TRIAL WATCH

Remote digital monitoring in clinical trials in the time of COVID-19

Remote digital monitoring technologies can be used in clinical trials to evaluate novel end points that provide information that was previously difficult or impossible to obtain. These technologies could also make trials more efficient and less burdensome to participants while providing a more meaningful and complete understanding of patients' conditions and responses. However, despite these potential benefits, of the >73,000 active clinical trials listed on ClinicalTrials.gov, only 55 digital efficacy end points are currently being used in industry-sponsored trials of new medical products. Here, we highlight key points from a February 2020 workshop on remote digital monitoring convened by the Foundation for the National Institutes of Health Biomarkers Consortium, which involved experts from regulatory agencies, government, pharma and biotech companies, technology developers, patient groups and a variety of consortia (see Related links for slides and recordings). We focus on points that could be immediately useful during the COVID-19 pandemic in situations where clinic visits are restricted by quarantine measures and travel restrictions and the eligibility and ability of patients to participate in trials is affected.

Key points

Determining what is new versus what can be repurposed with regard to a digital drug development tool. Determining the level of complexity associated with demonstrating that a digital drug development tool is fit for purpose for use in a clinical trial can be conceptualized using four categories:

- Existing concept with existing measurement
- Existing concept with new measurement
- New concept with existing measurement
- New concept with new measurement

Progressing through the categories corresponds to increasingly complex requirements to demonstrate appropriate performance of the digital measurement tool in a given context. To support the application of this framework, examples and considerations that may be relevant to clinical trials in the context of the COVID-19 crisis are presented in FIG. 1a.

Taking a modular approach to the evaluation of a digital tool. A framework for determining whether a connected sensor technology is fit for purpose for remote monitoring in a clinical trial is shown in FIG. 1b (*npj Digit. Med.* **3**, 55; 2020). This 'V3' framework — verification, analytical validation and clinical validation — builds on the biomarker qualification evidentiary framework (*Sci. Transl Med.* **9**, eaal459l; 2017) and is intended to unite the different disciplines that should participate. First, by parsing out distinct steps, medical product developers and developers of digital measurement tools can more readily connect with the right experts within a regulatory agency early and often during the development process. Second, it enables industry to develop and evaluate sensor technologies, algorithms and clinical relevance separately. Finally, it facilitates

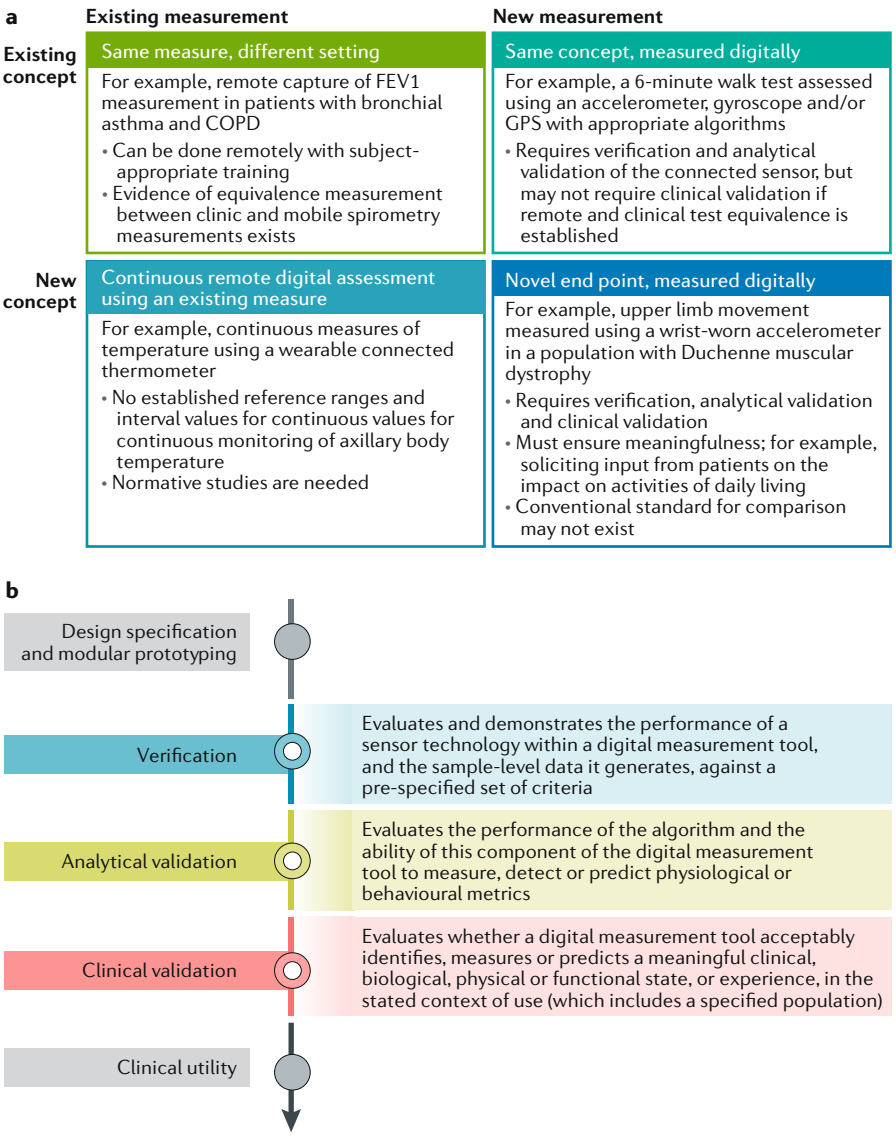

Fig. 1 | **Developing digital tools for remote monitoring in clinical trials. a** | A framework for evaluating the complexity of developing and using a new efficacy end point assessed with a digital tool in a clinical trial, with considerations for illustrative examples shown. **b** | Stages of the V3 framework for digital measurement technologies. Adapted with permission from *npj Digital Med.* 3, 55; 2020. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second.

the distribution of the evidentiary and documentation requirements across disciplines and organizations, and provides for the exchange and coupling of sensor technologies and algorithms based on the context of use.

Regulatory support for remote monitoring in clinical trials using digital tools. Regulators from the FDA and the EMA share values and approaches with respect to the evaluation of digital measurement tools for informing efficacy end points. The use of remote monitoring technologies is consistent at a high level with established frameworks for biomarker and clinical outcome assessment, and specific considerations for digital technologies are addressed by the V3 framework. During the COVID-19 pandemic, this regulatory support for the use of evidence-based remote monitoring technologies has been shown by the rapid issuance of temporary guidance by the FDA and the EMA (see Related links). The FDA recommends consultation with the appropriate review division where it is feasible to capture efficacy end points remotely and highlights the need for sponsors to evaluate the accuracy and reliability of remotely collected information. Similarly, the EMA emphasizes the need for the sponsors to discuss protocol changes that may impact clinical data interpretability with regulatory authorities and also suggests engaging an independent data monitoring committee to review the validation of outcomes that were measured differently during the pandemic.

In conclusion, the frameworks are in place to guide developers of medical products and digital measurement tools during the COVID-19 pandemic and beyond.

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Competing interests
J.C.G. is a part-time employee of HealthMode. E.S.I. is an employee of Koneksa Health and owns company stock. P.M.A.G. is an employee of Idorsia Pharmaceuticals and owns company stock. J.A.W. is an employee of Foresite Capital and a member of the FNIH Biomarkers Consortium executive committee.

RELATED LINKS
FNIH. Biomarkers Consortium - Workshop: Remote Digital Monitoring for Medical Product Development: https://fnih.org/what-we-do/biomarkers-consortium/programs/digitalmonitoring
FDA. Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency
EMA: Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic: https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic