A DISRUPTOR OR FALSE DAWN?

Remote Monitoring for Clinical Trials

Text by Dr Ng Wei Yan and A/Prof Daniel Ting

Clinical research has been an indispensable element in the advancement of healthcare. Prospective clinical trials, which embody the most rigorous of research methodology, are mostly conducted using age-old methods. These involve multiple scheduled on-site monitoring visits based on stipulated protocols throughout the entire study. Assessments are recorded at every visit by trained research personnel, with layers of monitors in place to ensure absolute Source Data Verification (SDV) in accordance with the Good Clinical Practice (GCP) guidelines. While these are held as the gold standard of research practice, they require tremendous amounts of time, effort and resources to reach a successful conclusion in reality. Large amounts of funding are required to sustain these research and the costs are invariably passed on to the patients once the study reaches commercialisation. This has led to some calls to explore more efficient and less demanding ways to conduct these studies by harnessing the power of technology. One of the key proposed conceptual changes involves the use of technological devices to enable remote monitoring of subjects. While such efforts are commendable, they have been met with relatively muted response due to the overall inertia and lack of interest within the industry.

What is remote monitoring?

The concept of remote monitoring in clinical trials involves the decentralisation of the study away from the designated site of the research. Clinical data is transferred virtually to the primary research site. This can include personal monitoring, video-conferencing monitoring as well as centralised monitoring in selected secondary sites. It requires a shift away from the hundred percent on-site SDV by assigned research associates to a remote SDV approach utilising risk-based monitoring. Risk-based monitoring focuses the verification efforts on high-risk research sites based on trigger events, thereby reducing the volume and frequency of monitoring required. The clinical sponsor will first need to perform a risk assessment to identify high-risk parameters and values, followed by a set of criteria that will serve as an alarm should such deviations occur. Once triggered, it will set off a cascade of risk-mitigation actions to ensure that (a) safety and rights of participants are not compromised, (b) reported data is accurate, complete and verifiable, and (c) trials are conducted to the highest standards in compliance with prevailing GCP requirements.

Remote monitoring of clinical trials is highly reliant on technological devices for the acquisition and transfer of research data digitally. Technological advancement has seen the rise of the Internet of Things such as smartphones, health monitoring wearables and fitness

wearables with increased connectivity through greater Wi-Fi/internet speeds and bandwidth. These technologies have sufficiently matured such that they can now be used to accurately gather data for clinical trials regardless of location, providing a combination of flexibility, automation and digitisation that was not previously possible. Video-conferencing, on the other hand, provides a different dimension of monitoring through a combination of a greater degree of social interaction and direct visualisation. This is of particular relevance when the research verifications require direct clinical visualisation or interaction (eg, symptom-based or user-experience assessment). A separate branch of remote monitoring involves centralised monitoring at distant sites separate from the original research site. This is usually conducted in peripheral centres with trained professionals and specialised equipment. These centres require purpose-built systems to aggregate, verify and transmit electronic health data securely.

Impact of COVID-19

The shift towards remote monitoring was recommended by the US Food and Drug Administration (FDA) in 2013. However, it failed to resonate with many sponsors and sites alike. This slow adoption has since seen a significant change when COVID-19 spread across the globe in 2020. Social distancing, lockdowns and movement curbs have made it increasingly difficult or even impossible to conduct clinical trials in the traditional way. Subject dropouts, poor-quality data collection and curtailed on-site verification ability have significantly hampered a vast majority of research trials. In addition, attention and manpower were redistributed to help combat the pandemic, resulting in increasingly strained clinical research resources. Lack of continuity put paid to significant efforts sunk into ongoing clinical research; hence many sponsors were forced into a radical rethink to cope with the altered healthcare landscape.

The oversight of clinical trials must be maintained against all odds in order to ensure participant safety. The impetus provided by COVID-19 has helped overcome inertia to adopt practice-changing models of care by shattering long-held beliefs. This has led to greater attention and translation to a remote monitoring model for clinical trials. However, this is by no means a straightforward and easy feat. A wholesale revamp in approach and protocols is required, accompanied by hardware and software restructuring to attain a high standard of remote monitoring. Furthermore, staff have to undergo urgent specialised training and deployment in order to deploy remote monitoring with haste.

One such example is the remote monitoring employed by Pfizer and BioNTech to push through their COVID-19 vaccine trials in record time. Due to lockdowns and social distancing measures, it was a logistical challenge to be able to conduct the large phase III trials using the traditional approach. It was out of sheer necessity that large-scale remote monitoring was employed and that provided the agility and dynamism required to successfully conclude the trial. Through the use of digital technologies such as Zoom and WebEx, they were able to overcome geographical barriers and significantly reduce turnaround akin to having round-the-clock continuous data monitoring.

Advantages of remote monitoring

Remote monitoring provides several unique advantages compared to the traditional on-site verification approach. Firstly, it reduces logistical barriers by decentralising monitoring, without the need for patient and personnel to travel to a single conducting site. As a result, monitoring and care is brought closer to home, saving time and cost. Furthermore, continuous or repeated measurements performed under such settings provide a better representation of real-life results.

Secondly, remote monitoring mandates the development of a set of supporting system capabilities. These systems improve access control by creating a secure unified or interoperable platform for sharing of source information to authorised individuals. This enables better tracking of source data which can reduce erroneous entries.

Thirdly, digitisation of data recording creates an audit trail which is crucial to deter fraudulent manipulation and correct any erroneous entry. The provenance of these data, including metadata such as timestamps and sources, is clearly recorded to ensure better integrity and accountability. It also replaces the traditional manual paperwork process which is time-consuming to transcribe, error-prone and laborious to both track and store.

Finally, remote monitoring standardises the reporting mechanism across multiple study sites. Proper stringent reporting requirements ensure better identification of any safety or protocol deviations in an early and reliable fashion. This is a crucial component prior to initiating a feedback loop which includes prioritised reviews, identification of compliance issues, and necessary corrective actions so as to ensure adherence to protocol stipulations.

Remote monitoring in practice

As the use-case for remote monitoring continually expands, it should be viewed as a complementary or alternative model, rather than a direct replacement, to the traditional on-site verification method. Not all parameters, and in essence clinical trials, are suitable for remote monitoring due to the complexities involved. Clinical trials that involve expensive or complex dedicated equipment would not be a natural fit for remote monitoring. Likewise, trials which require on-site attendance for clinical assessment will continue to adopt the traditional on-site model. Conversely, trials that involve monitoring using portable sensor technology and teleconferencing are most adapted for conducting trials remotely. Examples include symptom-based assessments for psychiatric research, cardiac monitoring devices as well as lung function assessments. The

methodologies of these studies could involve either new concepts of research with no established reference ranges, or new measurements using innovative digital products to achieve its aims. The novelty of such approaches, however, does require some level of pre-testing to be performed. The digital device has to undergo preliminary verification followed by clinical and analytical validation of the results before it can be put into larger clinical trials.

Proper application of remote monitoring into clinical trials will also require regulatory guidance and support. Due to lack of extensive experience, researchers can be befuddled by the requirements to assess the feasibility, safety and efficacy of remotely collected data. In this instance, the US FDA and European Medicines Agency have both released clear guidance to help sponsors and research sites transition from on-site to remote monitoring.

The future

Under the backdrop of a raging pandemic, it is likely that more clinical trials will be designed to adopt remote monitoring. This coincides nicely with the industry-wide push for digitalisation of healthcare as well as the ongoing need for movement control and social distancing to protect vulnerable patients. More advanced digital platforms such as blockchain technology could also come to the fore to provide even greater verification and tracking abilities. However, when the pandemic eventually subsides, whether this conceptual change possess sufficient momentum to change the research landscape irreversibly is really anyone's guess. Hopefully the infrastructural investment and experience gained by the research community during this COVID-19 pandemic will continue to spur efforts to decentralise clinical trials and adopt remote monitoring as the go-to standard whenever possible.

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