

COMMENTARY

Remote Monitoring in Clinical Trials During the COVID-19 Pandemic

Elena S. Izmailova^{1,*}, Robert Ellis¹ and Christopher Benko¹

The coronavirus disease 2019 (COVID-19) pandemic has rapidly challenged the pharmaceutical industry to implement remote clinical trials. The industry's lack of extensive experience with remote measurements initiates multiple questions about how to select candidates for remote collection, their validity, and regulatory implications of moving certain assessments to a remote mode. We propose a decision tree for migration of clinic to remote assessments and highlight activities required to ensure that these measurements are valid, safe, and usable.

The COVID-19 pandemic has rapidly changed clinical trials. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) expediently issued guidance on changes during the pandemic to protect patients and facilitate continued trial execution while maintaining good clinical practice standards.^{1,2} Both documents provide comprehensive guidance covering aspects of clinical trial conduct during the COVID-19 pandemic, such as starting new studies and continuation of ongoing studies vs. suspension. Both agencies strongly emphasize the importance of ensuring study participant safety, rights, and welfare. Both guidance documents cover aspects of clinical trial conduct, such as protocol amendment, communications with institutional review board/ethics committee, distribution of investigational product, remote site monitoring, handling informed consent in remote settings, and the importance of maintaining data integrity and audit trail. Additionally, the agencies promote consideration of whether trial visits can be conducted remotely, given that in-person visits may represent additional risk for specific patient populations. Moreover, at-risk populations in many geographies are requested to stay at home and clinic visits are often co-located with facilities repurposed for patients with COVID-19. The FDA guidance provides detailed recommendations for remote/virtual assessments, including considerations for remote data collection. For example, the agency acknowledges that not all assessments may support remote implementation. As a result, sponsors should consider the rationale and feasibility of such assessments, such as performance outcome (PerfO) assessments or interview-based clinician-reported outcome (ClinRO). Methods to ensure subject compliance and data collection consistency should be planned.

The opportunity for remote clinical trials has been recognized for some time and the industry is making inroads into this operational paradigm.³ The current pandemic, and the possible recurrence, have increased demand for remote trials and solutions for preserving trial integrity during the pandemic are being proposed.⁴ The lack of extensive experience leaves the scientific community with questions about how to determine whether clinic measurements are candidates for remote collection, including both safety and efficacy, and regulatory implications of moving certain assessments to a remote mode.

Remote data collection will not be feasible for all measurements. For example, certain assessments, such as bio specimen or imaging data collection, may require a visit to a local healthcare facility or home visit by a healthcare professional. However, certain instances, such as data collected via wearable devices, can support continuation clinical studies while protecting study participants and giving access to experimental treatments, which can be vital for many patients. The complexity of converting a clinic measurement to a remote one depends upon the availability of a reasonable remote counterpart, or whether an alternative measurement can be developed, requiring evidence of validity to be established. The effort required to deliver, technically and operationally, should be carefully considered.

Some key questions to consider for remote measurements are: (1) Which assessments are candidates for remote measurements? (2) Do the candidate measurements adequately capture a concept of interest? (3) What evidence is required to demonstrate that the candidate measurements are fit for purpose?

A decision tree can be defined to identify which clinic measurements translate to candidate remote measurements and determine the work required to define whether they are fit for purpose (**Figure 1**). Some clinic measurements have direct translations to remote measurement (e.g., pulmonary function test (PFT) or blood pressure test). Other measurements, such as a clinician assessment, may be suitable for remote implementation over video,⁵ whereas other clinician assessments, such as the postural stability test in Unified Parkinson Disease Rating Scale (UPDRS) Part III may not be safe to do at home. Patient questionnaires, such as the 36-Item Short Form Health Survey (SF-36), can be readily converted to a digital format and remotely deployed via a smartphone, tablet, or web browser. However, conversion to digital format typically requires confirmation that the

¹Koneksa Health, New York, New York, USA. *Correspondence: Elena S. Izmailova (elena.izmailova@koneksahealth.com)

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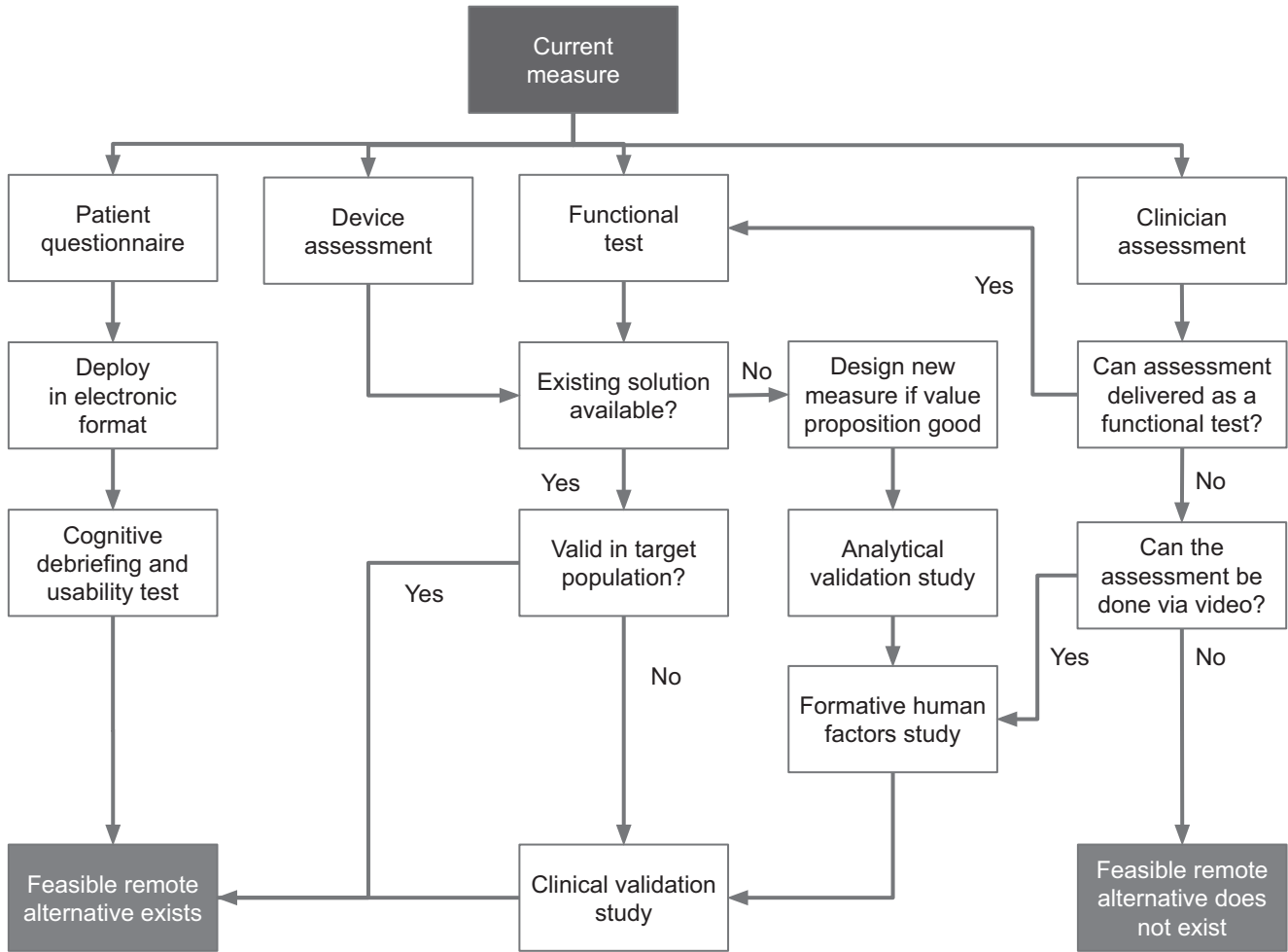


Figure 1 Decision tree for identification and implementation of remote measurements. Assessments under consideration can be categorized. For example, patient questionnaires, clinician assessments, device-based assessments, and functional tests. The decision on whether a certain assessment can be transferred to a remote mode depends on a remote counterpart availability (e.g., an electronic equivalent of a patient questionnaire normally taken during the clinical visits on the one hand, or the need for a remote assessment to be developed on another). For existing remote counterparts, the validity and usability in a population of interest and usability is a prerequisite. For novel assessments, both a design process and demonstration of analytical validity are required in addition to the requirements for existing counterparts.

migration does not change the meaning of the questionnaire, maintains usability, and does not result in additional patient burden.

Many clinic measurements, such as the 6-minute walk test or the Timed 25-foot walk test may be candidates for conversion into a functional assessment conducted via a functional assessment installed on a smartphone. The remote assessment may be supported with a patient diary or a clinician monitoring via remote video to ensure adherence to test protocol and provide test context for data analysis. Conversion of such clinic measures to remote functional assessments requires appropriate determination of analytical validity. Some measurements may also require clinical validity, given analytical validity has been established, because remote implementation of test protocol may not be exact and, as such, there may be variability in ability to capture end points due to variance in patient adherence to test protocol. Confirmation of usability and safe execution by patients in a

remote setting will be required depending upon the novelty of the implementation.

Additionally, measurements performed with devices that have wireless connected counterparts, such as heart rate or peripheral capillary oxygen saturation by means of pulse oximetry, can be also considered for remote data collection and constitute important safety assessments. The choice of a connected sensor should include evidence of analytical and, if appropriate, clinical validity along with human factor testing. The frequency and duration of data collection should be considered carefully. It is not given that a patient will be able to operate such equipment remotely or that the data collected is sufficiently valid “off-the-shelf.”

Attention must also be given to measurement frequency and schedule of assessments for remote measures. Many connected devices that measure vital signs can record the data in a continuous mode. Collecting clinical trial assessments in a remote mode, a.k.a. “in the wild,” is different

than during in person visits, and it has advantages and disadvantages. The biggest upside is that the data are truly reflective of how people feel and function in their natural environment. Very often a visit to the hospital creates inadvertent artifacts (e.g., whitecoat hypertension). On the other hand, the context of the data collection (e.g., emotional or physical activity state of the study subject), may not be available. Additionally, some of the data need to be triaged because it can contain motion artifacts or improper use of the device (e.g., a wrist-worn blood pressure cuff needs to be at the heart level to provide accurate readings). The data collected in the home setting may require a video connection with the site to ensure that the measurements are done according to the protocol and repeated if needed. Careful consideration of both implementation requirements and downstream data analysis and reporting/alerting is required to manage both the additional volume of data from continuous monitoring as well as protocols for responding to measures, which are outside reference ranges or below safety thresholds.

When considering the use of connected sensors for functional tests or switching to remote device-based assessments, it is important to understand the difference between device clearance for the purposes of legal marketing as a medical device in the United States and a tool for data collection in the context of human research. The main requirement for a device to be legally marketed in the United States under the auspices of the FDA 510(k) program is substantial equivalence to a predicate (already legally marketed) device using a similar engineering solution. The indications of use (specific patient populations and disease conditions) and the intended use (what is supposed to be measured) are part of the registration. There is a common misconception in the field that only devices with a regulatory endorsement, such as 510(k) clearance or exemption, can be used in clinical trials. No device is cleared for use in clinical trials; determination of unmet need, defining context of use and risk balance, as well as evidentiary criteria, which often includes analytical and clinical validity, are required.⁶

Regardless of the clinic to remote measurement pathway taken, several activities are required to ensure that the remote measurements are valid, safe, and usable. There is an opportunity to use pre-competitive studies to efficiently develop additional data to support remote measurement concepts for the industry overall. Examples of such a cross-industry collaboration could include:

1. Studies to assess the feasibility of diverse patient and caregiver populations self-administering vital sign assessments using connected technologies (peripheral capillary oxygen saturation by means of pulse oximetry, body temperature, heart rate, etc.). These studies should include development of reference ranges and test protocols, interpretation of continuous data collected in normal healthy volunteers and preferably in populations, which intersect high risk for hospitalization in the pandemic,⁷ and focus on significant therapeutic research areas, such as

diabetes mellitus type II, hypertension, asthma, or chronic obstructive pulmonary disease.

2. Known positive control or standard of care studies to demonstrate the utility, sensitivity, and statistical power of high-frequency or continuous remote technologies. Such studies provide the opportunity to determine if repeated measures support sample size reduction, minimizing the exposure risk at a population level. For example, PFT measuring values, such as forced vital capacity or forced expiratory volume, are currently deployed in 682 interventional studies available on clinicaltrials.gov. A remote PFT may facilitate the continued execution of these studies in an at-risk population.

In our experience, patient engagement is key to success and is underpinned by ensuring understanding and commitment to the utility of the measurement approach. The new measure should be easy to understand and manage by study subjects or quality and compliant data will not be obtained. In an ideal scenario, usability studies should be performed prior to device deployment in clinical studies. Usability studies may be conducted separately or incorporated into study screening periods.

The progress of adopting a decentralized clinical trial model and remote data collection was limited prior to the COVID-19 pandemic.³ However, the rapid adoption of telehealth during COVID-19 when remote doctor visits became vital and, in many instances, the only option for healthcare delivery demonstrated that many barriers can be removed within a matter of weeks.⁸ Clinical trials may take longer to adjust to the pandemic conditions but are likely to follow the same path. Many safety and efficacy clinical measurements can be performed remotely as attested by a number of feasibility studies.⁹ The rapid rate of adoption of remote measurements and sharing the experience and results can accelerate the field of clinical trials. During the COVID-19 pandemic, many details still need to be figured out; some of them will be done by trial and error. However, the current situation could be an opportunity to revamp the conventional clinical trial model making it more agile by opening access to a larger group of participants and revisiting what is essential and what is optional.

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