

Begin with the End in Mind: eCOA data from collection to analysis

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Abstract

Similar to Stephen Covey's *7 Habits of Highly Effective People*, Highly effective clinical trials should "begin with the end in mind". Rigorous analysis of data followed by successful submission to regulatory agencies should be the end goal of data collection. It sounds simple and straightforward, especially when dealing with questionnaire data often associated with electronic Clinical Outcome Assessments (eCOA) but, in an industry with increasing knowledge silos and outsourcing, it often is quite the opposite. Simple ideas like collecting data that are usable for analysis can often get lost in the machinery of running a study. Often data management and statisticians are left trying to make sense of incomplete, dirty, or *gasp* free text data. This paper will focus on steps that all stakeholders can take to make sure that the end goal is kept in mind, from design, to data collection, to analysis, and finally submission. We will touch on standardization, formatting, guiding a design team, asking the right questions, existing resources, libraries, and drafting a clear data transfer agreement. Most importantly this paper will address getting the right people in the discussion at the right time - the beginning.

Introduction

The use of electronic clinical outcome assessments (eCOA) offers numerous advantages for clinical trials, such as increased patient involvement, better understanding of the patient experience, uninterrupted data collection, and higher patient compliance. The use of eCOA assessment tools also brings additional challenges for sites and patients. There are many items that need to be addressed to maximize the gain from using patient centric technology like eCOA. These steps may include finding the right technology providers, evaluating sites' capabilities for data capture, developing detailed training plans, discussing reports to monitor compliance & remediation measures, considering data management needs, and data transfer mechanics. Each team intending to use their expertise may not be able to achieve the intended results if there are gaps in understanding and lack of collaboration. By proactive eCOA instrument design considerations and adopting the best practices for data collection and maintenance, high quality and compliant data can be achieved.

During Study Design and Protocol Development

As the industry moves away from paper entries, it is essential to brainstorm about how the eCOA data workflow would work while protocol development is happening. By including team members from cross functional teams into study design and scope meetings determination of how much and what data is required can be correctly specified. Therapeutic experts, outcomes research SMEs, clinical operations, biostatistics, data management, and advising team members from eCOA vendors should all participate and understand workflow, milestones, timelines, and provide input to the study design. An eCOA provider who has clinical and data science expertise can advise on best practices for data governance and patient experience. Thinking through patient visits, daily diary entries, and routine data collection needs will help in enhancing overall data quality. When evaluating data collection, it may be important to consider any provisions for unscheduled visits or the need for flexible visit schedules asking for assessment completion in a specific order, and not necessarily tied only to a specific calendar date or elapsed number of days. Incorporating compliance reporting and alerts when thinking of flexible visit schedules is something that may need to be addressed early on in study design.

Choosing Technology and Devices

It is essential to strategically choose eCOA devices for performance, security, lifecycle, and supply chain stability. Devices should ensure continuous, high data quality throughout the life of planned clinical research. Engaging with technology providers while entering the planning phase gives a chance to determine the best eCOA modalities that meet study protocol requirements. Sponsor study teams and the chosen eCOA technology team should start communicating during the planning phase. The types of questionnaires and the responses required for the clinical trial should be evaluated both by the study teams, and the procurement teams who select vendors. For instance, whether the eCOA vendor team has a questionnaire library that will allow configuration specialists to pull in any previously configured questionnaires and translations into a current study for a quick start, should not be assumed but should be discussed upfront.

Thoughtfulness For Users

Foundational elements begin with a focus on user experience best practices, with a design that considers every step of navigation and data acquisition from the perspective of the user. Key considerations include engaging with eCOA scientists to determine a sufficient questionnaire schedule that is not overly burdensome to the participant's daily schedule; keeping the questionnaires length to the minimum required using concise wording; and avoiding using the same assessment on multiple instruments in the same trial. These simple steps relieve patient burden and improve patient engagement. An eCOA provider's effective user experience design team should work closely with the sponsor team to map the path for data acquisition from the end user. Stakeholders from the patient technology team, therapeutic area leads, and User Interface designers should all collaborate for finalizing eCOA instrument and questionnaire design. Along with the eCOA vendor's testing team results, the sponsor teams' user acceptance testing findings are beneficial and vital. The input from of a few actual users testing the application to ensure it is working appropriately is priceless. Cohesive teamwork can save a lot of time and effort from re-work.

eCOA instrument design

Fully understanding the ins and outs of a clinical trial protocol before eCOA instrument design, and database creation is critical. It is important to hold design sessions which thoroughly cover the diverse topics of security control, performance optimization, longevity, global coverage, provision of data correction, efficient data transfer, and reporting needs. In addition to these technical items, it is also important to discuss study trial objectives and design including inclusion/exclusion criteria for subjects; visit schedules & visit windowing options; primary and secondary efficacy datapoints; adverse events treatment tolerability & monitoring; and recording, concomitant medications usage. It is very important to consider the study needs vs. any "nice to have" items. Expertly designed instruments that satisfy protocol objectives while also providing ease of use by patients and sites should be the overall objective. From a data perspective here are a few items to talk proactively about:

- How to create logic sequences to guide patients through the appropriate questions
- How to prevent patients from skipping questions, and entering inconsistent or conflicting data
- How to catch data issues at data capture
- Is there a need to add unscheduled visits for patients who may need additional time at the site due to a change in their diagnosis
- Should there be a provision of extending data entry windows to accommodate the availability of a caregiver to enter data additionally
- How the eventual data transfer will look and has the team reviewed what data is needed for eventual analysis
- What specific business rules as edit checks are created for the time of data collection to prevent inconsistency in questionnaires & answers

- Are there any cross instrument eCOA data checks required

Screen Reports and Importance of Annotations

Reviewing screen layout, checking correct and easy to understand verbiage, and evaluating if there is any branching-logic to be specified explicitly are a few essential checks to be completed during study build and testing, but not just by the testing team. Once screen reports are finalized, the recommendation is to annotate the location of collected data from patient or clinician devices to the corresponding domains and variables in intermediate and submitted datasets. The annotated screen report (aSR) provides easy access to study metadata for programmers and statisticians plus can be submitted along with the annotated Case Report Form (aCRF) to regulatory bodies to aid the reviewer. Due to the inherent changes that take place during the transition from paper to digital the need for a way to accurately provide the same traceability and usability as the aCRF has arisen in the eCOA/ePRO environment. Luckily, the fundamental principles that have been developed to annotate the Case Report Form can readily be applied to the approved screen reports without change. eCOA data delivery teams, and sponsor/CRO data management teams should get together earlier in the screen review process while planning annotations to seek efficiencies and avoid duplicate work.

Training to use technology

Consulting with eCOA technology partners earlier in discussions about site feasibility assessments can go a long way. Determining whether the sites and patients have capabilities to use a particular data capture technology, and how a detailed training plan can be developed to effectively implement the new technology will work wonders in establishing new sites and retaining existing sites with more compliance. Patients and caregivers receive training to use devices from site personnel and this signifies the need for continuous technical support and ensures timely collection of data. Patients and sites should be provided adequate education on the purpose of collecting the COA data to encourage compliance with completing COAs and help prevent and reduce the frequency of potential missing data in the first place. eCOA provider's helpdesk, customer care, sponsor, and site directors should come together for training planning and implementations. Well written instruction manuals, local language speaking helpdesk support, a study protocol trained customer care agent who is aware of visit windows and when patients would likely use devices contributes to overall patient engagement and compliance. It is important to highlight the fact that even after all considerations are made to get patient data, study teams should note that some patient-level COA data may be missing at the end of the clinical trial. The protocol and the SAP should address plans for how the statistical analyses will handle missing COA data when evaluating clinical benefit and when considering patient success or patient response. The knowledge of how this missing data will be handled should be shared with data management teams who receive data from eCOA vendors and provide it to the analysis team.

Data Management Kick Off Meeting

To conduct an effective data management kick-off meeting that ensures project team members walk away prepared to successfully execute the data management plan, all stakeholders from both the eCOA vendor and the sponsor/CRO should participate. Special mention to include not only eCOA data acquisition leads, but also data managers, statistical programmers, and biostatisticians who would eventually work on downstream analysis of these data. The data standards representative may be a critical person to have in this meeting. Creation and ownership for data transfer/integration guidance documents like global data transfer agreement, study specific data transfer specification (DTS), and data collection format should be discussed. Resource planning and timelines for data transfer testing, frequency of actual production transfer schedule should be added to the overall data management plan. Exchange of information about required documentation, process needs, sign offs, and timelines for completion of these activities are important to understand for both the sponsor and eCOA provider. Establishing clear roles and responsibilities for all the stakeholders is a critical step for success. Aligning

expectations about deliverables from data collection provider vs. sponsor/CRO data management activities like creating standardized datasets, and analytic variables in the datasets should be defined clearly. These activities bring accountability and path towards final goal of data capture and provision of the data for study's endpoints analysis and can only be achieved if all the relevant parties are in collaboration with each other.

Data Correction If Required

What would be the process of raising a data correction form, and how the data changes would appear in the data transfer should be discussed amongst all stakeholders in early stages of study planning. Sponsor, CROs, sites should be trained on using the correct kind of Data Correction Forms (DCFs). The sponsor/CRO data management team should also be aware of the timelines to process any ambiguous or missing information requiring further clarification in the DCFs. Rules and guidelines created for sensitive data correction should be shared with the entire study team. Each study would have its own configuration for what data change types would be allowed and associated permission and approval workflows would be there to support the changes. A reference guide listing an example of data change types could be created. A few examples are "change questionnaire information", "change subject visit", and "change questionnaire responses". An important element of compliance is to ensure that electronic records are supported with an audit trail, where event; user; timestamp; and a required comment are logged with electronic signature. Being 21 CFR part 11 compliant also means having a good grip on the issue of data integrity.

Data Standards

Clinical trials with Case Report Forms have been successfully implementing CDISC standards, but still, we see a big gap in eCOA studies. eCOA data is not structured as Study Data Tabulation Model (SDTM) dataset. Adopting standards in eCOA data ensures quality control, increased interoperability, and data lineage. Implementing CDASH or near SDTM in the eCOA environment would essentially mean SDTM is implemented as the operational standard across the full clinical trial process. Standardization means that commercially available industry tools can also be used for data validation and conformance checks. Standardization also increases the value of the eCOA data transfer as it eliminates the need for the data to be manipulated by the data management CRO. If possible, at the time of CRF development for eCOA involvement of statistical programming and biostats teams; creation of variable naming conventions; creating consistent codes for missing values; and thinking about data submission would bring lot of efficiencies.

Data Transfer Agreement

The practice of creating and following documents like global Data Transfer Agreements and study specific Data Transfer Specification (DTS) removes ambiguity and provides clear expectations for data exchange. The DTS describes the requirements for any data transfers or integrations in scope for the project. To start drafting the DTS, a meeting is required including all study team stakeholders from sponsor, CRO, and eCOA vendor. File delivery details; file format & field definitions; what types of transfer; cumulative or incremental data; frequency; destination of the transfer; and similar details should be noted in the data transfer specification. Considering eventual data transfer at the point of trial design and build can ensure that all data needed for analysis are collected and transferred in the manner and format they are needed.

Questionnaire Libraries

Creation of Questionnaire Libraries helps in reduction of overall timelines of delivery by speeding reviews. By ensuring data standards are included in Questionnaire Libraries teams would benefit by improving operational efficiencies and delivering better data quality. When there is a reduction in the need for mapping of data from one format to another, it allows data management and biostatistics teams to analyze more efficiently across studies and create automations.

Use Of Data Monitoring

Sponsors and eCOA vendors would benefit from discussing how automated and manual data review of select data points can provide an early alert warning system before potential compliance risks escalate into liabilities. Data monitoring not only allows study teams to address current compliance or safety risks in real-time but also provides the ability to reduce future risks. It helps studies run more efficiently through identification of outliers such as missing data; consistency of frequently collected data; query rates, site-level, or patient-level protocol deviations, and more. When monitoring is done in the context of protocol requirements, the questionnaire and instrument compliance patterns can be evaluated correctly for the scope and severity of the issue. Many times, rework and additional data gathering requirements can be avoided by understanding eCOA data in the context of the overall study data and how it will be used in the analysis and submission. Findings from alerts and reports make it easier to align the study with the protocol requirements but it is important to ensure these reports are meaningful by making clear design decisions. What kind of reporting needs are there? Would real time review of data by the study team be feasible? Would a scheduled data transfer of the compliance report be sufficient? Timely requirements gathering and process implementation of reports and alerts help study teams meet timely objectives. Finally, it is important for the team to consider who receives any reports and alerts? How often are they reviewed? Who follows up for conformance? These questions need to be discussed and answered collaboratively early in the design process.

Audit Trails

When contracts are signed with the eCOA team, it is important to bring awareness, and plan for scenarios when the FDA or other regulatory agency may choose to inspect records at the vendors' facility because required records are not available from the sponsor or the clinical investigation site. Submission database content should be traceable back to the original source data, including all changes that happened, by whom changes were made, and the reasons behind the changes. Audit trails to capture electronic record activities should provide changes along with date time stamps when these were made. Supporting documents of authorized signatories should be kept in the study binders. Any differences between edit checks to flag and provide the user an opportunity to correct data entries on the device before saving and the alerts to be sent after the data is submitted and anomalies have been discovered should be well documented. In eCOA studies when the user (subject, or caregiver, or clinician/site) confirms that their entries are complete on the devices and saves it, the audit trail begins. The details of the data origination, and the source should be described in the overall study plan. Compliance with all federal regulations should be well thought out. It is important for all parties to discuss and document how electronic records are maintained; how is compliance recorded to show all required electronic signatures are captured; what system is in place to make sure all signatories are aware of what documents they must sign and when these signatures are required. Clear communication, coordination, and collaboration are key to successful audit implementation.

Archive File as Final Data Deliverable

The format and the time of delivery of the archive file should be discussed in conjunction with the timelines for final submission to the authorities. Some of the items the archive file should include are the final data transfer, a file per patient for attributes, all patient diary entries, all questionnaires and their answers, database extracts of data clarification forms per patient, screen reports, and any approved system requirements and testing documents. The key to having the deliverables ready during the process of study closeout is engagement of data management teams, information technology groups, quality teams, and other stakeholders and ensuring all understand the scope and timelines.

Conclusion

As we continue to adapt to the electronic way of capturing the clinical outcome assessments, the need for consensus, breaking down of information silos, and getting better together is of the utmost importance. In comparison to the paper method of collection, eCOA data collection offers numerous efficiencies, but still has limitations like inconsistency of data collection, lack of database standards, and varied nomenclature of variables. eCOA data has been challenging for data standardization, especially the custom designed questionnaires. Annotated screen reports of the electronic devices and a well-defined data transfer specification provide excellent references to understand study data. Unavailability of these standards creates difficulty for the generation of analysis datasets. Bringing data management; analytic programming teams; and teams who are creating submission documents with the teams who are stakeholders in selecting eCOA technology; site selections; and eCOA vendors together is invaluable. Knowledge of the relationships between the analysis results (tables, listings, and figures in the study report), analysis datasets, tabulation datasets, and source data has come very handy in our organization when brainstorming the implementation of eCOAs with the sponsor study teams. Defining the eCOA workflow and specifying the expectations by working together is the way to go!

RECOMMENDED READING

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