CDISC-HL7 Project Document
Post-HL7 RCRIM Meetings 17-20 September 2007

Sponsored by CDISC and FDA

Outline

INTRODUCTION

This document serves two purposes:

- To describe the results of the CDISC HL7 Exploratory Project to officially conclude that project
- Describe the high-level steps necessary to support message development

Stage I A. Completion of HL7 RCRIM CDISC Content to HL7 Message Exploratory Project Stage

A. FDA Business Case

The US Food and Drug Administration (FDA) receives massive amounts of clinical research data in extremely disparate formats using a variety of proprietary standards. This makes it extremely difficult, if not impossible, to do cross-study and application reviews. FDA wishes to receive, in regulatory submissions, standard clinical study information content developed by the Clinical Data Interchange Standards Consortium in an HL7 message exchange format. This is approach is vital to the FDA strategic initiatives to integrate pre-marketing clinical trial data and post-marketing safety data to improve public health and patient safety.

- Enhance FDA regulatory decision making and address complex public health questions through improved data management
  - Standardize data - exchange and terminology standards to facilitate data aggregation, analysis, data mining and signal detection
  - Improved access to aggregate data – JANUS data warehouse
  - User friendly tools for review
- Part of the FDA Critical Path Initiatives supporting regulatory research
  - Safer, effective products
  - More efficient product development

More specifically, the FDA has the following rationale for this message development.

- The existing transport format (SASXPT V5) is outdated and requires excessive constraints, such as 8 character field limits. XML is the recommended format.
- SDTM as a metadata standard currently allows for too much variability across companies making regulatory submissions.
- SDTM does not inherently capture all of the relationships between study data, or the relationships between the design of a study and the study data as desired by FDA.
- HL7 message formats are used for other FDA messages that will carry content to JANUS (i.e. product information - SPL, safety surveillance – ICSR, regulated product submission - RPS)
- FDA is committed to ensuring harmonization of all exchange standards with the HL7 RIM (using the Biomedical Research Integrated Domain Group (BRIDG)

model as the Domain Analysis Model in the case of standards for protocol-driven research information).

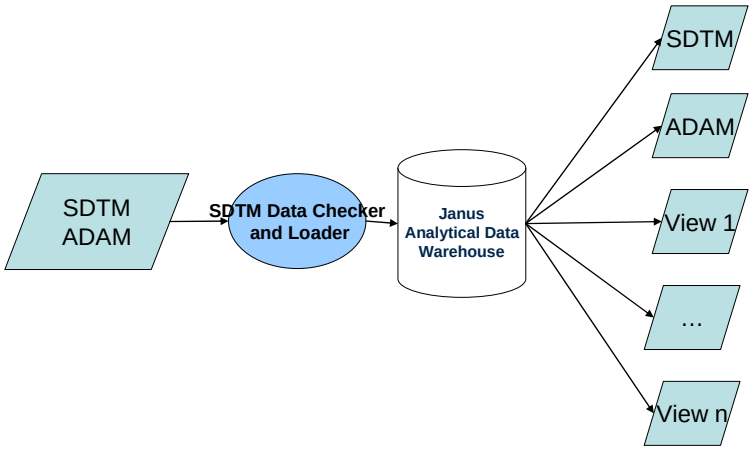
- HL7 is the preferred electronic exchange format for healthcare information, per the Department of Health and Human Services. It is an ANSI-accredited standards development organization with ISO Liaison A.Status with TC215. Harmonization with HL7 standards is expected to provide positioning for a future world with wider adoption of electronic health records that can provide information for international safety surveillance and medical research.
- CDISC is the preferred semantic standard for clinical research data, as a global standards development organization with an open, consensus-based process, ISO Liaison A Status with TC 215 and a charter agreement with HL7 (including a commitment to harmonize CDISC standards with the HL7.RIM (through the BRIDG model that was initiated by CDISC in 2004 for this purpose).
- Title VIII of the Food and Drug Administration Amendment Act (FDAAA, 2007) now requires that, except for preliminary studies, all clinical trials on drugs, biologics, and devices provide trial registry information. An HL7 exchange standard for this information is highly desirable and urgently needed to support this legislation.

Anticipated benefits of an HL7 exchange format for CDISC Content include:

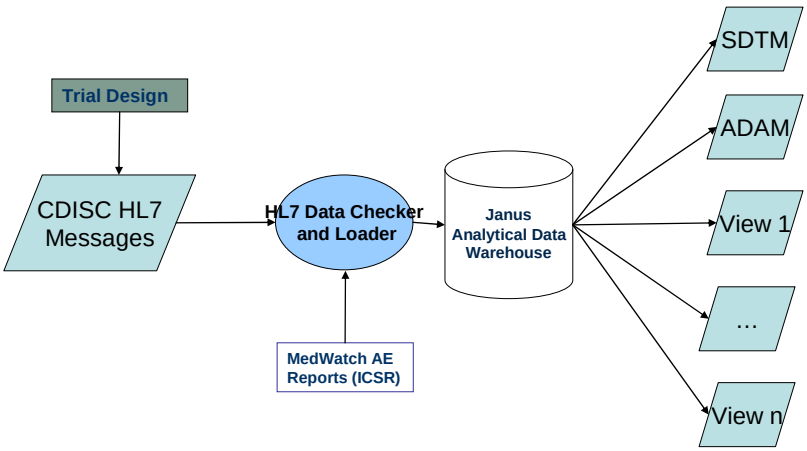
- Greater flexibility in naming variables and storing information
- Improved validation process
- Improved terminology management
- Ability to model complex relationships associated with clinical encounters
- Better integration with JANUS

B. FDA Use Case

The following figure depicts the current state of exchange for regulatory submission content.



The following figure depicts the future FDA goal for regulatory submissions.



C. FDA Explorations and Rationale for Proposed HL7 Message Development from CDISC Content

The FDA has identified four categories of information to populate JANUS, answering the following questions:

- What is going to be done? (Study Design)
- Who is involved in the conduct of the trial? (Study Participation)
- What was observed during the trial? (Subject Data)
- What reportable adverse events were observed? (Individual Case Safety Report)

Based upon initial explorations of the information desired for populating the JANUS data warehouse, CDISC content and available HL7 messages, FDA has identified four messages that should be available to carry the desired data, along with reference HL7 messages and CDISC standards. These are in the following table.

Exchange	Reference	Information	Use
Study Design	• CDISC SDTM • HL7 Clinical Statement CMET • Clinical Trial Enrollment • HL7 SPL	• Encounters (Visits) • Interventions • Observations (Assessments) • Inclusion Criteria • Study Characteristics	• Study Protocol • Clinical Trial Registry
Study Participation	• CT Lab • Clinical Trial Enrollment	• Sites • Investigators • Subjects	• Add/changes to participant information • Annual reports • Study result submission
Subject Data	• CDISC SDTM • define.xml • ADaM • Clinical Statement CMET • ICSR • SPL	• Encounters • Interventions • Observations • AE • Link to Trial Design	• Study result submission
ICSR	• SPL	• AE Reports	• AE reporting

D. Mapping of HL7 RCRIM CDISC Content to HL7 Message Exploratory Project Charter and Proposed Messages

The charter for the CDISC Content to HL7 Message Exploratory Project stated "This project will specifically include a) study summary (clinical trial registry), b) eligibility criteria, c) trial design (including parts I and II: arms, elements visits, planned assessments, and planned intervention(s)), d) statistical analysis plan, e) collected data/study data tabulations and f) derived data/analysis datasets, all of which are currently defined by the CDISC standard. The use case for this project is sending the aforementioned content to a regulatory authority to support a regulatory submission."

The four proposed messages can be mapped to the six subsets of content in this charter statement as follows:

Proposed HL7 Message	**CDISC Content (from Exploratory Project Charter)**	**Comments**
Study Design	a) Study Summary (Clinical Trial Registry) b) Eligibility Criteria c) Trial Design d) Statistical Analysis Plan	a) still needs BRIDG harmonization b) still needs more standards development c) trial design is mostly in the BRIDG d) SAP still needs more standards development
Study Participation	e) collected data/study data tabulations (SDTM DM domain)	In process of being harmonized into BRIDG
Subject Data	e) collected data/study data tabulations f) derived data/analysis datasets	e) SDTM is a production standard and is primarily in BRIDG f) ADaM is a production standard, but needs to be harmonized into BRIDG
ICSR	e) collected data/study data tabulations (SDTM AE domain)	In process of being harmonized into BRIDG

E. FDA Proposed Timelines

The following timelines were proposed; these will be revisited in the next stage of the project.

	Phase, Major Deliverable, Activity or Milestone	Date
	Create Project Charter (all messaged run concurrently)	October 16, 2007
	Create storyboards (iterative process)	Sept 07 - Jan 08
	Create CIM from BRIDG / HL7 artifacts (iterative process)	Sept 07 - Jan 08
	BRIDG harmonization (iterative process)	Jan 08 - Feb 08
	Prepare ballot documentation	Dec 07 – Feb 08
	Quality verification to go to ballot	February 2008
	Conduct ballot (work with Publishing Committee)	March 2008
	Ballot reconciliation	May 2008

F. RCRIM Vote to Move Beyond Exploratory Stage

On 17 September 2007, at the HL7 Working Group Meetings in Atlanta, GA, the RCRIM Technical Committee voted to move the CDISC Content to HL7 Message Exploratory Project beyond the exploratory stage. There was a request, however, for deliverables from this stage. The deliverables are intended to be covered in this document as well as Stage IB. The project will now be called the CDISC-HL7 Project until such time as a more suitable name may be proposed, e.g. when the revised charter is written.

On 19 September 2007, at the HL7 Working Group Meetings in Atlanta, the RCRIM Technical Committee further clarified that the deliverables should include a more clearly articulated business case (see page 2) and a roadmap for the 6 explored CDISC content areas to the project recommendation (see page 6).

Stage I B. CDISC Development of Requirements for CDISC-HL7 Project

A. Initiation of CDISC Sub-Team to support Stage II Activities

Because of the extensive CDISC content to be exchanged using the HL7 XML message format, and in order to conduct a gap analysis and develop a set of requirements and an overview plan for this project, CDISC will create a small (7-10 member), multidisciplinary/cross-functional sub-

team to document the business requirements, storyboards, conduct a BRIDG gap analysis, and provide recommendations.. The HL7 RCRIM TC has agreed to this, with the understanding that this sub-team will provide regular update reports to RCRIM at the regular RCRIM teleconferences. FDA and CDISC will co-lead this sub-team.
The proposed team is as follows, including the functions/disciplines(s) that each individual will represent and/or contribute.

Stakeholder Affiliation(s)	Relevant Skill Set(s)	Name	Role(s) in Stage IB
FDA	JANUS SDTM Issues	Jay Levine	FDA Co-lead: Regulatory Requirements
CDISC	XML, define.xml, CDISC Roadmap	Dave Iberson-Hurst	CDISC Co-lead: Input on requirements and gap analysis; Collate Overview plan
FDA Contractor	HL7 Message Development ; ICSR, etc.	Mead Walker	ICSR Harmonization and Support as needed
FDA Contractor	RPS Development	Jason Rock	Document requirements and gap analysis
HL7 RCRIM, Pharma	BRIDG, Protocol	Cara Willoughby	Advise on Protocol Standard; represent pharma
HL7 RCRIM, CDISC, Pharma	TDM, BRIDG, SDTM	Diane Wold	Advise on TDM, SDTM and BRIDG; represent pharma
NCI	JANUS, BRIDG	John Speakman	NCI support; technical input when needed
CDISC, HL7 RCRIM	BRIDG	Julie Evans	Advise on BRIDG, as needed
Advisors			
FDA		Armando Oliva	FDA Sponsor; support, as needed
CDISC, HL7 RCRIM		Rebecca Kush	CDISC Sponsor; Support, as needed
SAS, CDISC, HL7 RCRIM		Edward Helton	CDISC and SAS Support, as needed
FDA	Adverse Event Reporting	Lise Stevens	FDA ICSR lead and Support, as needed

Additional advisors with specific expertise to be contacted as appropriate:

- Phil Pochon, Covance; co-developer of LAB message and PGx standards
- Isabelle DeZegher, Novartis, Europe; informatics
- Chris Decker, SAS; leader of FDA-CDISC Pilot # 2 (Integrated Safety Data)

B. Regular reporting of Stage I B Activities to HL7 RCRIM

The RCRIM Technical Committee holds teleconferences every other week. The progress on this project will be reported regularly on these calls by the CDISC team leaders.

C. Requirements

The overall requirements of the project must be documented, including information needed to support each of the use cases identified by FDA and other interested stakeholders.

D. Storyboards

The use case(s) should be described in a storyboard or appropriate set of storyboards for all interested stakeholders.

E. Gap Analysis

A Gap Analysis should be done to determine the following:

a) Based upon the requirements, the content that has been harmonized into the BRIDG model already vs. the content that has not been harmonized into the BRIDG model;

b) Reuse of applicable existing HL7 messages and their status and availability;

c) Proposal for CDISC HL7 messages for transporting the CDISC content and successfully loading the JANUS data warehouse.

This analysis will be conducted with the intent to align the message development with the HL7 RIM and BRIDG harmonization to achieve the best use of resources and to enable the most efficient timeline.

F. Recommendations

A set of recommendations will be developed from stage IB. This set of recommendations will include documented Requirements, results and recommendations from the Gap Analysis, input into the Plan for Modeling and Message Development for Stage II, recommendations for the Project Scope and recommended Deliverables and any other recommendations that the Stage IB Sub-team members (in consultation with other stakeholders) deem appropriate and useful for Stage II. These recommendations from Stage IB will be leveraged for the steps described and work to be done in Stage II.

The approach will be iterative, such that Stage II will begin before Stage IB is complete. However, it is essential that the work in Stage II be based upon the recommendations in Stage IB at each iteration.

Stage II. Modeling and Message Development

A. Project Plan for Modeling and Message Development

The Requirements, Gap Analysis and Recommendations should allow for a 'roadmap' for modeling and message development, based upon the HL7 process. This roadmap will include timelines for each message, whether they are concurrent or staggered. These recommendations will be used to inform the project charter per HL7 PMO requirements. FDA will lead stage II activity.

Stages IB and II will occur in parallel. We see an iterative approach in conducting these two steps. The existing requirements in BRIDG will support initial phase II work. As stage IB progresses, additional requirements will support future stage II activity. Stage II will take into account the outputs of Stage IB.

B. Scope Statement

The first step in the HL7 process is the creation of a scope statement. The project scope's objective is to communicate the type of activities a group is undertaking to achieve specific objectives or to produce specific work products. The project scope should provide sufficient information to allow inexperienced individuals to anticipate what a group is working on and decide if they wish to become involved.

C. Project Charter

The next step in the process is to create a project charter. The Project Charter identifies the project's deliverables, timing, and scope. It also includes specific reference to the project's governance and project benefits. The project charter is a living document.

D. Use of HL7 Development Framework

The relevant portions of the HL7 Development Framework will be followed for the CDISC-HL7 Project modeling and message development. The work will be open and transparent to the public. The ongoing efforts of Stage IB informs the work effort of Stage II.

E. Use of HL7 RIM and BRIDG

The message development will be done following an “Iterative Incremental” approach using the BRIDG model as the HL7 RCRIM Domain Analysis Model holding CDISC content. The BRIDG, JANUS, SDTM and other CDISC Content will be kept ‘in sync’ or ‘harmonized’ with each other to ensure that the developed messages maintain semantic interoperability with all of the CDISC standards and other RCRIM TC standards.

Terminology binding and RIM harmonization will be done following the HL7 Development Framework and applicable stakeholder processes.

Although the actual modeling and message development is typically performed by a small group (in this case, Jason Rock, Mead Walker, Dave Iberson-Hurst, and Jay Levine), the CDISC sub-team formed in stage IB will form the core group that will review and validate the modeling work that is done. However, others are welcome to participate in the vetting process at this stage in the spirit of openness and transparency consistent with the HL7 Development Framework.

Stage III. DSTU Testing

Applicable HL7 development processes will be followed for testing. FDA will lead the testing.

Testing should be done against the work efforts from Stage II.