COVID-19 COMPENDIUM

WHITE PAPER

Maintaining Accuracy and Precision of Evaluations in Medical Trials During COVID-19

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COVID-19 COMPENDIUM

This informational white paper is part of a compendium intended to share best practices and ongoing learnings related to the impact of COVID-19 on ongoing and planned clinical trials. Content is authored by a dedicated team of experienced scientists, clinicians, technologists, and data quality experts. To read other white papers in the series, please visit **www.signanthealth.com/covid**

The COVID-19 pandemic of 2020 has placed clinical trials in a new, unique state. Social distancing guidelines as well as the virus itself have forced the industry to modify its practices and procedures overnight. And, while the clinical research industry has dealt with disruptions in the past, the speed, scale, and duration of the COVID-19 pandemic present challenges never before seen.

As a result, the industry is in a period of rapid transition during which it must carefully analyze, plan, and adjust to protect patient safety and trial integrity now, while also preparing for a "new normal" in trial design and conduct in the future.

Maintaining accuracy and precision of data evaluations during COVID-19 presents unique challenges. At Signant Health, we're continually consulting with customers regarding data collection practices, data monitoring, and data analysis to help ensure that impacted trials are ultimately interpretable and valid. When considering endpoint data and how to maintain study validity, there are two primary approaches: simplification and modification.

SIMPLIFICATION

First, **the amount of endpoint data at risk should be determined**. If the study is nearing completion, it may be advisable to manage a small amount of missing endpoint data during the final statistical analysis rather than to potentially introduce additional complications through changing endpoint data collection methods or using surrogate endpoints. All statistical analysis plans (SAP) are equipped to handle missing data. It is important to meet with the study statistician to determine if additional or alternative missing data analyses are required to specifically address missing data resulting from operational and logistical challenges brought about by COVID-19.

It may also be possible to **simplify by modifying the protocol to collect less data**. The visit schedule should be scrutinized and unnecessary visits and data collection should be reduced or eliminated. This can ease the burden on investigative sites and patients while decreasing the number of protocol modifications which otherwise may need to be considered.

Another option for simplification would be to **consult with the Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)**. As these committees are often privy to unblinded efficacy data, it would be appropriate to ask the committee to evaluate whether there is evidence of either futility or overwhelming benefit. Evidence of either could simplify further decision making about any modifications being considered. It is possible and reasonable, though maybe logistically challenging, to convene a DSMB/DMC in-study for those clinical trials which do not already have one in place.

MODIFICATION

When considering modifying endpoint collection methodologies for an ongoing trial, it is highly recommended to consult with the study statistician, subject matter experts, Institutional Review Board (IRB)/Ethics Committees (EC), and DSMBs/DMCs before implementation.

Given the unique challenges presented by the COVID-19 pandemic, it is reasonable to consider methodologies such as telephone visits and video visits for remote administration of rating instruments and collection of endpoint data. Consultation with subject matter experts and review of the literature may reveal that some, but not all, rating instruments have already been validated for remote administration. For those that have not, it will be important to thoughtfully collect the necessary ancillary data that would allow for in-study validation of the remote administration methodology and thus improve the final interpretation of the study. Additional data such as the mode of administration (telephone, video, home health visit), who administered the assessment (investigator, study nurse, other), and why the assessment was performed remotely rather than in the clinic (investigative site closed, travel restrictions, patient illness) should all be captured and the EDC or other electronic data capture platforms should be modified accordingly.

Care should be taken to standardize any change in the administration of rating instruments. It cannot be assumed that assessments performed over telephone or video produce the same data as assessments performed in person, and correctly assessing a patient reported outcome (PRO) over the telephone is not as simple as it may seem.

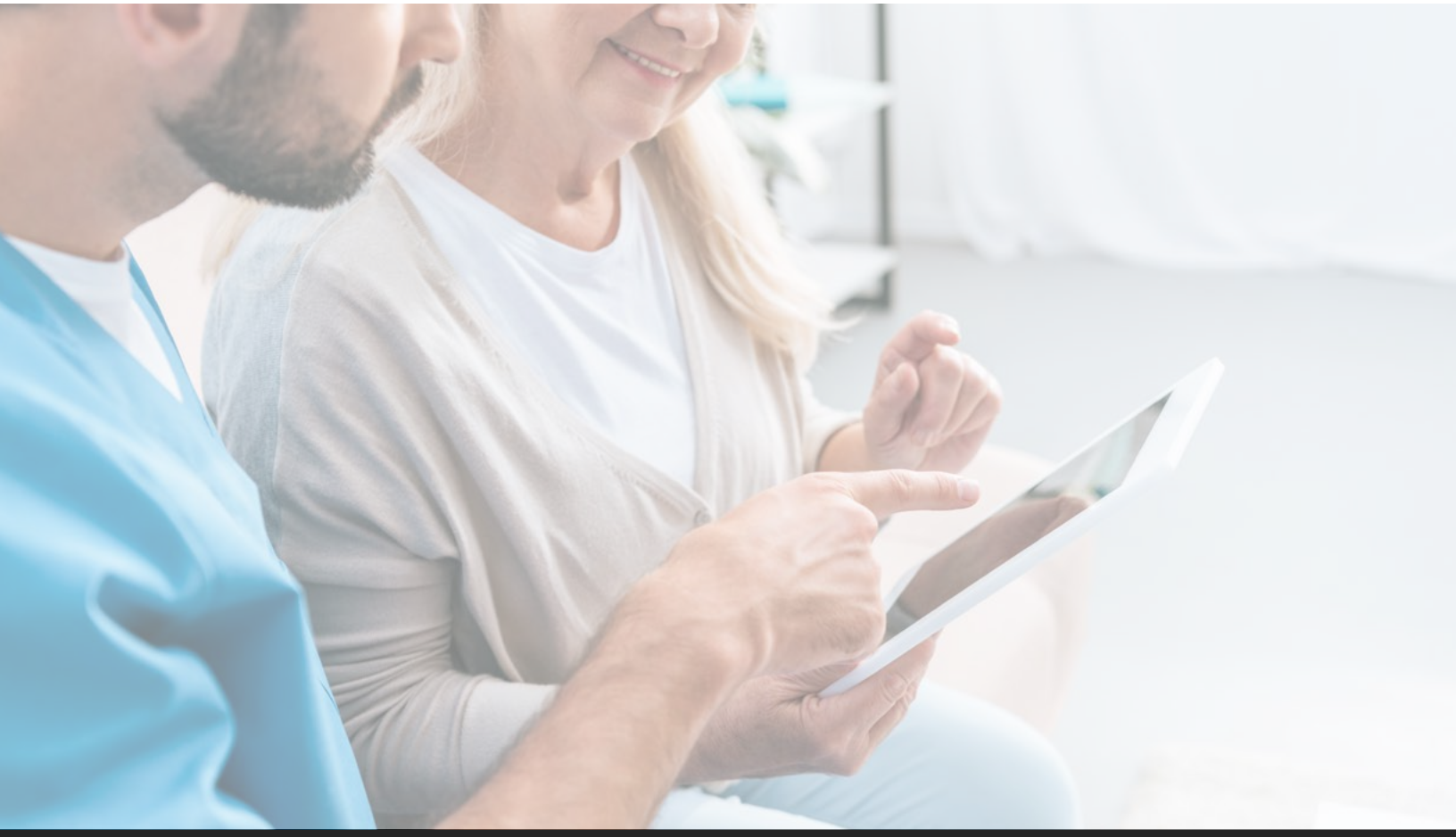
TRAINING THE PERSONNEL WHO WILL BE ADMINISTERING REMOTE ASSESSMENTS WILL BE ESSENTIAL TO DECREASE VARIABILITY AND REDUCE INTRODUCTION OF BIAS AS MUCH AS POSSIBLE.

Consideration should be given to implementing enhanced centralized statistical monitoring of endpoint data such as Signant Health's Blinded Data Analytics. Endpoint monitoring would allow for near real-time evaluation of outliers, patterns, or trends in the endpoint being collected remotely compared to the data previously collected in-person. Quick identification of data anomalies and the implementation of mitigation strategies would decrease variability and improve future validity analyses.

Statistical analysis plans will need to be updated to evaluate the impact of changes in endpoint assessment methodologies, as ongoing multi-year studies are likely to end up with three unique data subsets: data obtained before COVID-19, data obtained during and impacted by COVID-19, and data collected after COVID-19. Time and effort should be invested now in planning the additional statistical analyses necessary for this unique scenario.

LOOKING FORWARD

While focusing on the urgency of the here and now, preparing for the future "new normal" is equally important. It is anticipated that investigators and patients alike will realize remote visits are more effective than previously thought and that incorporation of remote visits in future trial designs will become commonplace. There will be an urgent need to validate existing rating instruments for remote administration and to develop new novel methodologies for remote assessment of disease endpoints. Something positive should come out of the widespread disruption caused by the COVID-19 pandemic, and this something should be the rapid modernization and decentralization of clinical trials that has been discussed, but not implemented, for the past decade.



WHO IS SIGNANT HEALTH?

The best technology succeeds in the background. Signant Health provides solutions that simplify every step of the patient journey to make it easier for people to participate in, and for sites and study teams to run, clinical trials. Signant unites eCOA, eConsent, Patient Engagement, IRT, Clinical Supplies and Endpoint Quality into the industry's most comprehensive patient-centric suite – an evolution built on more than 20 years of proven clinical research technology. Our intense focus on the patient experience, deep therapeutic area expertise and global operational scale enable hundreds of sponsors and CROs (including all Top 20 pharma) to extend the reach of drug development, expand patient opportunities and improve data quality – helping them bring life-changing therapies to our families and communities around the world. Take a significant step toward patient-centricity at signanthealth.com.

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