly gained momentum of research activities after the lockdown period. This will provide insights into the identification of areas of support needed by researchers and best practices that could be applied should similar situations arise in the future. Additionally, we also suggested some practical ways that can drive non-COVID-19 related clinical-based research forward. The main suggestions included (1) screening of pooled biological samples (i.e., faecal samples) for SARS-CoV-2 for acquisition and handling of human biological samples for research and (2) replacement of site visits with telemedicine for data acquisition from participants of non-COVID-19 clinical-based research. Based on the lessons learned from the pandemic, we then recommended a few measures that can be taken by research centres and institutions of higher learning as well as researchers (including early career researchers) who rely predominantly on output through wet laboratory- or clinical-based experiments to move their research forward during potential outbreaks in the future.

Sustaining research output throughout the lockdown restrictions

The "new normal" amidst the pandemic required lots of adaptation from every aspect of human lives. "Social distancing", in particular, prevented members of our the research team from close physical contact, which would have been normal in the laboratories before the pandemic. Nevertheless, from a favorable perspective, the constant engagement via online

platforms (i.e., Google Meet and Skype) and social media messaging (i.e., WhatsApp) made the team stronger. Constant virtual interactions not only gave our research team a "sense of purpose", but also fostered discipline and accountability amongst the members. This was in line with Sutherland, Taylor (2) who found social engagement through the Laboratory Book Club and Journal Club, amongst others to be beneficial in increasing group cohesion and promoting understanding, loyalty and mutual care.

The online weekly progress meeting, which started one week after the commencement of the Movement Control Order (MCO), facilitated discussions on the analysis and interpretation of data, design of questionnaires as well as preparation of various forms of write-up. More importantly, it helped the team to stay focused on one-step-at-a-time progress instead of complaining and lamenting over problems which arose from the pandemic. It is noteworthy that the success of each progress was dependent upon careful settings of realistic and achievable weekly and monthly goals. The periodical updates of paper submission or acceptance, and the sharing of positive words of encouragement via internal communications were crucial towards spurring the team on.

On top of the long wait for before returning to the laboratory in which our research team used to work daily, members of our research team were also particularly worried about the collection of probiotics, cell lines, blood samples, tissues and chemicals that required perpetual storage at low temperatures. The breakdown of either chillers or freezers and the interruption of the supply chain for the fast-evaporating liquid nitrogen would have caused all the blood, sweat and tears invested in building up these precious collections to go to waste. Fortunately, supporting staff who were allowed to enter the faculty only for essential tasks were instrumental in monitoring the operation of the refrigerated equipment and replenishing the liquid nitrogen.

Overall, although the pandemic had put unprecedented pressure on the research team, especially in terms of the progress of research, the temporary suspension of research activities had given the team time to pause and rethink the strategy, as well as re-prioritize its focus. Ironically, the unanticipated interruption due to the COVID-19 pandemic appeared to have forced the research team into re-evaluation of some areas of concern, which had long been put aside due to time constraints in the past. Additionally, the MCO period also provided the opportunity to team members to dedicate part of their time to participating in formal continuous professional development programs conducted through online seminars or workshops.

Driving non-COVID-19 related clinical-based research after lockdown

Upon stage-wise relaxation of the COVID-19 lockdown, researchers and postgraduates were finally allowed to re-enter the laboratories but with some restrictions. Nevertheless, the resumption of research activities was not as straightforward. More hurdles lay ahead before research could return to a normal level of productivity. Whilst some cryofrozen cancer cell lines and probiotics were able to be revived and regrown very quickly, cultures of slow dividing normal cells took a relatively longer time to reach confluence.

Analytical protocols which were optimised before MCO had to be re-tested due to the change of instrument like the High Performance Liquid Chromatography in replacement of those that were broken down. Certain experiments that involved imaging techniques remain on hold because of the untimely breakdown of equipment like transmission electron microscopes that required a longer time to repair. Also, the rescheduled delivery of animals like NU/NU nude mice and the restriction of working during weekends required re-planning of the in vivo studies and re-designing of subsequent experiments.

Whilst the main issue of resuming laboratory-based research after lockdown turns out to be a matter of racing against time, the obstacles against clinical-based research during this pandemic are far more complex. In the face of this dilemma, O'Brien, Teherani (3) has recently proposed a detailed framework to aid the decision-making process on whether to pause, persist or pivot research at times of uncertainties during the pandemic. Elsewhere, Wigginton, Cunningham (4) recommended the previously halted clinical-based research to be restarted in a stepwise approach at a phase when the transmission status of the pandemic is minimal or none. Another challenge faced by non-COVID-19 related clinical-based research during this pandemic was the lack of guidelines for sample acquisition and handling. Current available human sample acquisition and handling guidelines during the pandemic which are developed by the Centres for Disease Control and Prevention (CDC) and World Health Organization (WHO) focus on individuals infected with COVID-19. Although non-COVID-19 human sample acquisition and handling guidelines had been proposed for clinical practice (5, 6), these guidelines are not suitable for research purposes. In the research setting, the acquisition of faecal samples, for instance, requires collection from participants (usually at their homes) and immediate delivery to the laboratory for processing. Yet another challenge faced by non-COVID-19 related clinical-based research during this pandemic was the restriction to perform face-to-face data acquisition

from participants. Researchers were unable to meet patients in person for interviews or surveys especially during times when physical distancing and self-quarantine can save lives. All these obstacles raised the need for carefully planned procedures based on "safety comes first" and in line with the "new normal". For this purpose, some practical ways that can drive non-COVID-19 related clinical-based research forward are proposed.

Acquisition and handling of human biological samples for research

It is essential to consider two important factors during the acquisition and handling of human biological samples for non-COVID-19 related clinical-based research: i) transmission of SARS-CoV-2 and ii) presence of SARS-CoV-2 in asymptomatic individuals. Since vaccine for SARS-CoV-2 was unavailable then, avoiding human contact was crucial in stopping transmission of the virus. Nevertheless, merely avoiding individuals with COVID-19 symptoms might be inadequate as recent studies reported about the transmission of SARS-CoV-2 via asymptomatic individuals. In China, four-fifths of COVID-19 cases were identified as asymptomatic (7). In Italy, the identification and isolation of asymptomatic individuals successfully eliminated the virus in a village (8). In order to minimise potential exposure to COVID-19, the acquisition of biological samples at a non-hospital setting is recommended to avoid unnecessary trips to the hospital.

SARS-CoV-2 RNA is known to be present in human blood, urine and faecal samples. Whilst the highest amount of RNA was found in faeces, low level to absence of RNA was reported in blood and urine. The presence of SARS-CoV-2 RNA in faeces suggests the possibility of faecal-oral transmission. Although there is no evidence of faecal-oral transmission in asymptomatic individuals, there remains such a possibility as this particular mode of transmission has been reported in symptomatic patients (9). Should this happen, it can greatly impact non-COVID-19 related clinical trials that involve the collection of human fecal samples given that asymptomatic individuals could be mistaken for healthy participants. Furthermore, the presence of SARS-CoV-2 RNA in faecal samples could be a confounding factor which might compromise the outcome of the gut microbiome study.

During the MCO, when the COVID-19 cases are high, biological samples (i.e., faecal samples) can be possibly collected from eligible participants who show no symptoms at a non-hospital setting by a trained laboratory personnel who is given the clearance to perform sample collection. The trained laboratory personnels should essentially wear personal protective equipment as per the standard guidelines provided either by the local health institutions or the World Health Organization (WHO) (10). The biological samples, which are contained within sterile containers, can then be packaged in multi-layer bags before transportation to the laboratory. Upon arrival at the laboratory, the containers should be placed in a fume hood first and then the thermostat was set to 56 °C for 30-40 minutes. The package should be opened within the fume hood and every time a layer of a packaged bag is opened, 75% alcohol should be sprayed (Yang et al., 2020). On the other hand, during the recovery MCO (RMCO) period [e.g., 10th of June - 14th of October 2020; when the curve was flattened and transmission of the virus reduced to the minimum (single digit of new cases on most days in September, 2020)], faecal samples can be possibly collected from eligible participants who showed no symptoms at a non-hospital setting using delivery service. The participants can be briefed before hand and be supplied with a stool collection kit in advance of sample collection.

The samples should be pooled and screened for SARS-CoV-2. It is essential that the samples are processed in a biosafety level (BSL)–2c before the pooled samples are subjected to real-time RT-PCR assay. Only samples that are negative will proceed to gut microbiome studies. It was reported that a single negative test was insufficient to exclude the presence of SARS-CoV-2 in stool. It is recommended to test the samples from donors at multiple timepoints, since the level of viral RNA present in stool can fluctuate around the margin of laboratory detection (11). Pooled samples with positive PCR results, on the other hand, should be sent to the Institute of Medical Research (IMR) Malaysia for further confirmation.

Replacement of site visits with telemedicine for data acquisition from participants of non-COVID-19 clinical-based research

In our case of clinical-based cognitive frailty study, we have turned our face-to-face surveys to teleconsultation to minimise the risk of infection during the course of the pandemic. In fact, telemedicine is deemed an effective tool that facilitates early diagnosis and monitoring of Alzheimer's disease (12). More importantly, the use of telemedicine was found to be feasible and revealed an equal level of satisfaction as compared to clinic visits (13, 14). A clinical trial conducted via telemedicine by Takeda, Guyonnet (15) during lockdown, for example, found the majority of the patients preferred to continue with the clinical trial. Telemedicine can be easily set up with a smartphone, tablet, laptop or computer using widely available video communication applications such as Skype, Facebook Messenger video chat and Apple FaceTime, and when patients have no access either to video communication or internet, telephone is also used (16). Other very useful tool in telemedicine also include e-diaries and sensors (17). Information such as screening for travel,

exposure to and symptoms of COVID-19, medical history, and e-consent form can be collected with video or telephone.

Although data collection can still be continued by using telemedicine, the collection of some data such as magnetic resonance imaging (MRI) scan to access cognitive function remains impossible and can only be done in the clinical setting. Alternatively, researchers could use a telemedicine platform with questionnaire-based cognitive assessment that correlates with MRI, to a certain extent. On another note, the barriers to the use of telemedicine applications amongst older adults need to be identified and eliminated in order to increase the prevalence of telehealth use (18). High cost and cultural resistance have been identified as the main barriers to implementing telemedicine in developing countries (19). The top barriers to the global implementation of telemedicine, on the other hand, are technology-specific. It could, however, be overcome through training, change-management techniques, and alternating delivery by telemedicine and personal patient-to-provider interaction. It could be effectively managed by focused policy (20), particularly during this COVID-19 pandemic.

CONCLUSION

Altogether, the research community should essentially learn from the COVID-19 pandemic to become more resilient in the future. In particular, this unprecedented pandemic reveals the inadequacy of the current level of risk assessment to minimise losses and maximise the sustenance of wet laboratory- or clinical-based research. Research centres and institutions of higher learning need to proactively formulate procedures and mechanisms that can help researchers to respond quickly to future pandemics to avoid another reactive situation like that seen with COVID-19 laboratory closures. Official guidelines on pandemic responses should be similar to other emergency response guidelines already in place to ensure consistency in implementation, minimise potential chaos or confusion as well as reduce the need for abrupt changes in policy and sudden closures (21). In addition, researchers should now have a stronger sense of crisis and essentially develop the ability to re-prioritise and re-strategise activities when faced with potential outbreaks in the future. Under uncontrolled situations caused by the sudden restrictions of movements by the government, researchers who rely predominantly on output through wet laboratory- or clinical-based research should essentially consider other alternatives like systematic review and meta-analysis, analysis of previously collected data, mathematical simulation/ computational/ molecular modelling, data mining by using public access to online databases and focused literature review amongst others to move their research forward (22). Given that some of these approaches may fall outside the knowledge of the researchers, it is important to solicit the assistance of additional expertise through collaboration (23). During times of relaxed lockdown but with continued social distancing requirements, researchers may consider the use of a shift schedule for wet laboratory-based research activities or clinical trials to stay within regulations (24). Researchers may also want to capitalise on technologies like smartphones, movable webcams, video-conferencing softwares amongst others to set up social distancing compliant platforms for remote supervision and training of wet laboratory- or clinical-based research activities (24, 25). Also, as part of efforts to reinvigorate scientific progress and make greater strides in research, the global scientific community should seize all opportunities to share resources, communicate ideas and collaborate in tandem (26). On the downside, the crisis has left behind many unresolved problems, some beyond recovery. Early career researchers who were hit the hardest, for instance, certainly need the most support. Unlike established researchers, the novices are likely to experience shortage of resources and the lack of publishable data, both of which are essential for sustenance of their research career. Research centres and institutions of higher learning should essentially support them to present their work both nationally and internationally to raise their professional profile as well as build connections and generate collaborative opportunities (27). Funders may also want to consider allocating more funding schemes as research laboratory transition assistance for these early career researchers (28).

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