

The BRIDG Model and a “Model” Implementation: The Clinical Trial Registration and Results HL7 Message

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1 Introduction

The Biomedical Research Integrated Domain Group (BRIDG) Model is a Domain Analysis Model (DAM) representing protocol-driven research. A DAM is a conceptual, abstract representation of an area of interest, which can be used as input to the technical design of software, data interchange specifications, and databases. A DAM should be understandable and usable by domain experts and technology developers alike. Having been in existence for over five years, BRIDG is alive and well: semantic content is being added and an increasing number of projects are using BRIDG for the basis of their information requirements. One such project is the HL7 V3 Clinical Trials Registration and Results message. This article gives a brief summary of BRIDG followed by a description of the CTRR project.

2 BRIDG

2.1 Overview

CDISC initiated BRIDG in early 2005 to enable harmonization with healthcare and to also facilitate the alignment of CDISC standards with each other. Very soon after that, the National Cancer Institute became a founding stakeholder, followed by HL7's Regulated Clinical Research Information Management (RCRIM) Working Group and the US Food and Drug Administration.

The goal of the BRIDG Project is to produce a shared view of the dynamic and static semantics for protocol-driven research and its associated regulatory artifacts. This shared view enables computable semantic interoperability (CSI), which means, in short, the ability of computer systems to communicate information and have that information properly interpreted by the receiving system in the same sense as intended by the transmitting system.¹

This shared view is represented using the Unified Modeling Language, which is a software-industry standard for specifying software requirements for data (static) and process (dynamic or behavioral). The use of UML provides a rigorous approach to discussing and documenting the information and

processes needed for building software, interchange standards, and data bases. BRIDG currently contains concepts, concept attributes and relationships between concepts in the world of protocol-driven research. These concepts have come from specific stakeholder projects. Each concept, attribute, and relationship are defined and documented in BRIDG in detail.

BRIDG is managed by two groups: 1) the BRIDG Board of Directors, which sets strategic direction and addresses resourcing; and 2) the BRIDG Semantic Coordinating Committee, which harmonizes project information into BRIDG and manages the model.

The full scope of the BRIDG model is:

Protocol-driven research and its associated regulatory artifacts,

i.e. the data, organization, resources, rules, and processes involved in the formal assessment of the utility, impact, or other pharmacological, physiological, or psychological effects of a drug, procedure, process, subject characteristic, biologic, cosmetic, food or device on a human, animal, or other subject or substance plus all associated regulatory artifacts required for or derived from this effort, including data specifically associated with post-marketing adverse event reporting.

2.2 Evolution

BRIDG Release 3.0.3 was published in December 2011. Starting with BRIDG Release 3.0, the model was re-designed to address the needs of its various audiences: subject matter experts, HL7 V3 message developers, BRIDG model managers, and UML modelers. See Figure 1 below for a visual explanation of these perspectives.

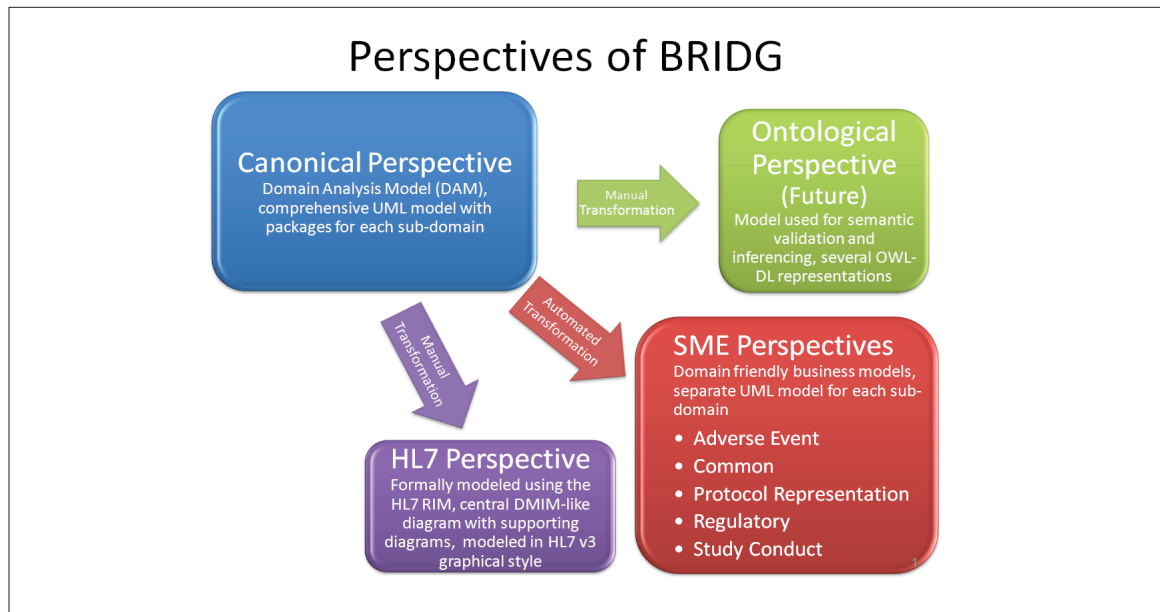


Figure 1: The four perspectives of BRIDG.

The Canonical Perspective is primarily for the BRIDG model managers (also known as the BRIDG SCC) and other UML modelers interested in a comprehensive view of the model. The Subject Matter Expert (SME) Perspectives are intended for domain experts

that are interested in a logical subset of information contained in BRIDG. The HL7 Perspective is intended to be used by HL7 V3 message developers and is a mapping of the Canonical UML Perspective to HL7's RIM Version 3. The Ontological Perspective is an OWL (Web Ontology Language) representation and is available in draft form at <https://ncisvn.nci.nih.gov/svn/bridg-model/trunk/Model%20-%20OWL/> for BRIDG Release 3.0.1.

2.3 BRIDG Contents

The concepts in BRIDG have been developed by “harmonizing” stakeholder projects into BRIDG. Harmonization is the process of ensuring that a project's concepts are in BRIDG, and if they are not, adding them. A project within BRIDG's scope can request to harmonize with BRIDG by preparing the required deliverables (a fully-specified project DAM and project-to-BRIDG mapping spreadsheet) and contacting the BRIDG SCC at bridgTHC-L@list.nih.gov as soon as the project determines they want to harmonize with BRIDG. Table 1 below lists the projects whose concepts have been harmonized into BRIDG.

Release	Project	Stakeholder
R1.0	Regulated Product Submission (RPS)	FDA/HL7 RCRIM
	Patient Study Calendar (PSC)	NCI
	Clinical Trial Object Model (CTOM)	NCI
	caXchange/LabHub	NCI/HL7RCRIM TC/CDISC
R1.1	Study Data Tabulation Model (SDTM)	CDISC
	Trial Design Model	CDISC
R2.0	Adverse Events	CDISC, NCI, NIH, US Federal Gov't, FDA
	Player / Scoper for Person and Org	NCI, CDISC
	Patient Registry (C3PR)	NCI
R2.1	Clinical Trial Registry (COPPA, ct.gov, WHO, PRV1.0)	CDISC, NCI
	Protocol Abstraction (COPPA – Correlations, Organizations, People and Protocol Abstraction)	NCI
R2.2	CDISC HL7 Message Study Design (partial)	FDA
	CDISC HL7 Message Study Participation	FDA
R3.0	(Architecture Redesign only)	
R3.0.1	Clinical Trials Registration and Results	HL7 RCRIM
R3.0.2	caBIG® Central Clinical. Participant Registry (C3PR)	NCI
	Cancer Adverse Event Reporting System (caAERS)	NCI
	Patient Study Calendar (PSC)	NCI
	LabViewer	NCI
R3.0.3	Integrated Case Safety Report (ICSR) Release 2	FDA
	Study Data Tabulation Model (SDTM) Implementation Guide v3.1.2	CDISC
	Clinical Data Acquisition Standard Harmonization (CDASH) v1.1	CDISC

Table 1: Projects with concepts in BRIDG as of December 2011

2.4 BRIDG as a Global Standard

In 2009, BRIDG passed the initial balloting through the ISO Joint Initiative Council (JIC) process. About 250 comments were received and addressed by the BRIDG SCC. Another round of balloting is expected to take place in 2011. After passing the next round of balloting, BRIDG will be an approved global standard of ISO, HL7 and CDISC, which are all members of the ISO JIC.

2.5 For More Information

For more information about BRIDG, please see www.bridgmodel.org.

3 The CTRR HL7 Message – A “Model” Implementation of BRIDG³

3.1 Background

In 2005, the International Committee of Medical Journal Editors (ICMJE) introduced a policy requiring investigators to provide information about trial design into an accepted clinical trials registry before the start of patient enrollment. This policy was designed to make certain that information about the existence and design of clinical trials was available to the public, a principle that leaders in evidence-based medicine have championed for years. In response to this requirement, the World Health Organization's (WHO) International Clinical Trial Registry Platform (ICTRP) was re-energized and has grown rapidly. The ICTRP has developed criteria by which a registry can become part of the ICTRP network. In addition, the use of ClinicalTrials.gov, a registry sponsored by the US government, has burgeoned.²

In order to streamline the process of providing information to registries, a group of pharmaceutical companies funded an effort to create an HL7 V3 message for exchange of registry data. The intent of this effort, called the CTRR project, was to create a comprehensive and generic interchange standard for Clinical Trial Registries that includes all required and optional elements of most external clinical trial registries; including, but not limited to, European Medicine Agency's EudraCT, United States clinicaltrials.gov, US National Cancer Institute's Physician Data Query (PDQ), and WHO. This interchange standard (also called a message), has been created, and the CTRR HL7 V3 message passed HL7 Draft Standard for Trial Use (DSTU) ballot in May 2010.

The clinical trial registration process includes a submission of a clinical trial protocol specification to a registration authority. This same interchange structure may also be useful for data exchange from one registry authority to another or from a sponsoring organization to an ethics review body; however, these specific alternate use cases have not been fully explored.

3.2 Process

The process used to create the CTRR message is visually described below in Figure 2. Further explanation can be found in this section below Figure 2. Please note that the inclusion of this and other figures is intended to provide a general idea of the process and its output. For the official ballot, which contains these figures and more, please see the HL7 ballot at www.hl7.org.

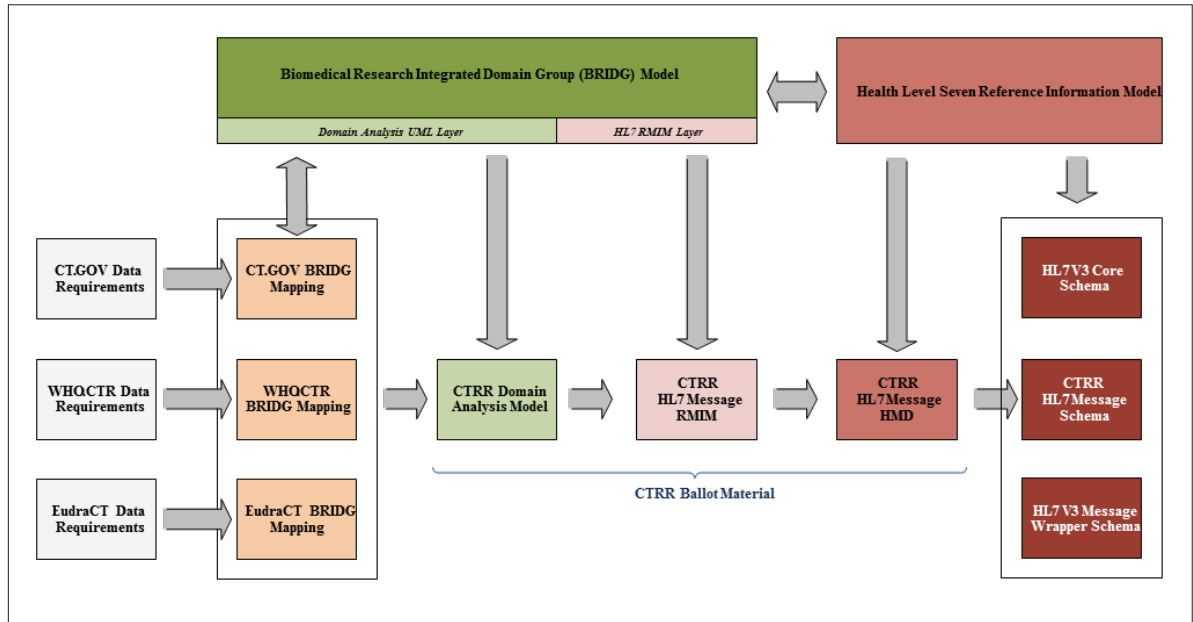


Figure 2: Process for creating the HL7 CTRR message using BRIDG

1. Define CTRR Data Requirements – The first step of the process was to identify the data elements that the registries want to contain. This process includes not only identifying the elements, but also defining each element in a clear and concise manner. Figure 3 below shows an example of data requirements for WHO.CTR and CT.gov.

Req ID	Required Element	Requirement Definition	WHO.ctr	CT.gov
001	Accepts on Healthy Volunteers Indicator	Indicate if persons who have not had the condition(s) being studied or otherwise related conditions or symptoms, as specified in the eligibility requirements, may participate in the study. Select Yes/No.		Accepts on Healthy Volunteers?
002	Acronym	Definition: Acronym or initials used to identify this study, if applicable. Enter only the acronym. If supplied, the acronym is automatically displayed in parentheses following the brief title. Example: Brief Title: Women's Health Initiative Acronym: WHI Displayed on ClinicalTrials.gov as: Women's Health Initiative (WHI)	Acronym	Acronym
003	Arm Description	Brief description of the arm. This element may not be necessary if the associated intervention descriptions contain sufficient information to describe the arm.		Arm Description (note: above data element definition incorrect?) (aka Group/cohort Description)
004	Arm Label	The short name used to identify the arm. Examples: - Metformin - Lifestyle counseling - Sugar pill		Arm Label (aka Group/Cohort Label)
005	Arm Type	Select one - Experimental - Active Comparator - Placebo Comparator - Sham Comparator - No intervention - Other		Arm Type
006	Backup Central Contact Degree	Degree		Backup Central Contact: Degree
007	Backup Central Contact Information	Phone number of the Office phone of the facility contact person. Use the format 123-456-7890 within the United States and Canada. Otherwise, provide the country code. Ext: phone extension, if needed. Email: Electronic mail address of the facility contact person.		Backup Central Contact: Information (phone, e-mail)
008	Backup Central Contact Name	First Name, Middle Initial, Last Name		Backup Central Contact: Name (first, middle int, last)
009	Backup Facility Contact Degree	Degree		Backup Facility Contact: Degree
010	Backup Facility Contact Information	Phone number of the Office phone of the facility contact person. Use the format 123-456-7890 within the United States and Canada. Otherwise, provide the country code. Ext: phone extension, if needed. Email: Electronic mail address of the facility contact person.		Backup Facility Contact: Information (phone, e-mail)
011	Backup Facility Contact Name	First Name, Middle Initial, Last Name		Backup Facility Contact: Name (first, middle int, last)
012	Biospecimen Description	Specify all types of biospecimens to be retained (e.g., whole blood, serum, white cells, urine, tissue).		Biospecimen Description

Figure 3: A set of sample data elements required for CTRR

2. Map CTRR Data Requirements to BRIDG: The second step takes each data element identified in Step 1 and maps it to BRIDG. The step involves determining if the data element currently exists in BRIDG, and if not, determining how to add it. Figure 4 below shows an example of the mapping between several CTRR data elements and BRIDG.

ID	Required Element	BRIDG 3.0 Mapping	
001	Accepts on Healthy Volunteers Indicator	InterventionalStudy	acceptsHealthyVolunteersIndicator
002	Acronym	Study	acronym
003	Arm Description	Arm	description
004	Arm Label	Arm	name
005	Arm Type	Arm	typeCode
006	Backup Central Contact Degree	Person	name
007	Backup Central Contact Information	Person	telcomAddress
008	Backup Central Contact Name	Person	name
009	Backup Facility Contact Degree	Person	name
010	Backup Facility Contact Information	Person	telcomAddress
011	Backup Facility Contact Name	Person	name
012	Biospecimen Description	Material	name
012	Biospecimen Description	Product	nameCode
013	Biospecimen Retention	StudyAgent	functionCode
014	Blinded Roles	InterventionalStudy	blindedRoleCode
015	Blinding Design	InterventionalStudy	blindingSchemaCode
016	Brief Summary	Study	purposeStatement
017	Central Contact Role	StudyContact	roleCode
018	Clinical Trial Phase	Study	phaseCode
019	Comparator dosage/regimen info	DefinedSubstanceAdministration	doseRegimen
020	Comparator Route of administration	DefinedSubstanceAdministration	routeOfAdministrationCode
021	Completion date, estimated or actual	StudyOverallStatus	anticipatedIndicator
021	Completion date, estimated or actual	StudyOverallStatus	statusDate
022	Concurrency	InterventionalStudy	controlConcurrencyTypeCode
023	Condition	Study	diseaseCode
024	Configuration	Study	designConfigurationCode
025	Control	InterventionalStudy	controlTypeCode
026	Coordinating investigator	Person	name
027	Countries of Recruitment	Study	participatingCountryCode
028	Data Monitoring Committee	Organization	name
028	Data Monitoring Committee	OversightCommittee	typeCode
029	Date of First Enrollment	StudyOverallStatus	statusDate
030	Description of investigational treatments	InterventionalStudy	interventionDescription
031	Description of study design	Study	designConfigurationCode
032	Dose regimen	DefinedSubstanceAdministration	doseRegimen
033	Expanded access indicator	Study	plannedStudySubjectExperience
034	Expanded Access Status	Study	plannedStudySubjectExperience
035	Facility Contact Role	StudyContact	roleCode
036	Facility Recruitment	StudySite	accrualStatusCode
037	FDA Regulated	Organization	name
038	Financial Sponsor	Organization	name
038	Financial Sponsor	Person	name

Figure 4: A set of sample CTRR data elements and how they map to BRIDG

3. Create CTRR BRIDG Subset Model: This step involves taking the classes from BRIDG that have CTRR mappings and creating a subset of BRIDG containing only the concepts that CTRR needs. Figure 5 below shows the CTRR BRIDG Subset Model. Please note that this figure is included to provide a general idea of the process output, but is not intended to be readable. For an in-depth look at this subset model, please see the HL7 Ballot at www.hl7.org.

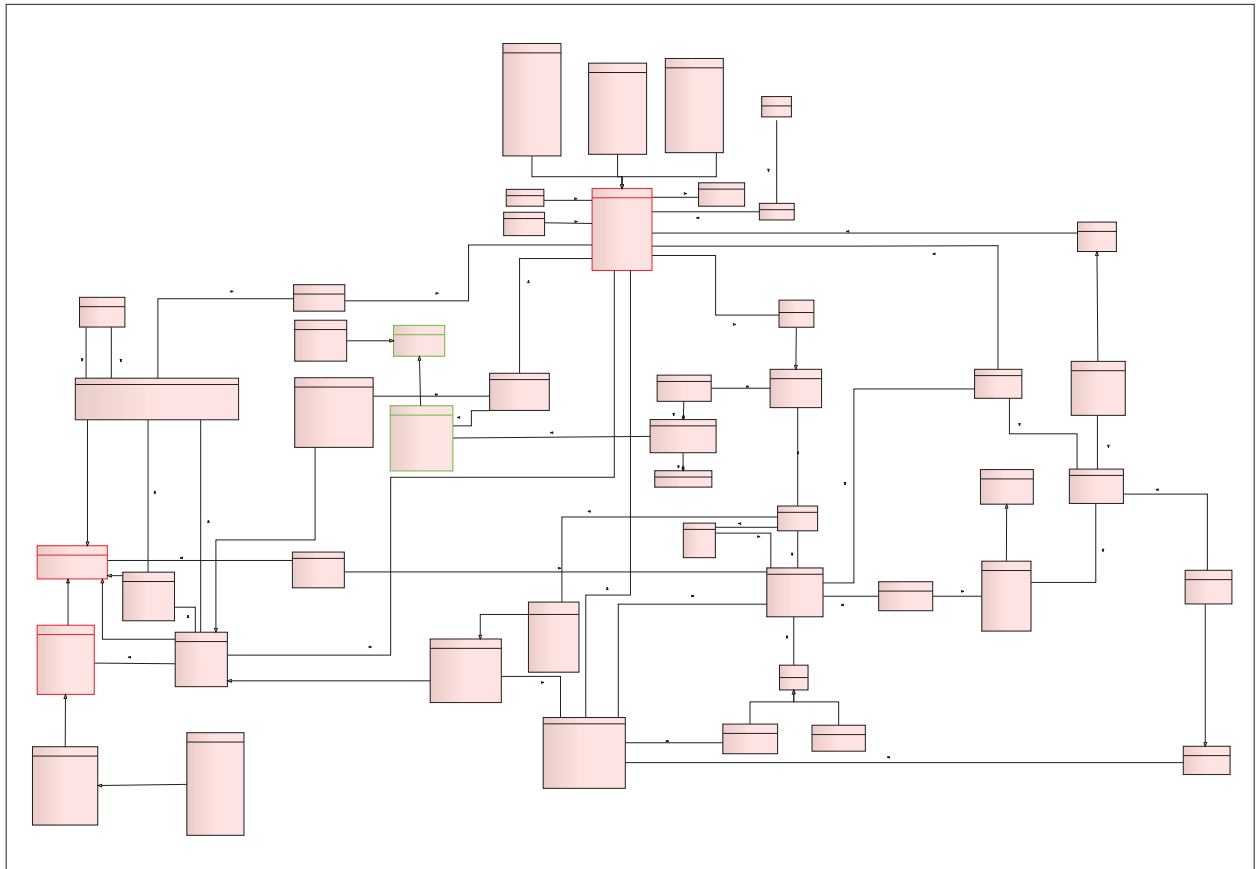


Figure 5: A bird's eye view of the CTRR BRIDG Subset Model

4. Create CTRR RMIM Specification – This step involves mapping each class and attribute in the CTRR BRIDG Subset Model to the HL7 RIM and then using this mapping, creating the Refined Message Information Model (RMIM) diagram. The HL7 perspective of the BRIDG plays a critical role in informing the BRIDG to RIM mapping. Figure 6 shows the mapping from CTRR BRIDG Subset Model to the RIM. Figure 7 shows the resulting CTRR RMIM specification. Note that the RMIM uses an HL7 customization of the UML diagramming convention. After the RMIM is created, HL7 tooling is used to automatically generate the XML schema used for the message.

/attribute/@className	/attribute/@name	/attribute/@rimAttribute	/attribute/@rimClass	/attribute/@rimModel
Activity	identifier	id	ActDefinition	COMT_MT000004US
Activity	reasonCode	reasonCode	ActIntent	COMT_MT000004US
AdverseEvent	categoryCode	code	WorkingListEvent	REPC_RM000012US
AdverseEvent	duration	effectiveTime	ObservationEvent	REPC_RM000012US
AdverseEvent	endRelativeToReferenceCode	typeCode	SourceOf	REPC_RM000012US
AdverseEvent	expectedIndicator	actionNegationInd	PredictionEvent	REPC_RM000012US
AdverseEvent	gradeCode	value	GradeObservation	REPC_RM000012US
AdverseEvent	highlightedIndicator	negationInd	Component4	REPC_RM000012US
AdverseEvent	hospitalizationRequiredIndicator	negationInd	Outcome3	REPC_RM000012US
AdverseEvent	occurrencePatternCode	value	OccurrenceObservationEvent	REPC_RM000012US
AdverseEvent	onsetDate	effectiveTime	ObservationEvent	REPC_RM000012US
AdverseEvent	resolutionDate	effectiveTime	ObservationEvent	REPC_RM000012US
AdverseEvent	seriousnessCode	value	SeriousnessObservation	REPC_RM000012US
AdverseEvent	severityCode	value	SeverityObservation	REPC_RM000012US
AdverseEvent	subcategoryCode	code	WorkingListEvent2	REPC_RM000012US
AdverseEvent	unexpectedReasonCode	reasonCode	PredictionEvent	REPC_RM000012US
AdverseEventActionTaken	delayDuration	pauseQuantity	Trigger	REPC_RM000012US
AdverseEventActionTaken	typeCode	code	ActEvent	REPC_RM000012US
Animal	breedCode	code	Animal	COCT_DM000001US
Animal	description	desc	Animal	COCT_DM000001US
Animal	reproductiveOrgansPresentIndicator	genderStatusCode	Animal	COCT_DM000001US
Animal	speciesCode	code	AnimalKind	COCT_DM000001US
Animal	strain	strainText	Animal	COCT_DM000001US
Arm	description	text	ArmClusterIntent	PORT_DM100002US
Arm	name	title	ArmClusterIntent	PORT_DM100002US

Figure 6: A sample from the CTRR BRIDG Subset Model mapping to the HL7 RIM.

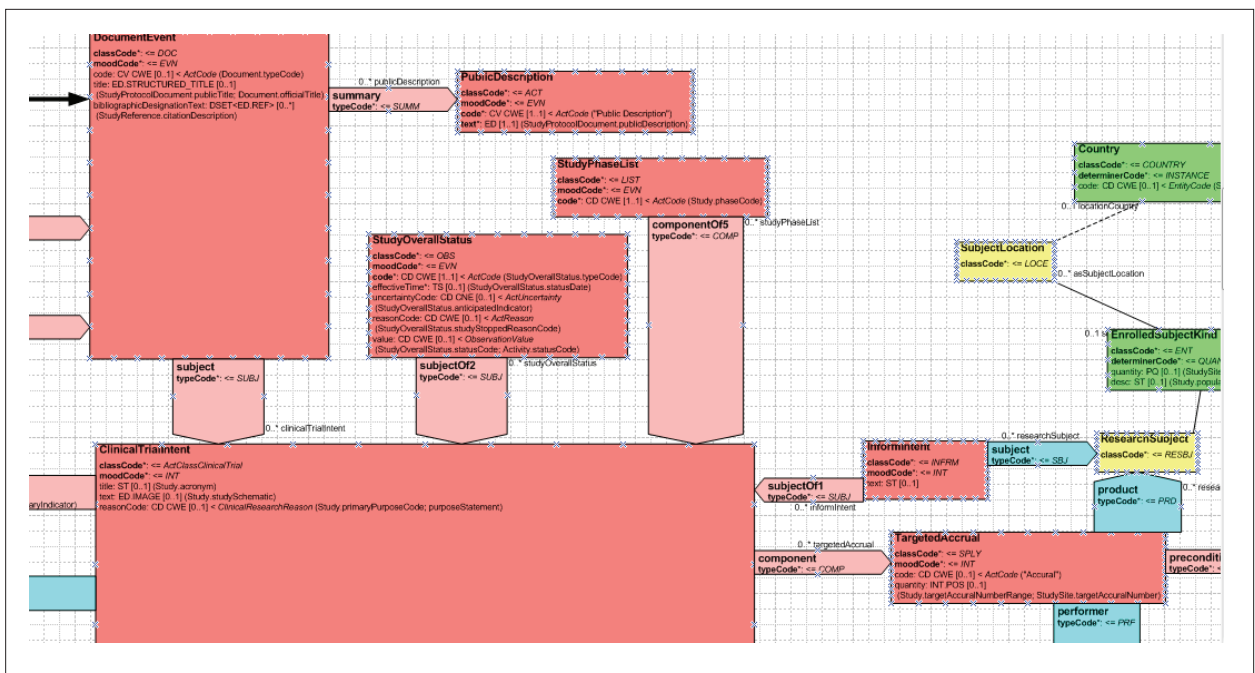


Figure 7: A sample from the CTRR RMIM Specification

3.3 For More Information

For more information about the CTRR HL7 message, please see the HL7 ballot at www.hl7.org.

3.4 Conclusion

The need for Computable Semantic Interoperability is increasing as clinical research complexity increases. A Domain Analysis Model such as BRIDG is essential as a foundation for CSI. The development of the CTRR message provides a real working example of how a DAM can be used.

3.5 Acknowledgements

This article is simply a report containing information regarding a much larger effort to create, expand and maintain the BRIDG Model, which has been developed in large part by the BRIDG Semantic Coordination Committee: Steve Sandberg, Wendy Ver Hoef, Lloyd McKenzie, Becky Angeles, Smita Hastak and Charlie Mead.

Footnotes

1. Definition from http://en.wikipedia.org/wiki/Semantic_interoperability.
2. <http://www.annals.org/content/147/4/275.full>
3. From HL7 V3 Ballot Material at www.hl7.org

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