Post COVID-19 reboot of clinical trials in Asia Pacific

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INTRODUCTION

The recent restrictions imposed by many countries in response to the recent COVID-19 outbreak has impacted ongoing clinical research. As these restrictions are now being lifted, it is instructive to observe the policies that clinical research sites in China, the first country impacted by the outbreak and now showing signs of recovery, are implementing in monitoring visits by sponsors and clinical research organizations (CROs). IQVIA has a unique perspective on clinical research activities in China with over 22 years of experience across broad therapeutic areas, and at multiple sites in the country as well as the region overall. This enables us to observe how research sites are utilizing a variety of measures, including diagnostic tests, to screen site monitors for COVID-19, in an attempt to minimize risk of external transmission of the infection to staff and patients at the site.

The state council of the People's Republic of China has created a nationwide mobile application for all citizens which is used to track a person's travel for the 14-days prior to entry into a city or region. This serves as a foundation for entry into all clinical research sites (hereafter referred to as "sites") in China. When individuals enter public buildings like hospitals, the app needs to be scanned and individuals who have passed through a high-risk city or country during the past 14 days will not be permitted to enter. Individuals with no at-risk travel will be given a green arrow in the app and progress to the next stage of assessment for entry. Beyond this national tracking application, we have observed sites adding additional requirements to permit entry of field-based third-party staff. In this paper, we investigate these additional requirements as they inform the changing clinical research landscape in China as well as being a leading indicator to what other countries may adopt as they emerge from COVID-19 restrictions. We also briefly discuss the merits of the various methodologies that have been observed in China and globally.

METHODOLOGY

We performed a survey of sites in China through our clinical research associate (CRA) staff and present here the key considerations they are using. In addition, the team conducted a literature search on the merits of the various methodologies. Discussions held by the COVID-19 Medical Council of IQVIA (a multidisciplinary team of medically trained staff throughout the world) has also been summarized to provide insight into the merits and limitations of the potential solutions.

RESULTS

Feedback regarding site-specific screening was obtained by IQVIA CRAs at active sites in China over a continuous period up to 5 June 2020. Complete responses were obtained from 174 sites.

Table 1 summarizes the various diagnostic tests utilized to aid decision making and the percentage of sites requesting for each. As this is a dynamic situation, including time-specific positions and increasing responses to our survey, Table 1 is accurate as of 5 June 2020. As time progresses, we will be updating this analysis and adding in more data from other countries as they resume activities.

Viral nucleic acid testing from nasopharyngeal swabs is the most common form of diagnostic test requested by sites with 65% of the respondents requesting a negative test before a visit is allowed. The next most common test is antibody serology with a 18% of sites making this request. Radiographic imaging with chest computer tomography (CT) and chest radiography (x-ray) were required respectively at 9% and 2% of surveyed sites. Finally, 6% of sites required a blood hematology panel.

Depending on a clinical study design and the need for specific experiences, CRAs may travel between cities and provinces to monitor sites. To address the risk of travel, local quarantine is applied to CRAs visiting from another city/province and usually consists of a 14 day stay in the area before being allowed to do their monitoring visit. In some cases, this quarantine period is waived or reduced if some diagnostic test is performed.

Frequency of testing varies but is typically requested 3-7 days ahead of a visit.

While not necessarily a diagnostic test, all sites surveyed requested some form of questionnaire assessing travel history, exposure history, symptoms and temperature checking as a baseline.

Table 1: percentage of surveyed sites (n=174) requesting a variety of diagnostic methods before admitting CRAs to sites for monitoring visits

VIRAL NUCLEIC ACID (THROAT SWAB)	CHEST CT	X-RAY	ANTIBODY (IGM+IGG)	HEMATOLOGY	LOCAL QUARANTINE	QUESTIONNAIRE ON TRAVEL/ EXPOSURE AND TEMPERATURE MONITORING
65% (113)	9% (15)	2% (3)	18% (31)	6% (10)	11% (19)	100%

DISCUSSION

Given the diversity of approaches, we take the opportunity here to review the medical evidence supporting the use of each of these measures in reducing risk.

1. **History of travel, symptoms, exposure and temperature measurement**: Given its simplicity and relative effectiveness at risk reduction, there is value in employing these non-invasive screening tools. IQVIA endorses this type of screening and is in the process of deploying a mobile-based, intuitive and easy-to-use version of this application to its field-based staff (details of components in Table 2). Importantly, the scientific validity of the way in which this questionnaire is implemented, as well as high-grade security and alignment of local data privacy and employment regulations is critical to meet country based statutory requirements.

In addition, integration into a business system enables business continuity planning and forecasting. This application permits CRAs to provide a categorical assessment of COVID-19 risk status to sites while maintaining confidentiality of health and personal information. Answers that identify an elevated risk and potential for transmission of COVID-19, warrant exclusion times of 14-21 days to account for incubation periods and to further reduce any risk.

2. **Viral RNA detection:** From oropharyngeal or nasopharyngeal (or other upper respiratory tract) swabs, using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) is a commonly used and reliable test for COVID-19 diagnosis, particularly in those at risk. A plethora of manufacturers have emerged with solutions that enable such testing to be done with the lead time, from test to results, being in the range of several days. Typically, viral RNA is readily detectable at the onset of symptoms, peaking at around a week after exposure to SARS-Cov-2 and often declines around week 3 after symptom onset[1]. One potential challenge with the test is sensitivity, with meta-analysis reporting pooled sensitivity of RT-PCR to be 89% (95% CI: 81%, 94%; I2=90%)[2]. As such, false negatives are a limitation of this approach and are related to the collection procedure and the viral detection assay use. Given the wide spread availability and relative low invasiveness, RT-PCR is a reasonable approach to screen for COVID-19 transmission risk in areas where contagion is high. However, screening of asymptomatic individuals diverts resources and needed testing from higher-risk populations, and for this reason it should be avoided when testing capacity is constrained or access limited.

3. **Measuring host immune response through serology:** Testing is another simple way to detect exposure to the SARS-CoV-2 virus responsible for COVID-19 infection, especially for those beyond 2 weeks post-exposure to SARS-CoV-2. IgM and IgG seroconversion has been reported to occur between the 3rd and 4th week of clinical illness with IgM declining and reaching undetectable levels by approximately week 7-8[1]. This could also be a potential tool to identify individuals who could be immune from the disease in the future. However, currently no serology tests are indicative of protective antibodies (i.e. neutralizing antibodies) and furthermore, at present it is still unknown if such protective antibodies can persist for a long period of time[1]. Given the wide spread availability of the test, relative low invasiveness, and utility in later stages of COVID-19 infection, serology testing can also be a useful adjunct to viral RNA detection in areas where risk of contagion is high. In terms of timing and frequency of viral RNA detection and serology, common sense would dictate that the testing should take place as close as possible to the visit date allowing for the time latency between testing and results availability.

4. **Chest imaging**: Bilateral multiple patchy areas of ground glass opacity and consolidation predominately in the periphery of the lungs are characteristic imaging features of COVID-19 on a chest CT[3,4]. Chest imaging has been reported to be a useful adjunct to viral RNA testing in the diagnosis of patients at risk of COVID-19 or with a symptomatic clinical presentation[5]. However, in a setting where a CRA is asymptomatic and has no at-risk features on history, its role is not as clear[6]. Moreover, the repeated use of imaging raises concerns over radiation exposure and utilization of healthcare resources. Scientific reviews have highlighted that radiation exposure from repeated chest imaging can lead to an increased risk of cancer[7,8]. The employee population making up CRAs are also often younger women of child bearing age, making it difficult to implement broadly. To this effect, multiple radiological organizations have stated that CT should not be relied upon as a diagnostic/screening tool for COVID-19[9,10,11].

5. **Hematology**: While there are multiple publications describing hematological changes and their potential risk for severe presentation of COVID-19, there is little describing changes seen in well, asymptomatic patients[12,13]. In general, so-called hematology markers are associated with prognosis of severe complications and not as a diagnosis aid to identify individuals at risk of having been exposed to SARS-CoV-2 and develop COVID-19 infection. As such, its use in a general screening is limited.

Table 2: questionnaire covering key areas of risk that can be implemented to reduce the risk of CRAs and Clinical Research Coordinators entering sites

RISK CATEGORY	QUESTIONS
Symptoms	• New onset symptoms such as cough and shortness of breath that have developed over the past 2 weeks or similar timeframe
Temperature	• Temperature measurement and excluding those with an active fever. Exact cut offs can vary depend on local practice.
Past history	• Exposure to individuals treated or diagnosed with COVID-19 • Known diagnosis (either clinical or lab confirmed) of COVID-19

Conclusions

Restarting clinical trials following the COVID-19 pandemic is a critically important activity. We have described a number of useful methods to manage this risk. The careful use of history to exposure, symptoms and temperature measurement, should form the foundation of any assessment in letting research staff back to sites because of the relative simplicity of these measures. In certain higher risk scenarios, RT-PCR may be of value. Likewise, when protective immunity can be detected by serology testing, this too will have significant value; unfortunately, such conclusive test is lacking at this time. Conversely, radiographic imaging is not an effective tool for screening asymptomatic individuals, and instead carries a small, but measurable risk, especially if applied frequently. Thanks to the availability of technology, a multitude of diagnostic tests and experience managing the pandemic, there is a pathway to sensibly restarting clinical trials in Asia Pacific that balances the risk of further outbreaks with the need to conduct medically important research.

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