Study Design Standards

Study Design Standards: An Overview

Study Design is a critical activity in the lifecycle of a clinical research study. It is the foundational blueprint for the execution of the study, forming the basis for the study protocol.

Because of its importance in a study, the research protocol information is not only used throughout the study, but also requested by regulatory authorities such as the US FDA and study registries worldwide such as WHO, the European Medicines Agency and US clinicaltrials.gov.

Even for protocols with complex study designs, each research study has common information that has been standardized to enable data sharing and aggregation. This common information includes eligibility criteria, the schedule of planned assessments and interventions, and the experimental design (including arms, epochs, randomization points and more).

Several standards currently exist to address protocol representation. The CDISC Protocol Representation Model (PRM) addresses all of the aforementioned common information: eligibility criteria, study design, and study registration. This article focuses on the standards that relate directly to the study design part of PRM.

BRIDG: The Standard for Study Design Semantics

The Biomedical Research Integrated Domain Group (BRIDG) Model was started by CDISC in 2003 to support the harmonization of all CDISC standards as well as to support the research link with healthcare. Since then, BRIDG has become a collaborative effort engaging stakeholders from CDISC, the HL7 Regulated Clinical Research Information Management Technical Committee (RCRIM) Work Group, the US National Cancer Institute (NCI), and the US Food and Drug Administration (FDA). The goal of the BRIDG Model is to produce a shared view of the information used in protocol-driven research and its associated regulatory artifacts so that information can be reliably exchanged and aggregated.

BRIDG contains semantics from several study design-related projects including CDISC’s Protocol Representation Model (PRM), CDISC’s Study Data Tabulation Model Trial Design Model (SDTM TDM), HL7’s Clinical Trial Registration and Results (CTRR), NCI’s Clinical Trial Reporting Program (CTRP) and Patient Study Calendar (PSC), and part of the HL7 Study Design Structured Document (HL7 SD SD). The purpose of such an information model is to provide standard data item definitions, data types, and relationships for any project using study design information so that information and its meaning can be shared and aggregated. The projects described in this article use study design information, and have various degrees of alignment with BRIDG.

It may be helpful to further elaborate the relationship of BRIDG to the projects below and other projects that use BRIDG as a foundation. BRIDG is primarily intended to be a conceptual information model, which represents the informational requirements of a particular topic by defining the concepts, attributes, relationships and other critical aspects of the domain’s informational semantics from the perspective of domain experts.
Before an interchange standard, software application or exchange message can be created, a conceptual model such as BRIDG needs to be transformed into more technical models, sometimes called logical and implementation models, which are much more technical in nature and define the semantics from the perspective of software architects and implementers. Then the “implementation” (interchange standard, exchange message, or software application) can be created. All parts of the implemented solution should be traceable back to the conceptual model to ensure alignment with the requirements. These ideas, which are part of the software industry software engineering methodology, are useful in building interchange standards and in ensuring that they enable interoperability among systems.

**CDISC Protocol Representation Model (PRM)**

The PRM forms the heart of the BRIDG Model. The study/trial registration elements, which support the requirements for registering studies in the WHO International Clinical Trial Registry Platform, EMA’s EudraCT and the US NIH/NLM’s clinicaltrials.gov have all been harmonized into BRIDG.

The CDISC Protocol Representation Model Version 1.0 (PRM V1.0) is intended for those involved in the planning and design of a research protocol. The model focuses on the characteristics of a study and the definition and association of activities within the protocols, including "arms" and "epochs". PRM V1.0 also includes the definitions of the roles that participate in those activities.

The scope of this model includes protocol content including Study Design, Eligibility Criteria, and the requirements from the ClinicalTrials.gov and World Health Organization (WHO) registries. The majority of business requirements were provided by subject matter experts in clinical trial protocols.

PRM V1.0 is a UML model that is based on the BRIDG Release 3.0 Protocol Representation sub-domain. It includes all classes in the BRIDG Protocol Representation sub-domain plus some classes from other BRIDG sub-domains, generally classes required for ClinicalTrials.gov and the WHO registries.

The CDISC Protocol Representation Group (PRG) is continuing to build on the PRM V1.0 standard. The team recently released the Study Outline Concepts Standard and announced availability of the Protocol Outline Web Wizard Tool ([https://cdiscprm-sandbox.imedidata.net/](https://cdiscprm-sandbox.imedidata.net/)), which produces a Study Outline PDF document and/or related SDTM domains as defined in the CDISC PRM Study Outline. This tool is part of the PRM Toolkit.

Further information about the PRM and the PRM Toolkit is available at [http://www.cdisc.org/protocol](http://www.cdisc.org/protocol).

**CDISC SDTM Trial Design Model (SDTM TDM)**

ICH E3, Guidance for Industry, Structure and Content of Clinical Study Reports, Section 9.1, calls for a brief, clear description of the overall plan and design of the study, and supplies examples of charts and diagrams for this purpose in Annex IIIa and Annex IIIb. Each Annex corresponds to an example trial, and each shows a diagram describing the study design and a table showing the schedule of assessments. The Trial Design Model in the SDTM provides a standardized way to describe those aspects of the planned conduct of a clinical trial shown in the study design diagrams of these examples. The standard Trial Design Datasets will allow reviewers to:

- clearly and quickly grasp the design of a clinical trial
- compare the designs of different trials
- search a data warehouse for clinical trials with certain features
- compare planned and actual treatments and visits for subjects in a clinical trial.

Modeling a clinical trial in this standardized way requires the explicit statement of certain decision rules that may not be addressed or may be vague or ambiguous in the usual prose protocol document.
Prospective modeling of the design of a clinical trial should lead to a clearer, better protocol. Retrospective modeling of the design of a clinical trial should ensure a clear description of how the trial protocol was interpreted by the sponsor. Note: This information was excerpted from the SDTM Implementation Guide 3.1.2 at www.cdisc.org/sdtm.

The SDTM Trial Design Datasets are:

- **Trial Arms (TA)** – This dataset is the core of the Trial Design Model. It contains one record for each occurrence of an Element (basic building blocks of sequenced steps) in each planned path through the trial.
- **Trial Elements (TE)** – This dataset contains the definitions of the elements (building blocks of sequenced steps) that appear in the Trial Arms (TA) dataset.
- **Trial Visits (TV)** - This dataset describes the planned Visits in a trial. Visits are defined as "clinical encounters".
- **Trial Inclusion Exclusion (TI)** - This dataset contains all the inclusion and exclusion criteria for the trial, and thus provides information that may not be present in the subject-level data on inclusion and exclusion criteria.
- **Trial Summary (TS)** - This dataset allows the sponsor to submit a summary of the trial in a structured format. Each record in the Trial Summary dataset contains the value of a parameter, a characteristic of the trial. For example, Trial Summary is used to record basic information about the study such as trial phase, protocol title, and trial objectives.

These domains have been completely mapped to BRIDG as of SDTM-IG V3.1.2 and are final approved standards. They are intended to be submitted to the US FDA as part of a submission package.

**CDISC Study Design Model - XML**

SDM-XML allows organizations to provide rigorous, machine-readable, interchangeable descriptions of the designs of their clinical studies. As an extension to the existing CDISC Operational Data Model (ODM) specification, SDM-XML affords implementers the ease of leveraging existing ODM concepts and re-using existing ODM definitions. SDM-XML defines three key sub-modules – Structure, Workflow, and Timing – permitting various levels of detail in any representation of a clinical study’s design, while allowing a high degree of authoring flexibility.

This standard was initially developed based on BRIDG R2, and is a final approved CDISC standard. It is intended to be used in any situation where two parties interchange study design information.

**HL7 Clinical Trial Registration and Results**

The Clinical Trial Registration and Results message is an HL7 message specification for sending clinical trial protocol information (at this point the information specifically needed for study registration) between a clinical trial protocol authoring organization and a registration authority and also for sending this information between clinical trial registration authorities. (The results part has not yet been addressed.)

The HL7 CTRR project used BRIDG as the starting point for information requirements and the resulting standard is completely harmonized with BRIDG. It is classified as a Draft Standard for Trial Use (DSTU).
HL7 Study Design Structured Document (HL7 SD SD)

As per the HL7 ballot for this project, the HL7 SD SD describes a research study protocol in the form of an HL7 structured document. The study design structured document will transport the human-readable protocol and machine-readable trial design and eligibility criteria information in a standardized format, with particular emphasis on communicating the following in a structured manner: arms, epochs, subject assignment, planned encounters (visits), planned interventions, planned observations (assessments), eligibility criteria and other study characteristics.

The HL7 SD SD is partially aligned with BRIDG and did not use BRIDG as a starting point. Of the roughly 200 elements in HL7 SD SD, about 80 have been analyzed and addressed (mapped to BRIDG, changed in BRIDG, or changed in HL7 SD SD). CDISC also contributed domain expertise to this project. HL7 SD SD is a Draft Standard for Trial Use (DSTU) in HL7.

Note: Prior to the HL7 SD SD DSTU, another HL7 Study Design message was developed, which has now been replaced by this new DSTU.

Conclusion

The primary benefit of these standards is to support the exchange of study design information in a reliable way that enables clear understanding of the study design (semantic interoperability) as well as facilitating aggregation of study design information from different sources. Only the standards that are harmonized with BRIDG will allow for these benefits to be realized.

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