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Smart Clinical Research Protocols

By Fredric J. Cohen

Protocol Implications

The protocol is the central document in a clinical trial. It provides the foundation for other documents such as the clinical trial agreement (CTA), informed consent form (ICF), case report form (eCRF), subject diary (ePRO), source document worksheets, and study manual, as well as the interactive voice recognition system (IVRS), clinical trial management system (CTMS), clinical data management system (CDMS) and statistical management system (SMS). It is the one document that incorporates input from all functional groups at the study sponsor: operational, regulatory, scientific, medical, data, and marketing. It is used by all of these groups, as well as the research site, ethics committee, CRO, laboratory and regulatory personnel.

Because of this central role, any error or ambiguity in, or change to, the protocol can propagate through other documents and systems, with potentially profound consequences. Consider a study that requires a comprehensive physical exam at the first and last visits, but only brief exams at the interim visits. Perhaps the protocol's schedule of events narrative correctly describes these activities, but the schedule-of-events table, in the interest of brevity, calls for only a "physical exam" at the last visit. Because the word "comprehensive" is omitted, the authors of the eCRF, source documents, database design, etc. do not create the necessary data fields. Nobody may notice the omission until the data are unavailable to complete the clinical study report. Or, it may be discovered part-way through the trial, and require an amendment to the informed consent form, reconsenting of study subjects, modification of the eCRF and database, etc. Perhaps some of the required changes will be missed, leaving missing safety data and inconsistencies to explain later to the FDA and authors of any resulting scientific publications.

The cost of a protocol amendment varies with the circumstances, and is difficult to calculate. It includes measurable costs for revising documents, reprogramming systems, publishing the amendment to investigators, ethics committees, and regulators, reconsenting subjects, renegotiating contracts, etc. It also includes costs that are more difficult to measure, such as diversion of key personnel from more productive activities, delays in the study timeline, and less-than-optimal data. One industry consultant has estimated the direct, measurable costs of a protocol amendment to a Phase 3 clinical trial at $200,000.[1]

Even if an error or ambiguity does not require a protocol amendment, it can waste substantial time interpreting eligibility criteria, dealing with protocol violations, and other management of the resulting confusion. Similarly, implementing a legitimate change to a protocol is costly and prone to error because each document and system must be manually reviewed to find each implication.

When protocols are written from scratch, authors may make subtle errors. When they are cut-and-pasted from other protocols, the pieces may be inconsistent or leave gaps. When changes are made during the drafting process, they may create inconsistencies. Multiple authors may generate other gaps and inconsistencies. Templates, text blocks, checklists and style guides can reduce but not eliminate such problems. They can become obsolete or diverge as technologies change, new therapeutic areas arise, companies merge, people come and go, etc.

Quality control of the protocol is a time-consuming and error-prone manual process that requires experts to closely review the various study documents and systems for errors, ambiguities, inconsistencies, gaps and illogic. Spell-checking software cannot even flag a "regular" heartbeat that should be "irregular."

Smart Protocols

The above problems are common because today's clinical research protocols are created using "dumb" word processing tools that do not "know" the meaning of concepts such as "physical exam." One protocol author may use the term "physical exam" as shorthand for the concept "comprehensive physical exam," while another may use it as a synonym for "brief physical exam." One author may assume that the concept "EKG" includes interpretation, while another may assume that it does not. One author may assume that a particular "psychological assessment" requires performance by a trained expert, while another may not share that assumption. Readers of the protocol may not share the author's assumptions.

Protocols incorporate these concept elements into structures. For example, physical exams are components of study visits. Just as there can be errors and ambiguities in individual activities such as physical exams, there can be problems with the structure. For example, the protocol author may combine informed consent, screening and randomization activities into an "initial visit," even though it is physically impossible to determine a subject's eligibility in that visit without violating regulations about pre-consent screening activities. Different protocol authors may have different ideas about the proper order of screening, enrollment and randomization.

"Smart" protocols minimize these problems by "understanding" the concepts and their structural relationships. This understanding is accomplished through the use of metadata – data about data. For example, metadata for the concepts "comprehensive physical exam" and "brief physical exam" include the data elements the exams generate. The concept "physical exam" may be prohibited because of its ambiguity. A structural ("semantic") rule can require that vital signs be taken at every study visit. Another rule can require that the subject give informed consent at least 12 hours before any lab tests that require fasting. Metadata can include descriptive text that is automatically included in the informed consent form, as well as data field types, lengths and edit checks for the eCRF and database design.

Over time, study sponsors can build reusable libraries of concepts and relationships that are much more complete and robust than cut-and-paste text blocks. The methodology is well-established in other fields; software developers have been using it for decades with data dictionaries, object-oriented programming (OOP), and eXtensible Markup Language (XML).

Authors can build smart "extensible" protocols from these reusable components. Then, when a characteristic of an element changes, the change will be applied automatically to every occurrence of the concept in the protocol and other study documents and systems that employ the same components. For example, if a comprehensive physical exam adds a requirement for two blood pressure readings, the instructions for all relevant study visits will be updated. Plus, data fields can be updated automatically in the eCRF and study database.

With an extensible protocol, quality control is largely built-in, because many of the components have been pre-built and are automatically consistent. Computer programs can automatically flag inconsistent and missing elements and violations of the structural rules. New concepts are readily identifiable for special attention. With reusable components, protocols can be more consistent across an entire clinical research program. Institutional knowledge is preserved. It is also faster to assemble protocols from reusable components.[2]

Industry Standardization

If a clinical trial uses systems from different vendors, communication between them ideally will use a common technical language and common conceptual elements. The non-profit organization CDISC is leading efforts to create industry-wide clinical research data interchange standards. CDISC's Operational Data Model (ODM) is a vendor-neutral, platform-independent format for exchanging clinical trial information. The model provides for communication of study concepts and associated metadata, including administrative data. In theory, when vendor-specific extensions to ODM are used, all of the information that needs to be shared among different information systems can be shared using a single ODM-compliant XML file. The model itself is compliant with FDA regulations and guidance for computer systems used during clinical trials.

In a recent proof-of-concept demonstration of the CDISC ODM, an extensible protocol was developed using Fast Track Systems' TrialSpace Designer XCP protocol-authoring product. The contents of the protocol were communicated to EDC systems from ClinPhone, Formedix, invivodata, Medidata, and XClinical, solely through an ODM-compliant XML file. Each EDC system used the file to automatically configure roughly half of the forms required for data collection in a typical clinical trial. Data was manually entered into the forms and then communicated through another XML file to analytical and publishing systems from Insightful, Lincoln Technologies (now Phase Forward), and SAS.

Conclusion

The technology now exists to create smart extensible protocols and to exchange data among multiple CDISC ODM-compliant clinical trial systems. Leading study sponsors have begun to use this technology to improve the quality, cost and timeliness of clinical trials. As use of the technology spreads through the industry, study sponsors, research sites, ethics committees, regulatory authorities, and study subjects will all benefit.

References

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Author

Fredric J. Cohen, M.D., is Vice President, Clinical Strategy of Fast Track Systems, Inc. Contact him at 1.215.358.1400 or fcohen@fast-track.com.

