

Collecting Patient Experience Data During the COVID-19 Outbreak

Commentary on Best Practices



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The power of **knowledge.**
The value of **understanding.**

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ABBREVIATIONS

ClinRo	clinician-reported outcome
COA	clinical outcome assessment
eCOA	electronic clinical outcome assessment
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HRA	Health Research Authority
IEC	independent ethics committee
IRB	institutional review board
MHRA	Medicines and Healthcare Products Regulatory Agency
ObsRO	observer-reported outcome
PCOA	Patient-Centered Outcomes Assessment
PED	patient experience data
PerfO	performance outcome measure
PRO	patient-reported outcome
RTI-HS	RTI Health Solutions
UK	United Kingdom
US	United States

1 INTRODUCTION

The COVID-19 pandemic has introduced the potential for unprecedented challenges for the conduct and interpretation of results from both clinical and observational studies. These challenges could result in delays in the ability to complete studies as planned, as well as pose threats to the internal and external validity of these studies. For example, COVID-19 may impact the physical health of some study participants and will almost certainly influence the emotional and psychosocial functioning of all study participants, potentially confounding study results. Travel limitations due to social distancing, quarantine, or shelter-in-place orders may limit patient and study team access to sites and other resources. Study participants may be unable or unwilling to attend in-person visits, electronic clinical outcome assessment (eCOA) data collection could be impacted by slow or lost Internet connections, and researchers may not be available to conduct in-person assessments. Notably, these examples do not comprise an exhaustive listing and other unanticipated obstacles may emerge.

The Food and Drug Administration (FDA) has recognized and described logistical implications of the COVID-19 pandemic in the emergent guidance document *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic* (FDA COVID-19 Guidance). Within this guidance, the FDA acknowledges there may be “unavoidable” protocol deviations and provides some recommendations (FDA, 2020a). In addition, although the FDA’s *Patient-Focused Drug Development Guidance: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making* (FDA PFDD discussion document 4) is in early stages of development and not specific to COVID-19, it does include an estimand framework which incorporates the occurrence of intercurrent events defined as “events that occur after randomization/treatment initiation/or trial start that either preclude observation of the variable (and potentially subsequently the endpoint) of interest or affect its interpretation” (FDA, 2020b). Outside of the United States (US), the Medicines and Healthcare products Regulatory Agency (MHRA, 2020) and the Health Research Authority (HRA, 2020) in the United Kingdom (UK), as well as the European Medicines Agency (EMA, 2020) in the European Union (EU), have provided additional recommendations to support research and recognize specific challenges related to the COVID-19 pandemic.

To help mitigate some of these impacts of COVID-19 on the collection and use of clinical outcome assessment (COA) data, RTI Health Solutions (RTI-HS) Patient-Centered Outcomes Assessment (PCOA) staff have collaborated to create a best practices document. The goal of the document is to (1) recognize patient safety as paramount and (2) support research and the collection of high quality, evaluable data as generated from COAs.

The content of this document is based upon current FDA recommendations for patient-focused drug development (PFDD) and other more emergent regulatory commentary

specific to COVID-19, as well as guidance from sources outside the US such as the MHRA and HRA in the UK and, more broadly for the EU, the EMA. Finally, this document represents the combined expertise of the members of the RTI-HS PCOA staff, including qualitative and quantitative research experts, and provides general best practice guidance. Researchers should ALWAYS consider the specific elements of individual studies, reporting requirements, and institutional review boards (IRB)/independent ethics committees (IEC) when applying this guidance.

2 DETERMINING GO/NO GO DECISIONS

Determine path forward -- Stop study? Delay study? Consider alternative methods?

2.1 Patient Safety

As with all human research, patient safety is our first and foremost consideration. Teams must review current study-related COA procedures and requirements, which may impact patient safety in the light of the COVID-19 pandemic or may not meet current guidance from world or local health agencies.

For example, the prevalence of COVID-19 in a given area or guidance from world or local health agencies may impact study participants' ability or willingness to attend site visits as planned. This may impact completion of COAs for those that are self-completed or may interfere with standard administration practices for interview-based assessments, clinician-completed or administered instruments, or administration of performance-based measures. The EMA provides general considerations to lower study participant risk, including the conversion of visits from physical to virtual, postponement or cancellation of visits, or extension of trial durations. However, all such measures may influence the quantity and quality of COA data, and these repercussions are not discussed in any of the current FDA or EMA guidance documents.

Notably, for studies determined to be appropriate for continuation that utilize COAs, continuity in data collection is typically recommended by RTI-HS if there are no threats to patient safety in collecting the COA data and if the data collected can be captured with reasonable reliability and accuracy. Each research team must carefully consider these factors based on each individual study.

2.2 Continuity in Data Collection

In consideration of alternative methods...

Second to patient safety is the ability to collect high-quality data that will be both useful for interpretation and accurate to address the study research questions. Teams should evaluate the following elements of each COA: the MODE and METHOD of administration, the context

of use of the measure, and the relationship between MODE/METHOD and instrument interpretability. Researchers must determine if the COA's established measurement properties are likely to be stable across different administration modes and methods (FDA, 2020b). Notably, requirements for IRB/IEC approvals for changes in design or methods will vary by region. For example, the FDA COVID-19 Guidance encourages engagement with IRBs and IECs to review emergent changes to study protocols or informed consents (FDA, 2020). The guidance notes that changes to eliminate hazards may be implemented and documented as protocol deviations but study-wide changes require approval and still need to be described in an amendment (CFR § 312.30(b)). The MHRA and HRA do not include this stipulation and instead provide specific circumstances for which an amendment or submission is not required.

Key steps of maintaining continuity in this data collection process are outlined below:

- Determine and prioritize all COAs impacted and map the administration schedule; determine the importance of data collection (mandatory vs. exploratory).
 - Patient-reported outcome (PRO)
 - Clinician-reported outcome (ClinRo)
 - Observer-reported outcome (ObsRO)
 - Performance outcome measure (PerfO)
- Review instrument user manuals to determine standardized administration modes, methods, and scoring algorithms.
 - Determine options specified by the instrument developer.
- Determine the availability of different accepted modes of administration for each COA and if a faithful migration to an updated mode is necessary and feasible.
 - Self-report
 - Observer report
 - Interview
- Determine availability of different data collection methods and whether a faithful migration to an updated method is necessary and feasible.
 - Paper
 - Computer-assisted/electronic (including telephone)
 - Web-based performance measures
- Consider how the method of data collection may impact the mode; i.e., can this information still be accurately captured?

- Determine language/cultural technological implications for alternative modes or methods.
- Determine appropriate migration steps to shift MODE or METHOD.
 - Instrument characteristics – is it possible to migrate? Impact of migration on data validity/reliability
 - Paper to electronic: maintaining elements of paper (ability to skip, multiple items per page, etc.)
 - Electronic to paper: skip patterns/computer-aided technologies; loss of time/date stamp
 - Complexity: multidimensional vs. symptom checklists
 - Scaling
 - Visual elements
 - Timelines to complete or execute
 - Licensing to allow alternatives:
 - Are alternative modes/methods available?
 - Are alternatives supported by the developer?
 - Does use of alternatives require special permissions?
 - Determine logistical implications.
 - Need for data entry
 - Data transfer
 - Ability to quality check data
 - Data integrity and maintenance of protected information
 - Review recall period of each instrument.
 - Modify administration schedule if needed.
- Review study consent; evaluate need for consent modification and/or determine need and potential for reconsenting.
- Prepare site training.
 - Determine needs/methods for site training.
- Prepare patient/subject/participant training.
 - Determine methods for administration/support
- Consult/submit to IRB/IEC.
 - Carefully consider all regional issues relative to IRB/IEC approvals and requirements.

- Requirements will differ by region and organization.
- Consult FDA if COA contributes to an efficacy end point (see Determine Documentation and Needs for Reporting section below).
 - Per FDA COVID-19 Guidance (FDA, 2020): “Protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens” should be discussed with the FDA. “The sponsor can document protocol deviations using its standard processes, or given the larger expected number of such deviations, use alternative documentation approaches. For example, if visits are to be conducted by telephone/video contact rather than at the investigational site as specified in the protocol, documentation that provides a listing of all study visits (e.g., listing study reference number, patient ID, date of visit) that are deviations from the protocol due to the current COVID-19 situation generally would be acceptable.”
 - “For a study-wide change in protocol conduct, protocol amendments that are necessary to prevent imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND or IDE.”
 - “Protocol amendments that are not required to prevent imminent safety risks to patients can be implemented once they are submitted to FDA and IRB approval has occurred.”
- Prepare, administer and document site training.
 - Prepare patient/subject/participant training.
 - Best practices based on mode and method should be followed.
 - All sites should confirm that COAs may be completed with reasonable comfort and minimal distractions.

3 THREATS TO EXTERNAL AND INTERNAL STUDY VALIDITY

Multiple factors are related to the external and internal validity of a study conducted during the COVID-19 pandemic. Some internal validity parameters may be addressed through faithful migration of instrument mode or method and/or adaptation within developer-approved modes/methods that are determined to be reasonable and feasible in light of study design. Missing data may constitute an internal threat to validity.

The generalizability of COA data may be influenced by response shift, which is also relevant to this discussion.

3.1 Missing Data Implications

Missed site visits due to travel restriction or confinement, problematic eCOAs without manned help desks, changes in data-monitoring ability, or other study interruptions during the COVID-19 pandemic may result in significant amounts of missing data. Large amounts of missing data could impede the ability to interpret results from COA measures. Methods to address missingness may be COA specific, or teams may introduce study-wide data-handling conventions. Sensitivity analyses should be considered when applying missing data rules. Regardless, all methods should seek to support the most reliable and valid data interpretation.

Key methods to address missing COA data are outlined below:

- Review COA data collection tools to build processes to avoid missingness.
 - Missing event-driven data: provide option to report additional events
 - Missing scale-level data: provide a data-handling convention to distinguish between data that do not exist and data deemed unreliable/not meaningful
- Review statistical analysis plan/psychometric analysis plan.
 - Review user manual.
 - Add details prior to database lock how protocol deviations will be addressed.
 - Sensitivity analyses
 - Supplementary analyses
- Apply appropriate statistical methods.
 - Account for missing data and any implications for evaluating clinical benefit.
 - Verify inferences are robust.
 - Assess for deviations/limitations in the data—deviations from assumptions.
 - Ensure sample sizes are adequate for the anticipation of missing data and any correction schemes are prospectively defined.

3.2 Response Shift

A response shift is defined as the phenomenon “by which an individual’s self-evaluation of a construct changes due to internal standards of measure, change in values or priorities or a personal definition of a target construct” (Sprangers and Schwartz, 1999; Schwartz et al., 2007). Response shift can sometimes explain paradoxical findings in COA scores over time (Sprangers and Schwartz, 1999; Schwartz et al., 2007). Individual experiences of COVID-19 may initiate or increase the likelihood of a response shift, and, consequently, they may impact whether COA data can be considered meaningful in the context of a study setting. Notably, some instruments may be more vulnerable to response shift, such as generic

measures designed to assess psychosocial impacts, health-related quality of life, or well-being. Measures designed to assess more proximal aspects (core signs or symptoms) of disease may be less susceptible. However, disease-specific measures may be influenced by a respondent contracting COVID-19 (confounding signs or symptoms) or fear of contracting or actively avoiding contracting COVID-19 (impeded activities of daily living).

Key steps to determining and addressing threats to internal and external validity of COAs are included below:

- Determine the concept of interest for each study's COA measure.
 - Determine susceptibility of measure to response shift.
 - Generic vs. disease specific
- Determine types of analyses to evaluate the possibility of a response shift.
 - Review of effect indicators such as skewed distributions
 - Sensitivity analyses
 - Correlation-based methods (e.g., factor analysis, structural equation modeling, construct validity correlations)
- Recognize that COVID-19 is likely to have the same impact across groups for randomized studies.
- For studies on hold, determine “safe” restart period.

4 OTHER METHODS FOR THE CAPTURE OF PATIENT EXPERIENCE DATA

Patient experience data (PED) may be captured through means other than use of COAs or surveys. For example, PED is commonly captured through qualitative methods, including but not limited to concept elicitation, screening, and exit interviews, as well as focus groups. PED that is captured using qualitative methods during or around the time following the COVID-19 pandemic may be impacted in ways similar to data captured using COAs and surveys. Data collection efforts in which face-to-face interviews are planned, similar to other COA data collection, may be impeded. Recruitment may be difficult in light of more pressing life events, or participant responses may be influenced as described within the Response Shift section of this document.

Key methods to address qualitative interviewing challenges during COVID-19 outbreak are described below.

Qualitative interviews (including focus groups):

- Consider implications for subject identification/recruitment.

- Remain vigilant and sensitive to the patient-lived experience (e.g., patients who are immunocompromised may have more concerns, have greater impact).
- Capture experience relevant to the patient's experience with the pandemic at interview outset before focusing on study objectives.
- Consider population/therapeutic area of interest: do symptoms (even mild) or experience of COVID-19 preclude participant ability to respond accurately?
 - Incorporate appropriate inclusion/exclusion criteria.
 - Address any sampling bias.
- Determine feasibility of telephone or web-based interview techniques.
 - Update guide/materials.
 - Provide participant with any needed written materials/devices, etc.
 - Be aware of any HIPAA (Health Insurance Portability and Accountability Act of 1996) compliance concerns using technology to conduct or record interviews.
 - Use compliant systems as required.
 - Determine appropriate consent processing (e.g., wet signature/verbal consent).
 - Consider smaller groups to facilitate online participation for groups.
- Review IRB/IEC designation: determine need to resubmit.

Screening/exit interview:

- Consult with clinical trial teams to determine impact/feasibility based on population of interest and any modifications to a clinical trial design.
 - Understand implications of shifts in timelines
 - Need for additional interviews (i.e., screening)
 - Determine the need for updated process to identify or schedule participants
 - Update interview guides to address potential response shift with participants during interview
- Determine IRB/IEC implications.

4.1 Determining Documentation and Needs for Reporting

Reporting requirements will differ by health authority; thus, best practice is to follow requirements and guidance specific to the study region. The FDA provides key elements for reporting in the FDA COVID-19 Guidance, and these elements are described in brief below along with other best practices to support COA data collection and use. Notably, this documentation should be fully supportive of the selected COA data collection approaches

that are implemented and provide justification/rationale for the selected approach(es). Limitations in the approach and methods to address them should also be detailed.

Key elements for reporting, per the FDA COVID-19 Guidance (FDA, 2020):

- Provide a listing of all participants affected by the COVID-19–related study disruption by unique subject number identifier and by investigational site, as well as a description of how the individual’s participation was altered.
- Describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites.
- Document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted.
- Explain the basis of the missing data, including the relationship to COVID-19 to missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.
- Provide analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Other best practices:

- Thoroughly describe methods/updated study methods.
- Justify selection and implementation in any changes to mode of administration or method of data collection respective to each COA.
- Demonstrate meaningful nature of COA or qualitative interview results.

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