Hybrid Remote Trials – Current Trends and Application

The global crisis caused by the coronavirus has disrupted our personal and professional lives in ways that seemed inconceivable only a few months ago. This is also true for the conduct and operation of ongoing clinical trials. Social distancing rules, and reluctance to visit public places have presented significant challenges for the continued operation of studies, the collection of important clinical endpoint data, and the continued care and oversight of participating patients by study investigators.

Our industry has adapted quickly by leveraging technological solutions that have been available for some time. However, these solutions were suddenly scaled from small use cases to broad general application. The result? Sponsors have been conducting components of studies remotely, adapting studies initiated prior to or during the COVID-19 crisis to become hybrid remote trials (HRTs). HRTs are trials where some but not all study conduct is implemented away from the study site. The necessity to shift to HRTs has expanded industry experience and understanding of how and where these approaches work well and work best, and which will serve clinical researchers well in the design of new studies and programmes during and beyond the pandemic.

Some of the most common technology components of HRTs include enabling electronic informed consent (and re-consent) to be completed by patients from home; video consultation and visits; adapting site-based clinician assessments to be conducted via secure video or telephone; implementing site-based electronic patient-reported outcome measures (ePROMs) from home via web or interviewer administration; dispensing study medication to the patient at home; and enabling more engaging review meetings between site staff and patient using video.

Remote Consent

Remote consent is often discussed in the context of a study where patients are recruited through online campaigns and those meeting qualification criteria are provided access to an eConsent solution to learn more about the study and offer their consent to participate. One major limitation of this model is in our inability to confirm the identity and diagnosis of patients that are not known to the study investigator(s). However, remote eConsent offers a ready, practical and convenient approach to conducting the informed consent process with patients already known or identified by the study site(s). Patients can review study information through a web portal, tablet, or mobile app, using a media-rich presentation to review the terms, confirm understanding, and confer with family and friends.

It's important that eConsent not be a patient-alone process. Thus, remote consent encourages flagging questions to ask on parts of the study information. This enables the patient and investigator to retain the discussion around trial participation ahead of any consent decision. This way, patients can provide written informed consent to participate while having time to fully review materials and learn more about areas of uncertainty through one-to-one conversations with the study site personnel. While not yet optimised for global use in completely site-less clinical trials, eConsent enables and significantly enhances the consenting process in traditional and HRTs.

Clinician Assessments and Ratings

Secure, compliant video solutions offer the opportunity to deliver telemedicine as an alternative to on-site appointments. The success of this approach centres around the type of clinical endpoints to be measured at each "virtual visit", and whether these endpoints can be measured accurately, reliably, and consistently using alternative approaches. Examples include the measurement of vital signs using at-home sensors provided to the patient for use during a supervised video consultation; provision of a scheduled stool sample using a sample collection kit with courier pickup; and the measurement of complex clinician-reported outcomes (ClinROs) through video interviews with the patient. The determination of the acceptability of a clinical endpoint for remote measurement requires scientific and clinical judgement. For example, a psychiatric rating scale that is normally implemented using a structured interview in a face-to-face setting may require specific considerations including:

- Does the scale assess non-verbal cues as part of the rating (such as facial expression and tone of voice), and can these be adequately assessed via video or audio?
- Does the scale include assessments of a physical nature, such as tremor or muscle rigidity? Can these be observed and assessed adequately via video, even over lower bandwidth connections?
- Is the patient able to use the technology independently, or can this be achieved through the help of a caregiver or home-visit nurse?

With respect to HRT technology capacity of patients, a recent study examining "telemedicine readiness" amongst older US adults (n = 4525; mean age = 79.6 years) identified factors such as possible/probable dementia, difficulty communicating, and individuals that had not emailed, sent an SMS or "gone online in the last month", as measures of unreadiness of older adults to use telemedicine as part of routine care assessments[1]. Assessing the appropriateness of remote assessment technology for the study population is of vital importance, and in some cases it may be important to be able to triage between independent use, caregiver-assisted, and home-visit nurse-assisted implementation on an individual patient basis.

Site-based Patient-reported Outcomes

Some PROMs, such as quality of life and work productivity questionnaires, are typically collected infrequently and during site visits. In HRTs, these may be collected at the site where a physical visit is scheduled or collected at home where on-site attendance is not required. When combined with home-based patient diaries (*e.g.*, a daily symptom diary), solutions provided to patients for home diary completion may switch use between "home-instrument" and "site-instrument" completion when patients attend site or when these assessments are scheduled for remote completion. In other cases, for example where PRO data is only collected at study visits, patients can complete instruments using on-site hardware during

site visits (*e.g.*, site tablet), or using alternative approaches for at-home completion (*e.g.*, via the web or through a telephone interview with a trained interviewer). As with clinician assessments, where flexibility in the collection approach is designed into the study, it is important to be able to distinguish the data collection approach used for each assessment so that the consistency between approaches can be measured and reported to support the combination of the data in the final statistical analysis.

Direct-to-patient Medication Supply

RTSM systems that control the dispensation of study medication and the study's medication supply chain are adaptable to different models of direct-to-patient medication supply. These include supporting site-to-patient "last mile" delivery logistics of medication provided from the on-site medication inventory; or shipping medication direct to patient directly from local depot or central pharmacy upon the investigator's instruction. For HRTs, the latter approach has implications on the medication supply chain model and parameters associated with depot and site inventories, thereby adding complexity to the modelling needed to predict required inventories in both locations. Moreover, ensuring investigators retain dispensing authority throughout the study independent of the direct-to-patient supply chain model used is of paramount importance. Ensuring an "Amazon-like" delivery experience for patients, such as integrated shipping tracking, notifications, and delivery day/time rescheduling is an important additional feature that RTSM solutions are beginning to incorporate. Integration with patient engagement and eCOA apps provides the capability to provide traceability all the way to the patient through, for example, medication pack scanning.

Patient Engagement

In HRTs, keeping patients engaged and informed in the presence of fewer in-person clinic visits is increasingly important. Engagement apps typically comprise solutions to provide dynamic and scheduled reminders relating to study progress and procedures with the aim of driving greater protocol adherence; and comprehensive study and visit-by-visit guides to keep patients informed of study requirements. While routinely available for traditional studies, their value is seen as higher in studies such as HRTs where in-person meetings are less frequent. Engagement and eCOA solutions also provide the framework through which other technology components can be implemented – such as courier interactions, video meeting components for site-patient interactions, and reimbursement solutions.

Summary

While the use of remote study components may have increased as a result of the pandemic, in general these solutions are not new. This trend, however, does increase our experience and understanding of the use of these HRT building blocks which will enable their continued and optimised adoption in the new studies we are designing and implementing now and post-pandemic. Originally considered "trials of the future", HRTs have the potential to become far more mainstream than ever before – benefiting patients and making trial participation more convenient and attractive. The future starts today, not tomorrow[2].

REFERENCES

1. Lam K, Lu AD, Shi Y, Covinsky KE. Assessing Telemedicine Unreadiness Among Older Adults in the United States During the COVID-19 Pandemic. JAMA Intern Med. Published online August 03, 2020. doi:10.1001/jamainternmed.2020.2671
2. Pope John-Paul II

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