COVID-19 COMPENDIUM

WHITE PAPER

Considerations for Mixing Modes of Patient-Reported Outcomes Data Collection in Clinical Trials Affected By the COVID-19 Crisis

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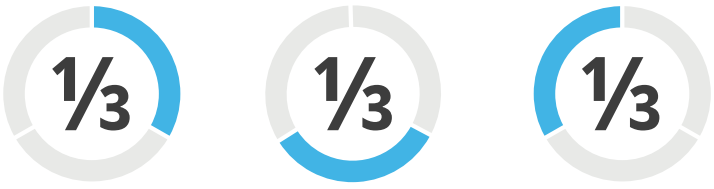
COVID-19 COMPENDIUM

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**

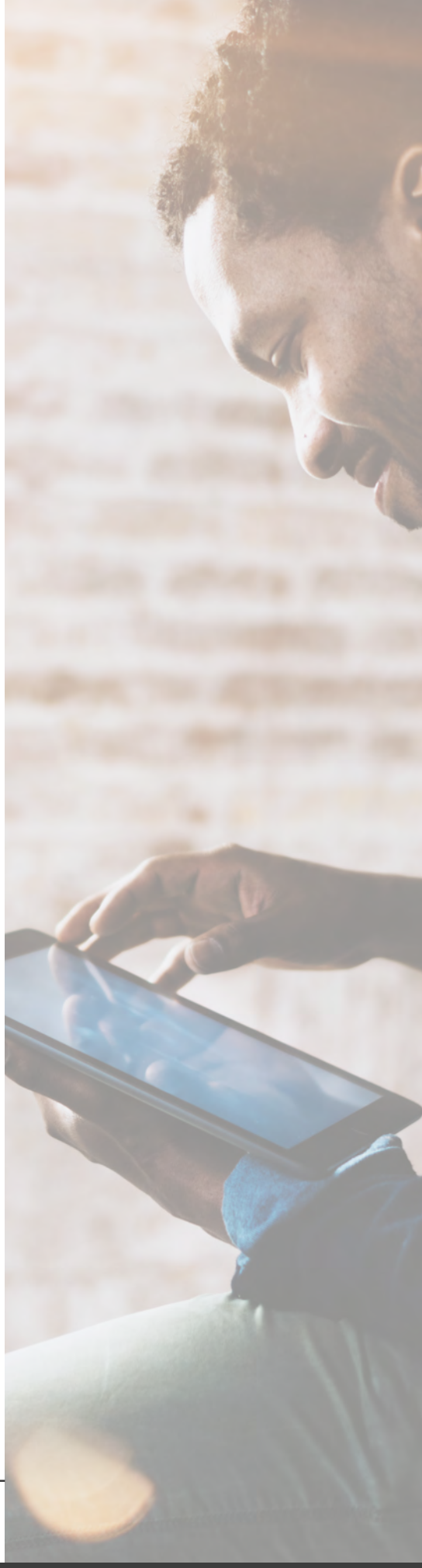
DATA COLLECTION IN CLINICAL TRIALS AFFECTED BY COVID-19

The global crisis caused by coronavirus has disrupted our personal and professional lives in ways that, only a few months ago, seemed inconceivable. This is also true for the conduct and operation of ongoing clinical trials. Traditional clinical trials rely upon face-to-face consultations between patients and the investigator and other site staff to assess whether it is safe and appropriate for their continued participation, and to collect important clinical safety and efficacy data to measure intervention and disease effects. While some patient-reported outcome measures (PROMs) are already collected at home, many still form part of the assessments completed by patients during a site visit (e.g., many quality-of-life instruments are implemented during on-site visits). At Signant Health, for example, we see approximately one third of studies requiring only home-based ePRO, a further third requiring only site-based ePRO, and the remaining third requiring both home- and site-based PROMs.



The sudden requirement for social distancing in many territories across the globe has made it impossible for patients (and sometimes site staff) to attend site visits and to complete site-based PROMs and other clinical assessments. Additionally, in areas where patients are free to move, some patients are unsure and reluctant to attend these visits. Not only are the sponsors of trials for critical medicines (such as oncology and rare disease treatments) seeking to continue data collection during this crisis, but many other studies are also seeking to implement alternative ways to collect data while physical on-site visits are not possible for many patients.

STUDIES ARE ALSO SEEKING TO IMPLEMENT ALTERNATIVE WAYS TO COLLECT DATA WHILE PHYSICAL ON-SITE VISITS ARE NOT POSSIBLE



ALTERNATIVE MODES OF DATA COLLECTION

Sponsors and vendors are adapting to implement alternative ways to collect site-based PROMs where on-site ePRO solutions, typically using tablet computers, were intended to be used. These alternative approaches include the provision of paper questionnaires, the use of video or telephone interviews to administer the instruments in addition to collecting other visit-related data, and the use of web backup capabilities. Each approach has potential advantages and limitations, but it is advisable to implement only a single alternative approach across all sites within a clinical trial.[1]

PAPER DATA COLLECTION

Paper data collection can be supported by the large body of evidence supporting the measurement equivalence of instruments when migrated to electronic screen-based formats, but (especially in unsupervised settings such as home completion) is associated with well known data quality and integrity limitations – it is hard to verify the timing of instrument completion, and there is increased potential for conflicting, ambiguous or missing entries. Despite these limitations, paper-recorded PROM data remains used and accepted in regulatory drug submissions. In addition, paper collection in this context is associated with additional challenges around unplanned production and distribution of paper versions and ensuring the safe return of completed forms. When transitioning to the use of paper it is recommended that, where practical, Sponsors utilise the original paper-developed formats of the instruments as these were validated for paper completion and also formatted for optimal and compact layout on paper. Many instrument license owners are receptive and responsive to requests for license changes and to provide paper versions during this crisis.

INTERVIEWER ADMINISTRATION

Interviewer administration by video or phone may mitigate some of the concerns over paper data collection as the site staff are able to validate the time/date of completion and mitigate some of the data quality concerns. However, site staff may feel they do not have the time to work through questionnaires with patients during telephone consultations. Some instruments are associated with a validated interviewer-administered version (e.g., EQ-5D), and where available it is recommended that these are used. However, many instruments do not have a validated interviewer version available and in these cases each PROM should be assessed for its suitability for interviewer administration – for example, does the scale contain response scale types that cannot easily be administered via interview (e.g., visual analogue scale), or is the nature of questioning thought to influence patients' responses in an interview setting as opposed to private completion using an electronic solution (e.g., questions of a sensitive or embarrassing nature)? Where scales are considered suitable for interview administration it is recommended that sites provide a copy of the paper version of the instrument to patients to act as a reference for the patient during the interview. Some instrument authors have recommended this approach as a way to help maintain consistency in instrument delivery when using this approach.

WEB BACKUP

Web backup has the advantages of electronic data capture including time/date stamping and data edit checks to eliminate missing, conflicting and ambiguous entries. However, web backup may be associated with delayed implementation times, complexities in providing alternative access credentials to patients, provision of training for patients and sites on use of the new solution, and troubleshooting suitable access using patients' own mobile devices and computers.

By implementing a new mode of data collection, we are mixing modes – that is, collecting data via one mode (site-based ePRO) and then also by a further mode such as one of those described above. While we seek to limit variability and potential sources of bias in our experimental designs by standardising around a single approach, in situations like the COVID crisis mixing modes may provide the only approach to ensuring data are collected as opposed to being missing.

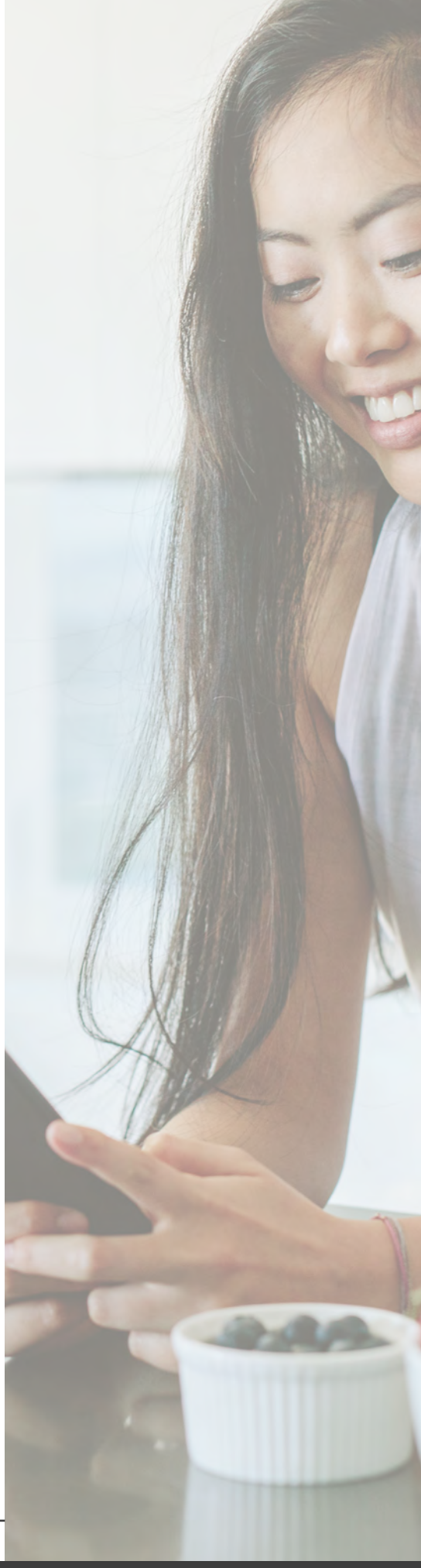
> MIXING MODES MAY PROVIDE THE ONLY APPROACH TO ENSURING DATA ARE COLLECTED AS OPPOSED TO BEING MISSING

CONSIDERATIONS FOR MIXING MODES

The ISPOR PRO Mixed Modes Good Researches Practice Task Force identified in their report of 2014 that mixing modes within a patient they consider to be associated with an "extremely high" risk to measurement equivalence.[2] Despite discouraging this approach, the task force identified that there may be cases in which data would otherwise be missing that may require mixing modes. This is the situation that faces us now.

Since the publication of the mixed modes recommendations and the earlier ISPOR recommendations on evidence to demonstrate measurement equivalence between paper and electronic formats in 2009 , there has developed a substantial body of evidence supporting measurement equivalence between modes of data collection when solutions are designed following ePRO design best practice principles. [4,5]

The majority of patient-reported outcomes (PRO) instruments are comprised of a small set of common response scale types: visual analogue scales, verbal response scales (including Likert scales and yes/no responses) and numeric response scales. In addition to these, the commonly used EQ-5D instrument contains a vertical index (the EQ-VAS) that is also well understood. The industry has substantial evidence already that the measurement properties of instruments containing these standard response scale types are maintained between common presentation formats when best practices are followed. Specifically, this evidence is provided in a number of meta analyses [6-8] and a synthesis of cognitive interview and usability studies.[9] In addition, a recent bring-your-own-device (BYOD) equivalence study[10] provided strong evidence that instrument measurement properties are maintained when mixing device types in a BYOD setting, where migration best practice is applied. These are well summarized in a recent commentary and industry textbook.[11,12]



Despite this, there is a subtle difference between implementing a new format to be used by all patients across a study, and switching patients to a different mode within a study. Subtle differences between modes could theoretically introduce additional error or bias into estimates of within-patient change when modes are interchanged within an individual. This risk applies to the move to any alternative mode of data collection mid-study, and while existing evidence would suggest that we have strong grounds to expect equivalence to be maintained in this scenario, we should do what we can to mitigate this and to prepare to defend the data when under future regulatory scrutiny. That in mind, Sponsors and vendors might look to consider the following (but not limited to):

> THERE IS A SUBTLE DIFFERENCE BETWEEN IMPLEMENTING A NEW FORMAT TO BE USED BY ALL PATIENTS ACROSS A STUDY, AND SWITCHING PATIENTS TO A DIFFERENT MODE WITHIN A STUDY

1 SUMMARISE EXISTING EQUIVALENCE DATA TO SUPPORT EQUIVALENCE BETWEEN MODES

This could include both data relating to the specific instruments used that is developed by the sponsor or vendor or reported in the literature, and the growing body of evidence relating to other similarly constructed instruments.[11]

2 ENSURE THAT DATA COLLECTED USING THE ALTERNATIVE MODE CAN BE CLEARLY IDENTIFIED IN THE ANALYSIS DATASET

Ideally this is accomplished using the electronic system if interview/ paper/ web data are entered directly into the same ePRO solution, but it may also be accomplished with suitable study documentation implemented throughout the new process (e.g., site attestation record for each telephone interview visit) or records contained in other systems such as EDC. This will enable summary statistics and analytics to be provided to support the notion that the data collected with each mode exhibits similar and consistent properties, and also that study conclusions are robust to the influence of data collected using the different modes, for example using a sensitivity analysis.

3 ENSURE THAT DATA INTEGRITY IS MAINTAINED

Sponsors should avoid enabling sites to enter data from paper records or telephone interviews by sharing the patient logon credentials as this will make it impossible to distinguish between patient-entered ePRO data and site-entered data; and would contravene CRF 21 Part 11 making it impossible to determine the identity of the user for each data entry. Instead, proxy user logons or "replacement patient instances" (where a replacement device function is used to create a new instance of an existing patient – often implemented to allow easy continuation of use in the event of a device loss or breakage) may provide a suitable approach when accompanied with appropriate process documentation and associated investigator approval/signature.

These are not unsurmountable considerations and, in my opinion, should not discourage the implementation of mixed modes when the alternative we face is loss of continued data collection. As we progress, Sponsors and vendors will continue to work together on pragmatic solutions to facilitate the continued conduct of our clinical trials, the support of patients and the important data they provide. We may look back on this as a time when we worked together more closely as cross-company teams with a common purpose, and learned more about our existing approaches to help refine and future-proof these for the new clinical trials that we will continue to design and develop once this crisis has passed.

> WE MAY LOOK BACK ON THIS AS A TIME WHEN WE WORKED TOGETHER MORE CLOSELY AS CROSS-COMPANY TEAMS WITH A COMMON PURPOSE

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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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