Center for Drug Evaluation and Research

HL7 STUDY PARTICIPATION

DRAFT STANDARD FOR TRIAL USE

TEST REPORT

FINAL

FEBRUARY 2013

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The National Cancer Institute

Johnson and Johnson

Regulatory Informatics Consulting

Sanofi

Center for Drug Evaluation and Research, Office of Scientific Investigations

Center for Drug Evaluation and Research, Office of New Drugs

1.0 INTRODUCTION

1.1 PURPOSE

This report contains the testing results of the HL7 Study Participation Draft Standard for Trial Use (DSTU). The purpose of the testing was to determine if the standard as designed is capable of capturing and exchanging clinical investigator qualification information, and related information about other entities involved in the conduct of a clinical trial, for submission to the U.S. Food and Drug Administration (FDA) / Center for Drug Evaluation and Research (CDER).

1.2 BACKGROUND

The HL7 Study Participation standard has been developed to support the exchange of information, in a machine-readable format, about entities that participate in a clinical investigation. These entities include investigators, research facilities (Investigational sites), service providers (e.g. contract research organizations (CROs), central labs), and institutional review boards (IRBs). This information is currently submitted to CDER to support regulatory processes, but not in a machine-readable format.

The study participation standard is currently a draft standard for trial use (DSTU) within HL7 and this report describes the results of CDER-sponsored testing of the standard to assess its ability to support its intended use. The testing described herein is limited in scope to testing of the standard. Out of scope was an evaluation of the processes and technologies needed to support the use of data submitted using the standard in an operational environment.

U.S. federal regulations (see 21 CFR 312.23) require that sponsors of clinical investigations report to the FDA

"*the name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.*"

The sponsor is also required to collect from each investigator (see 21 CFR 312.53)

"*a signed investigator statement (Form FDA-1572) containing: (i) The name and address of the investigator; (ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator; (iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted; (iv) The name and address of any clinical laboratory facilities to be used in the study; (v)*

The name and address of the IRB that is responsible for review and approval of the study(ies).”

In current practice, sponsors collect a signed 1572 and C.V. from each investigator. Although federal regulations do not require the submission of the 1572 to the FDA, it is common practice for sponsors to submit a copy of the 1572, along with the C.V. to convey clinical investigator qualification information.

CDER currently receives clinical investigator information either in paper format or PDF, which makes management of this information challenging. For example, clinical investigator information must be transcribed and manually entered into a database so that FDA inspectors can access this information to conduct their inspections. Receiving this information in a standard, electronic, machine-readable format would facilitate automated processes to manage this information, thereby increasing efficiencies and minimizing errors. Information about CROs, central labs, and IRBs are provided as unstructured information in paper or PDF, similarly limiting its usefulness. For example, it is not currently possible for CDER to easily determine which CROs are involved with which studies.

In December 2012, CDER published draft guidance “Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning.”[1] A number of the data elements identified in this guidance (that are currently not provided in a structured form to support queries or repurposing) can be submitted using the study participation standard. The standard potentially suggests an opportunity to submit the information once and repurpose it to support both review and inspection activities.

Informal discussions with sponsors also reveal inefficiencies and high costs associated with the management of this information in their organizations using manual, paper-based processes. Many at FDA and industry agree that a transition to an electronic exchange standard for this information will yield efficiencies for all.

To facilitate testing, CDER created a browser-based data entry tool (xForm) that enables testers with little to no HL7 or XML experience to generate valid HL7 study participation test files. In a recent FDA public meeting on

[1] See http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf. Last accessed 2013-02-05.

Solutions for New Study Data Exchange Standards (November 5, 2012),[2] a number of attendees noted that HL7 v3 standards are difficult to understand and implement. The use of xForm technology provides a pragmatic approach to demonstrate the utility of HL7 standards to those with little or no HL7 experience. The xForm also allows CDER testers to readily view the contents of a test file in a human-readable format. Testers did not need to use the xForm, and one tester instead generated the test file programmatically from their internal systems. This experience is described in the report.

2.0 GOALS

The goals of the Study Participation testing were:

- To create a valid Study Participation files (messages) for review by US FDA.
- To use simple testing tools (xForm, Style sheet) to create, edit, view, and save HL7 Study Participation files.
- To identify and utilize controlled vocabularies. Vocabularies are necessary to support creation of HL7 Study Participation messages. This will require the use of controlled terms, and where appropriate make the necessary additions and/or modifications to these terminologies and value sets.
- To identify business process and/or technical issues that may negatively affect efforts to implement the HL7 Study Participation standard
    - To identify issues, and (if feasible) propose potential remedies
    - To determine whether such issues will impact the further use and development of HL7 Study Participation, and if so to communicate these issues with the HL7 Study Data Standards (Stage II) team accordingly.
- To confirm a collective (if only general) understanding of how the process and technology will function together.
- To provide a proof of concept of HL7 Study Participation to the broader stakeholder community. Furthermore, to confirm (or to reasonably predict) the feasibility of implementing the HL7 Study Participation standard for use by sponsors of clinical trials in submitting data to the FDA.

3.0 APPROACH

CDER identified internal testers from CDER organizational components that receive and review this information. Other Centers were aware of the

[2] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm332003.htm. Last accessed 2013-02-05.

testing but did not participate formally. Industry volunteers came from the HL7 Study Data Standards project team (Stage II) within the Regulated Clinical Research Information (RCRIM) work group. Because an xForm was available, no technical experience with XML or the standard was required. However, those with more technical expertise were welcome; particularly those who desired to generate the test files programmatically from their internal information systems. CDER developed a test plan (see Appendix 1) and an evaluation form (see Appendix 2).

Tester volunteers received the Study Participation implementation guide, the schema, the testing tools (xForm/style sheet) and instructions for installation and use of the xForms. The plan was to conduct testing over a two month period, to allow sufficient time for testers to create and submit test files. Testers were asked to complete an evaluation form.

FDA testers evaluated the test files for format and content.

4.0 PARTICIPANTS

Six organizations participated in the testing and provided test files:

- Johnson and Johnson
- National Cancer Institute
- Regulatory Informatics Consulting
- Center for Drug Evaluation and Research, Office of Scientific Investigations
- Center for Drug Evaluation and Research, Office of New Drugs
- Sanofi

5.0 RESULTS

The results of each individual test file are described below. There were a total of 6 test files submitted. Three of the six files initially failed to validate against the schema but were easily corrected (details below). The six test files are described individually, and comments from both the creators and reviewers of the test files are captured.

5.1 NATIONAL CANCER INSTITUTE

The National Cancer Institute did not use the xForm and instead generated the test file programmatically from internal systems. The NCI test file consisted of two investigators and two sub-investigators from two real world 1572s although data were added or changed to make a more

representative complete sample. Also included were the referenced CVs as PDF files.

The NCI file is valid. There were no errors in this file.

Tester Comment [1.1]

The test file codes Investigator Name as a single block of text, which is consistent with the Implementation Guide. The xForm, on the other hand, codes names in parts.

e.g.

<name>Dr. John Black</name>

vs.

```
<name>
  <family>Black</family>
  <given>John</given>
  <prefix> Dr. </prefix>
  <suffix/>
</name>
```

FDA Note: The preferred approach is the more granular representation of the investigator name.

Action Item: [I.G.] Change Implementation Guide to capture name in parts.

Tester Comment [1.2]

II roots: The Implementation Guide specifies using specific OIDs for II roots for the Study and Investigators but not for other entities with Ids. For organizations, we used the II root specified by the system we retrieve these from. Is this the correct approach? We also wondered if we should actually be using our system's II root for Investigator Ids as well. Based on the Implementation Guide, there are also a number of instances where Ids are used to convey data (e.g. license ids, degree types) with no root specified. Is this also correct or are there specified roots to use for these as well?

FDA Note: Sponsors and CROs' don't currently have OIDs registered with ANSI. Only a few sponsors have. We feel it would be a burden to request submitters to use OIDs. HL7 SPL users use Dun and Bradstreet numbers (DUNS). Use of II element or ID is as a unique identifier. The suggestion is to use the same solution as SPL.

Action Item: [I.G.] Change the I.G. to use optional DUNS numbers for sponsors, CROs, and healthcare organizations associated with the Investigators.

Tester Comment [1.3]

Investigator status codes: We're currently not including Investigator.statusCode and effectiveTime but we could based on the registration application status and sponsor's approval date (if given). Our internal registration status codes are for the most part not useful externally as they indicate internal workflow states. What statusCode values would be useful for us to provide here?

Note: The standard allows submitter to state whether an investigator is active or inactive in a trial. There is currently no controlled terminology for this code. We are asking testers to suggest useful controlled terminology for this data element. we have not registered the statusCodes for investigators with NCI EVS yet. These attributes are optional in the HL7 study participation RMIM. See below role class, where the statusCode and effectiveTime are optional. Definition from the Study participation IG: Optional. The <statusCode> determines the state of the investigator's involvement in the study. This attribute is used to determine when investigators are involved in the study and should be used with effectiveTime.

FDA Note: Effective time is the time at which the investigator was actively participating in the trial. We recognize that investigators sometimes come and go. FDA gets a 1572 that says they're actively engaged and sometimes the investigator stops participating or is replaced.

Action Item: [Vocabulary] Propose two codes for investigator statusCode: Active and Inactive and develop definitions.

Tester Comment [1.4]

Appendix 2 in the I.G. uses the LicensedEntity.id.extension to specify the degree type or board certification type and this is what we've done in our mapping, but it seems problematic since these will not be unique. Do we have this mapped correctly? Could the type of degree be coded?

FDA Note: It is not our intention to use LicensedEntity.id.extension to specify the degree type or board certification type. The example in the I.G. Appendix 2 will be corrected.

The standard currently does not support coding the type of degree or board certification, as this is not a requirement in the 1572. Capturing this information would require a change in the RMIM and will be deferred to a future release if new requirements emerge.

Action Item: [I.G.] Change Appendix 2 example with UT Southwest Medical School to remove “MD” from extension.

Action Item: [RMIM] Consider for future release of the standard: capturing type of degree, board certification, and license.

Tester Comment [1.5]

The standard associates investigators at the study level, and then later they can be associated with the site. This is not how it is done in practice. In practice, the investigator is always associated with the site. Not every study has an investigator associated at the study level (this role is optional and sometimes referred to as a coordinating investigator).

FDA Note: We agree.

Action Item: [RMIM and I.G.] Change RMIM to associate investigator with the site (StudyActivitiesAtSite), with two codes: principal, sub-investigator. Add optional association with the Study, one code: coordinating investigator. Also update the Implementation Guide to reflect these changes.

Tester Comment [1.6]

The main challenge for us is in creating an accurate mapping for the StudyActivitiesAtSite. Our data model is based very closely on the Form 1572 itself where the associations are investigator-centric. In our model, an investigator is related to one or more practice sites, clinical labs and IRBs and zero or more subinvestigators in the context of a study. The StudyActivitiesAtSite supports a more fine-grained set of relationships, for instance the IRBs or subinvestigators associated to a particular practice site. Since we don't track this more specific set of associations, our data generation needs to make the assumption that all subinvestigators, labs and IRBs specified in a Form 1572 are associated to all of the practice sites listed. This may or may not be accurate. We'd like to know your thoughts around this issue.

FDA Note: As envisioned, StudyActivityAtSite is a “virtual site” that is always associated with one (principal) investigator. Each Study ActivityAtSite can be associated with one or more locations (which the NCI refers to “practice sites”). Using this approach, the NCI’s mapping is fine.

Action Item: [RMIM] Change RMIM to allow 1…n physical locations for StudyActivityAtSite

Tester Comment [1.7]

Should we map potentially related Clinical Labs as SecondaryPerformers within StudyActivitiesAtSite? There are potential inaccuracies here if we do. See the previous comment about complications in the mapping.

FDA Note: Yes, see previous response. For regulatory purposes, it is fine to assume that a service provider is active within the entire virtual site (StudyActivitiesAtSite).

Action Item: None

Tester Comment [1.8]

The PORT_MT100001UV01 version of the schema appears to have removed the commissioningOrganization element of EthicalCommittee, so we were unable to provide organization information for the IRBs associated to the study.

Action Item: [Schema] Fix the schema to match the RMIM by adding the commissioningOrganization element of EthicalCommittee.

Tester Comment [1.9]

The Implementation Guide states SubjectProtectionApproval.id element is optional but it required in the schema. In order to supply a value here as required by the current schema, we used the II of the IRB organization but it appears that this is not what is expected here which I think would be related to the approval act itself.

Action Item: [RMIM and schema] Change the RMIM and schema so SubjectProtectionApproval.id element is optional.

5.2 JOHNSON & JOHNSON

[2.1] The test file was created manually using the xForm, Windows 7, and IE 9. The tester originally hoped to auto-populate the form, but decided against it as the requested data is managed in multiple places.

The test file initially was invalid because the tester entered two physical locations for a site (which is allowed in the xForm, but not in the schema), the first location was at the Hospital of the University of Pennsylvania (HUP) and the second was at HUP-Radnor. It is the second location that causes the schema validation failure. Removal of the 2nd physical location resulted in a valid test file.

Action Item: [RMIM and schema] Allow multiple physical locations for each site. Current schema shows cardinality for location as 0…1. (see 1.6)

Tester Comment [2.2]

Despite some initial issues with IE9 and Windows 7, it was relatively straightforward to install the xForms and save the xForms. The show hints functionality needs to be improved. It was not always clear what area needed to be moused over to expose the hints. Also the hints were not always helpful or clear**.**

Action Item: [xForm] make hints clearer

Tester Comment [2.3]

If a field is required, recommend making it immediately visible on the respective tab (rather than being hidden until a user expands the relevant field).

Action Item: [xForm] Display all required fields by default.

Tester Comment [2.4]

We noted a problem when entering service providers without DUNS #. The full set or providers was not available in the drop-down list when completing site information.

Action Item: [xForm] fix xForms so all service providers appear in the drop down list, including those without a DUNS number.

Tester Comment [2.5]

Sponsor-assigned Study ID: Recommend more consistent and explicit guidance on the Study ID. If the assumption that this ID should match the StudyID in the SDTM dataset, then make this an explicit point.

Action Item: [I.G. and xForm] Make explicit that the StudyID is the SDTM StudyID.

Tester Comment [2.6]

Report Cutoff Date: Additional clarification is needed to determine what information is being captured. Would this be equivalent to the date the 1572 form was signed? If it does not, consider capturing a second date, which is the date the investigator signed the 1572.

FDA Note: The report cutoff date is the date the message was generated. It indicates that reporting information contained within the file is current as of that date. Since the submission of a signed 1572 to FDA is not a regulatory requirement, the submission of the date the 1572 was signed is not needed. However, this could be added as a future enhancement if it is of value to other stakeholders.

Action Item: [I.G. and xForm] make explicit the meaning of Report Cutoff Date

Action Item: [RMIM] Consider for future release: capturing the date the clinical investigator confirmed their information (i.e. the date the 1572 was signed).

Tester Comment [2.7]

Study Title is not supported in the standard, because Study Title exists in other parts of the submission and can be retrieved using the StudyID. Is this acceptable? In general, we do not see this as a problem. However, it may be helpful to consider this as an optional field.

Action Item: [RMIM] Add Study Title as an optional field.

Tester Comment [2.8]

What is the distinction between new and active accrual status? Some of these [i.e. terms used for testing] are arguably not accrual status. Suggest a definition of each term. Suggest ensuring consistent terminology with clinicaltrials.gov.

FDA Note: clinicaltrials.gov uses a single concept “Accrual Activity” to capture both accrual status and data collection status (see next comment). The value set used for this activity are:

- Not yet recruiting: participants are not yet being recruited
- Recruiting: participants are currently being recruited
- Enrolling by invitation: participants are being (or will be) selected from a predetermined population
- Active, not recruiting: study is ongoing (i.e., patients are being treated or examined), but participants are not currently being recruited or enrolled
- Completed: the study has concluded normally; participants are no longer being examined or treated (i.e., last patient's last visit has occurred)
- Suspended: recruiting or enrolling participants has halted prematurely but potentially will resume
- Terminated: recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated
- Withdrawn: study halted prematurely, prior to enrollment of first participant

Furthermore, clinicaltrials.gov collects this information at the study level, not at the site level. In order to align with clinicaltrials.gov, changes to the RMIM are needed

Action Item: [RMIM] Remove RegistrationEvent Act and DataCollection Act; replace with AccrualStatus Act as a component of the Study Act.

Action Item: [Vocabulary] Propose using terminology for accrual status that aligns with clinicaltrials.gov (see proposed terms in comment 2.8)

Tester Comment [2.9]

What is the distinction between new and active data collection status? Some of these [i.e. terms used for testing] are arguably not data collection status. Suggest a definition of each term. Suggest ensuring consistent terminology with clinicaltrials.gov.

Note: clinicaltrials.gov does not capture data collection status, but instead captures the concept within Accrual Status (see previous comment)

Action Item: see Action Items for 2.8.

Tester Comment [2.10]

Investigator ID: Might it be time to consider an approach that would allow for a truly unique ID for investigators versus an approach that is trial-dependent? As it stands now, a given investigator could be associated with multiple/different IDs (per sponsor).

FDA Note: This is a valid comment which would require an investigator registration service. This is outside the scope of this project.

Action Item: None. Consider for future implementation

Tester Comment [2.11]

Two types of Investigators are supported: Principal Investigator and Sub-Investigator (taken from ICH E6). Are these acceptable? Are there any others that are needed? It would be helpful to have a clear statement as to what are the expectations in terms of the extent to which sponsors should identify study personnel. Depending on this view, we do see some utility in identifying other study personnel by role: study nurse; pharmacist; study coordinator.

FDA Note: Currently there are no regulatory requirements to identify other roles and we are reluctant to propose adding additional roles that might be interpreted as a new reporting burden. However, this could be revisited in the future should additional external requirements emerge (e.g. if other stakeholders would find additional roles useful).

Action Item: None at this time.

Tester Comment [2.12]

Investigator status: We recommend clear definition for each of the status indicators. What is the intent of pending? Should there not be a status for completed; What is the meaning of terminated? Under what conditions would we have an investigator who is suspended or terminated? Furthermore, investigator termination/suspension is not a historical trigger for an update to 1572 – is this a change in FDA expectations?

FDA Note: the intent is not to change FDA expectations, but to develop a value set for investigator status that all find useful.

Action Item: [Vocabulary] Propose two codes for investigator statusCode: Active and Inactive. (see 1.3)

Tester Comment [2.13]

What status codes would you like to see in the drop-box for license/degree status? Do we need to specify the type of degree or certification? All licenses? What is the utility in capturing detailed info on professional /

medical license? Is this redundant to info on the CV? Is it critical to identify the issuer, issuer address, etc.?

FDA Note: the intent is not to change FDA expectations, but to develop a value set that all find useful. Currently, the 1572 does not require the reporting of the type of degree or certification, so this is not part of the standard (see comment 1.4)

Action Item: [Vocabulary] Propose two codes for license/degree status: Active and Inactive, until clearer requirements emerge.

Tester Comment [2.14]

Service Provider Status: What status codes would you like to see in the drop-box? Please clarify what is meant by start and end date for service provider (i.e., dates of operational activity? contract dates? Etc.) Is this needed if status is active? Recommend clear definitions of each status indicator.

FDA Note: the start and end dates intend to capture the dates the service provider provides and stops providing the service to the study, respectively.

Action Item: [Vocabulary] Propose two codes for service provider status: Active and Inactive, until clearer requirements emerge.

Tester Comment [2.15]

Service Provider Roles: Are the current role codes reasonable?

Suggest additional options. Rather than just safety board, there should be a distinction for Central IRBs, IRBs/IECs, Data Monitoring Committees, and Ethical Committees. There should be some consideration for specific vendors such as ECG readers, X-ray readers, etc. Otherwise, the majority of providers may be captured under "other"?

FDA Note: the only service provider that is required by regulation for reporting purposes are central labs. However, other provider types can be added if found useful.

Action Item: [Vocabulary] Consider these additional service provider codes: ECG reader; Imaging reader.

Tester Comment [2.16]

There needs to be a clear distinction between sponsoring organization and the site location. Should these be captured as separate entities?

FDA Note: the sponsoring organization is not required. The site location is needed for inspection purposes.

Action Item: [xForm] Clarify what information is needed for site location.

Tester Comment [2.17]

The standard supports more than one physical location for a site. Is this reasonable? If an investigator has more than one site will we need a unique id for each site (sub-site)?

FDA Note: We believe it is reasonable and desirable to allow multiple physical locations for a site. The unique id for each physical site is optional.

Action Item: See 1.6

Tester Comment [2.18]

Subject Protection Approval ID: Is an ID for the approval needed or desirable? In our experience, IRBs will differ in this practice. Is the id needed if all the other key information (e.g., approval date, effective dates) regarding the IRB is provided? The identifier should be expanded to cover Institutional Review Board/Ethical Committee versus just Ethical Committee.

FDA Note: Currently the ID and the DUNS number are required. They should be optional.

Action Item: [RMIM] Make the subject approval ID and DUNS# optional (see 1.9)

Action Item: [xForm] Rename the label of Ethical Committee to Institutional Review Board/Ethical Committee

Tester Comment [2.19]

Subject Protection Approval Dates: Three dates are supported: the approval date, and the start and end date of the approval interval. Are these reasonable? We assume that a stop date is entered only if subject protection approval is withdrawn.

In trials that span multiple years, the approval is often provided for a specific period and then renewed. At the time that this information may be transmitted should it not reflect the current effective period? Suggest detailed guidance for this.

Action Item: [I.G. and xForm] Provide clearer meaning of the three available dates for subject protection approval date and start/end of approval interval.

Tester Comment [2.20]

The subject protection approval date field is not stored by the xForm.

Action Item: [xForm] Fix xForm so that the subject approval date field is stored in the XML file.

Tester Comment [2.21]

We had varying success with information captured in the form appearing on the 1572. When more than one type of service provider is listed with the same role, only one of the listed providers is shown on the form. Also the Preview 1572 does not reflect what type of qualifications was provided and whether a pdf is attached.

Action Item: [xForm] Ensure that the 1572 style sheet displays service provider and qualifications information accurately.

Tester Comment [2.22]

It is essential that a decision is communicated regarding the "signing of the xForm/1572. This will have a major impact of workflow and cost. Adoption of a fully electronic workflow will have a major positive impact on the collection maintenance and transmission/submission of clinical trial and investigator information. We recommend acceptance of digital signatures versus "wet signatures." Are there other options for reflecting/capturing an investigator's acknowledgement of his/her responsibilities? See also comment 2.6.

FDA Note: for purposes of submission, FDA is interested in the information captured in the 1572, not the signed form itself. Therefore, digital signatures for FDA's use case are not needed.

Action Item: [xForm] Make it clear that a signed or digital signature is not needed for FDA submission.

Tester Comment [2.23]

We recommend consideration of a field to capture whether the information is new versus amended.

Action Item: [RMIM] Check with modeler to see what versioning capabilities are currently supported and consider adding this feature (if absent).

Tester Comment [2.23]

It would be extremely useful to have a clear definition of the types of updates that would drive updating of the form information.

FDA Note: this is a policy/process issue which does not impact the standard.

Action Item: None at this time. Defer for future FDA guidance.

Tester Comment [2.24]

If the expectation is that ISO standard abbreviations be used for addresses, the specific preferred standard should be stated.

FDA Note: there is no current expectation on the format of addresses.

Action Item: None at this time.

Tester Comment [2.25]
Are email addresses for investigators "required" or preferred? Will the failure to include an email address cause the form not to be validated?
FDA Note: the email address is optional in the form.
Action Item: None at this time.

Tester Comment [2.26]
To avoid confusion, recommend using hints to be very clear about the distinction between the Principal Investigator on the study tab, vs. the Principal Investigator on the site tab. Note that the system only allows one PI on study tab (implying that this refers to the overall study's single primary investigator), whereas the site tab allows multiple PIs (implying that this was intended to indicate the site-specific PI). May be worth considering using two different terms to help support distinction and prevent unnecessary confusion.
FDA Note: the standard will be modified to associate investigators with sites. See comment 1.3.
Action Item: See action item under 1.3.

Tester Comment [2.27]
Note that currently the "Preview 1572" tab generates multiple 1572s simultaneously for the total list of investigators/sites. For large or even mega-trials, this could be an inefficient process. Please consider adding functionality so that users can select specific 1572(s) to generate/preview instead of automatically generating all of them at once.
Action Item: [xForm] Modify xForm to allow user selection of which 1572 forms to generate/preview. It should not generate a 1572 for a sub-investigator.

5.3 REGULATORY INFORMATICS CONSULTING

Regulatory Informatics Consulting provided one test file:

FDA_StudyPart_WA3835g.xml

The test file is valid. There were no errors and the information displayed properly within the xForm.

Tester Comment [3.1]

The tool allows selecting service provider by name for a site, and assigning a different role than the one specified on the Service Provider tab**.**

FDA Note: Whereas in most instances, the role at the study level will be the same as the role at the site level, we understand that is not always the case (see comment 3.11).

Action Item: [xForm] Update xForm so the service provider role assigned at the study level is the default role selected at the site level (but can be changed to a different role if necessary).

Tester Comment [3.2]

Should selections for section 8 of Form 1572, study protocol information, be available with ability to attach?

- Selections can be checked after the 1572 is generated.
- Would the attachments overlap with the study design?

FDA Note: Section 8 of the 1572 provides 2 checkboxes. The first checkbox is checked if the investigator provides a general study outline for phase 1 studies. The second checkbox is checked if a protocol outline for phase 2/3 studies is provided. The submission of a study protocol is outside the scope of this standard as it is provided elsewhere in an IND. This information is not needed.

Action Item: None.

Tester Comment [3.3]

Status codes for accrual status and data collection statuses are unclear

Action Item: see action item for comment 2.8.

Tester Comment [3.4]

Investigator address usually includes institution and box or mailstop number. CV often has both business and home addresses, 1572 usually includes only the business address.

FDA Note: Only the business address is needed.

Action Item: None.

Tester Comment [3.5]

Should sub-investigator's names be listed in section 6 of the 1572, without contact information? Currently primary investigator is listed as a sub-investigator and separate 1572 forms, with required contact information, are generated for each sub-investigator. Sub-investigators are usually identified only by name and degree (MD, RN, DO) or certification (CCRC)

Note: We agree that full contact information for sub-investigator is not needed. Currently, the xForm requires at least a telephone number and email address.

Action Item: [I.G.] Ensure that I.G. states that contact information for sub-investigators is not needed, including telephone and email.

Tester Comment [3.6]

xForm only allows one principal investigator per study. We have submitted multiple 1572 forms for a study, one for each site, with a principal investigator for that site listed in section 1, and multiple sub-investigators, listed, by name and degree only, in section 4. Is the goal to only have one principle investigator per study, with investigators at additional sites are considered sub-investigators?

FDA Note: See previous action item 1.5. RMIM will be changed to associate investigators at the site level. This allows multiple principal investigators, one for each site.

Action Item: See 1.5

Tester Comment [3.7]

xForm indicates telephone and email address are required fields, phone number is not required for validation. xForm includes a '+' in the saved file, so the field isn't null if no phone # is entered, and includes two if '+' is entered in the phone number field.

FDA Note: all contact information in the schema should be optional (as is the case for sub-investigators, see previous comment). However, contact information is necessary for principal investigators, and this can be reflected as a business rule in the I.G.

Action Item: [schema/RMIM] Investigator contact information should be optional

Action Item: [I.G.] I.G. should include a business rule that contact information is required for principal investigators

Action Item: [xForm] Fix xForm to store telephone information correctly: null for no phone number and only one + sign for country code if entered that way.

Tester Comment [3.8]

What Investigator status codes would you like to see in the drop-box?

Active, Replaced, Suspended?

Action Item: Current recommendation is to use two codes: Active, Inactive. We can defer these additional terms to a future release should the need arise. See 1.3.

Tester Comment [3.9]

What license/degree type codes are needed? Licensure, by state, possibly.

Unclear when board eligibility would be used. Does stop date indicate date degree received, or like subject protection approval, degree withdrawn?

Is there a need to specify the degree, e.g. MD, RN, for sub-investigators, without completing Degree section? Currently can be included as suffix to the name.

FDA Note: We do not need licensure information by state. Suggest deferring. Agree it is unclear when Board Eligibility would be used; suggest removing. End date would capture when licensure or certification was revoked and is optional.

Action Item: [Vocabulary] Delete term for Board Eligibility for License/degree type.

Action Item: [I.G.] Include definition for license/degree end date.

Action Item: [xForm] Label for license/degree end date could be more descriptive. Date revoked (?)

Tester Comment [3.10]

Service Provider: DUNS number is drop-down selection of previously entered DUNS numbers. DUNS numbers should be unique for all providers, so selection should not be necessary. Better to select service providers per site by DUNS number, not name, since multiple locations might have the same name.

Action Item: [xForm] Modify xForm so selection of DUNS number for Service Provider, once entered, should not be necessary.

Tester Comment [3.11]

Role is a required field for Service Provider, but may be different for different sites. Role is required for each site but may not be the same as that specified on the Service Provider tab.

FDA Note: See comment 3.1

Action Item: None. Already addressed in a previous comment (3.1)

Tester Comment [3.12]

Suggested service provider codes: active, canceled, suspended

Action Item: [Vocabulary] Proposal right now is to use two codes Active, Inactive for service provider codes until clearer requirements emerge. See 1.3.

Tester Comment [3.13]

Service provider roles for a study. Are the current role codes reasonable?

Unclear how Safety Board would be used? Would that be a DSMB [data safety monitoring board]? If so, would provider name be the Chair? Would also need an organization in the address. eClinical vendor – is that EDC? What additional role codes would you like to see in the drop-box?

Not clear how the role codes will be used, they are not included on the 1572. Possible to use role selection as a way to capture transfer of obligations?

FDA Note: The only required reporting of information of other entities (besides the investigators) under 21 CFR 312.53 is the name and address of any clinical laboratory and IRB that is used (and is on the 1572). All other information is optional.

Action Item: [Vocabulary] see previous comment 2.15 on suggested additional (optional) roles for this class.

Tester Comment [3.14]

Principal investigator selection allows selecting investigators identified as sub-investigators. Sub-investigators are selected by last name only, which may not be unique across sites

FDA Note: this will be fixed in the RMIM to allow primary association between investigator and site. See previous comment.

Action Item: [xForm] Fix xForm to allow association of investigators to sites using the full investigator name.

Tester Comment [3.15]

Sites can have two addresses, one specifically for drug delivery, would that be considered another location? Including a 2nd location for a site generates an invalid XML file, so it seems the schema does not support it currently. (It is displayed correctly on the 1572 (see AW3836g–multiple locations.xml)

FDA Note: Yes, a site can have multiple physical locations.

Action Item: [RMIM] see 2.17 to allow multiple physical locations per site.

Tester Comment [3.16]

Service Providers At Site implies the providers must be on-site, rather than Service Providers used by the site.

Action Item: [I.G.] Clarify that a service provider at a site means the service provider is used by the site, not necessarily that they are on-site.

Tester Comment [3.17]

Selecting the same IRB for multiple sites is possible, as it should be, but if the DUNS number is the same for multiple sites, the IRB is not displayed on the 1572s (section 5) for the second site. Likely a style sheet issue, since the IRB is coded for both sites, with the same extension. See WA3839g-IRB1 (same DUNS #) and WA3839g-IRB2 (different DUNS #s).

Action Item: [xForm] Investigate why the same IRB is not displayed for the second site, and correct.

Tester Comment [3.18]

It is possible to assign an investigator with status of terminated as a sub-investigator at a site. Form 1572 is also generated for terminated investigator.

Action Item: [xForm] Fix xForm so 1572 is not generated for an inactive investigator.

Tester Comment [3.19]

The standard supports more than one physical location for a site. Is this reasonable? Unclear why this would be required, unless we capture a different address for drug delivery to the site.

FDA Note: See 2.1. A site may have multiple physical locations.

Action Item: See 2.1

Tester Comment [3.20]

Subject Protection Approval ID. Is an ID for the approval needed or desirable? Unclear how it would be used or who would generate it.

FDA Note: We agree.

Action Item: [RMIM or I.G.] Discuss with modeler on eliminating Subject Protection Approval ID or assigning a system-generated GUID in the I.G. See also 1.9.

Tester Comment [3.21]

Subject Protection Approval Dates. Three dates are supported: the approval date, and the start and end dates of the approval interval. Are these reasonable? We assume that a stop date is entered only if subject protection approval is withdrawn. Would start date and approval date normally be the same?

FDA Note: Other discussions indicate that sometimes start date and approval date are different, e.g. approval is granted on Jan 21 for a one year interval starting Feb. 1.

Action Item: See. 2.19

Tester Comment [3.22]

A 1572 is generated for all sub-investigators, in addition to being listing in section 6 of the principal investigator's 1572.

FDA Note: We agree this is not desirable

Action Item: [xForm] see 2.27. xForm should not generate a separate 1572 for sub-investigators.

Tester Comment [3.23]

Would be ideal if xForm would validate on Save to ensure required fields have values.

FDA Note: We agree.

Action Item: [xForm] Add validate on save functionality.

5.4 CDER OFFICE OF SCIENTIFIC INVESTIGATIONS

[4.1] CDER OSI created and provided one test file for a fictional study. A machine running Windows XP and IE7 was used. The test file did not validate initially. The file was missing two required data elements, the sponsor assigned site ID and the Approval ID for the IRB approval. Providing these two elements resulted in a valid file.

Action Item: [tester feedback] The site ID is a required field and must be provided.

Action item: [xForm] Add self-validation feature to reject missing required data.

Action Item: [RMIM or I.G.] As previously noted, the subject protection approval ID should either be removed, optional, or auto-generated by the system (e.g. GUID). See 1.9 and 3.20.

Tester Comment [4.2]

Study Title is not supported in the standard, because Study Title exists in other parts of the submission and can be retrieved using the STUDYID. Is this acceptable? Yes

FDA Note: see Comment 2.7

Action Item: None (see action item for 2.7)

Tester Comment [4.3]

Investigator Type. Two types are supported: Principal Investigator and Sub-Investigator (taken from ICH E6). Are these acceptable? Answer: yes

Action Item: None

Tester Comment [4.4]

Investigator Status: What status codes would you like to see in the drop-box? Answer: completed

Note: Proposal is to use two codes: Active, Inactive

Action Item: See 1.3

Tester Comment [4.5]

License/Degree Type**:** What type codes would you like to see in the drop-box? Answer: License

Action Item: [Vocabulary] Add new term “License” to License/Degree type value set.

Tester Comment [4.6]

Subject Protection Approval ID: Is an ID for the approval needed or desirable? Answer: desirable

Action Item: [I.G.] see 2.18, 2.19, 3.20 on approval I.D.; consider using system-assigned GUID.

Tester Comment [4.7]

Subject Protection Approval Dates: Three dates are supported: the approval date, and the start and end dates of the approval interval. Are these reasonable? We assume that a stop date is entered only if subject protection approval is withdrawn. Answer: yes

Action Item: See 2.19

Tester Comment [4.8]

The print button didn’t work for me. The printed form formatting isn’t quite right. CV and “other statement” checkboxes didn’t translate to printed form.

Action Item: [xForm] Fix print feature so formatting is corrected. CV and “other statement” checkboxes should translate to the printed form.

5.5 CDER OFFICE OF NEW DRUGS

[5.1] CDER OND created and provided one test file from an actual study. A machine running Windows XP and IE7 was used. The test file initially did not validate because an illegal character (“?”) was entered in two date fields (subject approval begin and end dates). Removal of these illegal characters and leaving the fields blank resulted in a valid file.

Action Item: [tester feedback] Inform that “?” are not allowed in date fields.

Action item: [xForm] Add self-validation feature to reject illegal characters upon entry or upon save. See 3.23.

Tester Comment [5.2]

There was no problem to create, edit, view, or save test files. Installation of xForm was initially unsuccessful but later resolved when the files were unzipped and saved to the root of the local hard drive (C:). However, the xForm after unzip was in Firefox, and had to be opened with IE.

A general comment that applies to all tabs is about addresses. The study I entered was conducted in France, which has three levels of administration: prefecture, département, and region, corresponding to city, county, and state in the U.S. The addresses are usually given for prefecture and department. I had to research the “region” to fill in the state for the purpose of the xForm. As well, the postal code includes the regular code and sometimes a CEDEX code. These may create potential difficulties in entry.

Action Item: [xForm and I.G.] Provide instructions how to enter international addresses.

Tester Comment [5.3]

NCT number may not be associated with older clinical trials or trials in some foreign countries. Report cutoff date may not be available if the clinical trial has not reached a stage worth reporting, interim or final.
FDA Note: NCT number is optional. Report date is the date the study participation file was completed.
Action Item: [I.G. and xForm] Clarify the meaning of the report cutoff date.

Tester Comment [5.4]

Subject Accrual Status: What Status Codes would you like to see in the drop-box? Change “new” to “not initiated”; “new” is not a pertinent status. “Aborted” and “canceled” need to be defined as they may overlap. Their relationship to “suspended” and “clinical hold” also requires clarification. “Active” is an ambiguous term; “ongoing” may be preferable.

FDA Note: We should harmonize with clinicaltrials.gov

Action Item: See 2.8

Tester Comment [5.5]

Data Collection Status of Study: What Status Codes would you like to see in the drop-box? Same as comments under “Subject Accrual Status”

Action Item: See 2.8

Tester Comment [5.6]

Investigator Tab: One major flaw in this tab is to include Sub-Investigators and want the same information from them as Investigators (see Comments below under “Preview 1572”.

Action Item: See 2.27 and 3.5

Tester Comment [5.7]

The address of the Investigator in this study includes the institution name, but the xForm asks for “Street Address;” thus the institution name is removed. However, the Sub-Investigators in reality have the same address but did not list the street or its number, and so I was obliged to put “Hôpital

de l'Archet 2" into the space for "Street Address". This creates inconsistency even though the information should be the same.

The Investigator email address has an asterisk (*) but was not provided in the submission.

Action Item: [I.G. and xForm] Add 2nd line to investigator address to capture optional organization information

Action Item: [RMIM or I.G. and xForm] Make investigator email address optional.

Tester Comment [5.8]

Investigator Type: Two types are supported: Principal Investigator and Sub-Investigator (taken from ICH E6). Are these acceptable? Are there any others that are needed?

FDA regulations do not recognize "principal" Investigators. Each site has an Investigator and potential Sub-Investigators. Even the so-called "principal" Investigator in charge of the overall study is an Investigator.
At the study level, there should be no need to enter Sub-Investigators. Sub-Investigators should be entered at the site level.

If the aim of the xForm is to populate Form 1572, there should be no need of any additional categories.

FDA Note: this is similar to a previous comment. Although principal investigator is not described in federal regulations, it is described in ICH good clinical practice guidelines and is widely used.

Action Item: See 2.11

Tester Comment [5.9]

Investigator Status: What status codes would you like to see in the drop-box? Prefer "completed" to "terminated" for the Investigator of a study which has been completed. However, I have used "terminated" as the Investigator status because the study has ended and report written. The participation dates of the Sub-Investigators are unknown, but assumed to be the same as the Investigator's.

Note: Current recommendation is to use Active and Inactive. Additional terms can be added in the future as the need arises. Previous comments will address how subinvestigator information is managed.

Action Item: [I.G. and xForm] See 1.3. Clarify the meaning of Active and Inactive for investigator status. In general, an "Active" investigator means that they are actively involved (and responsible, in the case of the principal investigator) for study-related activities at the site. "Inactive" means they are no longer involved (or responsible) for study-related activities at the site.

Tester Comment [5.10]

License/Degree Type: What type codes would you like to see in the drop-box? Degree, license and certification.

Board eligibility is neither a license nor a certification and so would not afford a “status code”; nor would there be an issuer to fill in the blanks. A physician Investigator should hold license, and the holding of a license gives inference that he/she possesses a medical (dental, or osteopathy degree). Thus it is not necessary for such an Investigator to fill in the information under “degree”. A physician Investigator may use both license and certification from the drop-box, and if so, there is need for two sets of data in this area. The regulations do not bar a non-physician to be an Investigator. Sponsors are required to select only Investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53(a)). For a non-physician to be an Investigator, it may be appropriate to use the code “degree” and provide that information.

Having said the above, it is important to remember that Form 1572 does not require degree, license or certificate information. The Investigator is qualified by education, training and experience (Section #2 of Form 1572), and so for a non-physician Investigator, it is possible that he/she does not possess any of the above, but still be an expert in the field.

Action Item: [Vocabulary] For license/degree type, use three codes: license, degree, certification

Action Item: [I.G.] Make License/Degree type entry optional (since it’s not required to be an investigator). It is therefore optional to identify any license, degree, or certification for the investigator.

Tester Comment [5.11]

License/Degree Status: What status codes would you like to see in the drop-box? The purpose of this drop-box is unclear. For a physician Investigator to participate in a study, the license must be active. If the question is regarding the status at the time of report writing, that information is not pertinent. At the most, the drop-box should only ask for “active” and “inactive”, but the need of this is questionable for the reason just stated.

A license may have an end date and a certificate may or may not, but a degree does not.
I do not have the name and address of the University that gave the degree to the Investigator. Neither do I have the address of the institution that gave the certification to the Investigator. Such information is not in the c.v. provided, and is not required by Form 1572. The dates for degree and certification are known only for year, and so I put month and day as 0000.

Action Item: [Vocabulary] See 2.13. Propose we go with two codes for now for license/degree status: Active and Inactive, until clearer requirements emerge.

Tester Comment [5.12]

Service Provider Comments: DUNS# is not applicable for the case involved here I use the Sponsor's Local Clinical Project Coordinator for service provider. There are otherwise no appropriate providers in the study I entered, such as laboratories. If this is not acceptable, then this tab will not be filled. I do not consider the research facility a Service Provider. If it is intended for the purpose of the xForm to use the research facility as the "Service Provider", it should be stated in the User Manual. It is unclear what the User Manual means by "Like the Investigator, a Service Provider is normally assigned to a Site." (p. 29) I do not regard the research facility as a "Service provider" because it is not assigned to, but simply made use of, by the Investigator.

The item "Service Provider" is not one specified in Form 1572. Form 1572 asks for the research facility for conducting the clinical investigation (Section #3) and clinical laboratory facilities to be used in the study (Section #4). Why are these headings not used? These facilities should be site specific, unless there is a central lab that serves all sites. Indeed, it is probably not necessary to have a "Service Provider" tab for the study, but rather have the information only under the sites. Currently there is substantial repetition of information entry in both areas.

Should I consider the Statistician a "Service Provider"?

FDA Note: All of this information is optional. A statistician is not considered a service provider as he/she is not involved in the conduct of the trial. A service provider is a third party entity (i.e. not the sponsor or the investigator) that provides a service during the conduct of the trial. For example, a data safety monitoring board reviews safety data during the conduct of the trial and makes recommendations to increase subject safety during the trial.

Action Item: [I.G. and xForm] Clarify the definition of a service provider.

Tester Comment [5.13]

Service Provider Status: What status codes would you like to see in the drop-box?

While the study is ongoing, there are really only two possibilities: active or inactive. A pending Provider should not even be entered.

When the study is completed, the question is whether one considers the Provider as terminated or still active if it is a functioning entity regardless of the study. I would say for the sake of the study, it is to be considered as "terminated".

Action Item: See 2.14. Current proposal is to use two codes for service provider status: active and inactive, until clearer requirements emerge.

Tester Comment [5.14]

Provider Role for Study: Are the current role codes reasonable?

For Form 1572, only “Central Lab” among the several choices in the xFrom is needed. However, Form 1572 is Investigator-specific, and so local labs are also needed. Section #4 of Form 1572 says “any clinical laboratory facilities”.
This brings up a fundamental difference between the xForm and Form 1572. The xForm caters to the study first and the site is a subset of the study, while Form 1572 is all about a specific Investigator and site. To reproduce a lot of site data under the various tabs for the entire study is unnecessary for the purpose of filling in Form 1572. If that is actually considered necessary for an xForm, then to be complete, local labs would need to be entered under the “Service Provider” tab, and an additional code created for this category.

What additional role codes would you like to see in the drop-box?

See above

FDA Note: Service provider information is optional. The xForm does allow associating a provider with a site. It should be noted that the scope of the xForm is broader than just the 1572 information

Action Item: None

Tester comment [5.15]

Site Location(s): The xForm supports more than one physical location for a site. Is this reasonable?

Yes. The term “Site” merely stands for the research facility or facilities where the investigation is to be conducted. The subject may have to go to several locations for that purpose.
Unfortunately the xForm has both the “Site” tab and the “Service Provider” tab and this can be confusing. These must be clearly defined in the User Manual.

Form 1572 is Investigator-oriented, not site-oriented. Essentially the Investigator’s research facility is the site. Here, it is not clear whether the xForm is to count the facility as the “Service Provider”. If so, there could be potential inconsistency with Form 1572.

Note: These are valid comments, which have also been captured previously (need for multiple locations, better definition of service provider)

Action Item: See 1.6.

Tester Comment [5.16]

Subject Protection Approval ID: Is an ID for the approval needed or desirable? Nice to have but not essential

Action Item: See 2.18, 2.19, 3.20.

Tester Comment [5.17]

Subject Protection Approval Dates: Three dates are supported: the approval date, and the start and end dates of the approval interval. Are these reasonable? We assume that a stop date is entered only if subject protection approval is withdrawn.

Although asking for these dates may seem reasonable, they are not pertinent to Form 1572. Form 1572 only requires commitment to "ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation" and provision of its name and address.
End date of the approval interval for a completed study does not mean approval withdrawal.
Approval withdrawal may result in termination of study at the specific site, or due to the Investigator withdrawing participation, in which case the approval end date would be subsequent to the end date for participation.

Requiring dates creates extra work. It is best to keep things simple, unless the dates add value.

FDA Note: These dates are optional

Action Item: See 2.19.

Tester Comment [5.18]

Preview 1572 Comments: No additional comments on the form *per se* are necessary, as this merely shows extraction of data from the xForm. However, there is no need of Form 1572s for Sub-Investigators. The presence of such forms is due to the fact that Sub-Investigators are entered under the Investigator tab, and cannot be distinguished from Investigators except via the drop-box codes "Principal Investigator"/"Sub-Investigator". One remedy to the problem of having Sub-Investigator Forms 1572 could be to not allow them under the Investigator tab - by eliminating the drop-box of "Investigator Type"; Sub-Investigators should only be under the Site tab. I attached the Investigator c.v. to the form, but when the 1572 is printed, the c.v. is not an attachment. It is unclear how attached documents can be viewed from the xForm. There should be an easy way for people viewing the xForm to get the attached document(s).

FDA Note: These are valid comments that have been previously captured. Regarding the xForm, its primary purpose is for data entry during testing. A future iteration could include enhanced printing capability.
Action Item: [xForm] Enhance printing capability to also print the attachment(s).

Tester Comment [5.19]
There should be functionality to include the protocol name, which is required in Form 1572.
Action Item: See 2.7

Tester Comment [5.20]
The 1572 can accommodate more than one protocol by the Investigator (see Sections #7 and #8 of 1572), whereas the xForm appears to be able to cater to one study only. This is a fundamental discrepancy, and would require multiple, different xForms supporting different studies for the same Investigator who files one 1572 which includes all the studies. Thus, it may be necessary to redesign the xForm in order to achieve the functionalities enabling a 1572 for multiple studies.
FDA Note: We agree with the observation. As currently designed, the standard captures information about a single study. Adding support for multiple studies would require a major change to the standard and practically not feasible for the first release.
Action Item: Consider for a future release: the ability to associate an investigator with multiple studies.

Tester Comment [5.21]
In the Investigator tab, there should be drop-box for the documentation of qualifications: cv or other statement of qualifications, in order for the box(es) in Section #2 of Form 1572 to be checked. In the Study Information tab, there should be a question on “phase” in order for the box(es) in Section #8 of Form 1572 to be checked.
Action Item: See 3.2

Tester Comment [5.22]
The xForm has not provided areas for signing and dating the document, as required under Sections #10 and #11 of Form 1572, respectively. See also comment 2.6 and 2.22
Action Item: See 2.6 and 2.22

Tester Comment [5.23]
The question of functionality relates to the purpose of the xForm and the question who is to use it. I see several scenarios: a) Investigator using it to make a 1572 for the Sponsor at the time he/she is being recruited, but before the study starts, b) Investigator updating a 1572 as study is ongoing, c) Sponsor monitoring the Investigator’s progress, d) Sponsor using xForm data to prepare for datasets for regulatory submission, and e) FDA examining xForm for research integrity and f) other researchers extracting data from xForms for their own purposes. The xForm is therefore a living document and there may be multiple versions from one Investigator for a certain study at different time points. Each scenario may demand unique functionalities. The current testing appears to be about filling in the xForm. The other scenarios should also be explored.
FDA Note: The purpose of the current version of the xForm is to support testing of the standard. We agree that additional use cases exist and merit exploration should the desire to use the xForm for other purposes emerge.

Action Item: [xForm] Consider future enhancements to the xForm to support additional use cases as described in 5.23 comment.
Action Item: [RMIM] Consider for future release: adding versioning capability.

5.6 SANOFI

Sanofi provided one test file: FDA_STUDYPART_ABC1234.xml

The test file was created manually using the xForm, Windows XP, and IE 8.

The test file is valid. There were no errors and the information displayed properly within the xForm.

Tester Comment [6.1]

The Installation Guide should inform the user that the Internet Explorer option "Enable third-party browser extensions" must be checked. The XForms do not work if the option is not enabled.

Action item: [xForm] Add in the documentation that Internet Explorer option "Enable third-party browser extensions" must be checked for xForms to work properly

Tester Comment [6.2]

Is there a plan for the information entered / provided on the Study Information Tab to be crossed checked with other sites (e.g. ClinicalTrials.gov website information)?

FDA Note: There are currently no plans to do so. The comment does raise an intriguing possibility long term.

Action Item: None

Tester Comment [6.3]

For the test data we deferred to Active **Subject Accrual Status**, but it is difficult to differentiate between

- New vs. Active
- Cancelled vs. Aborted
- Suspended vs. Clinical Hold

FDA Note: See comment 2.8
Action Item: See 2.8.

Tester Comment [6.4]

Why would there be an option to delete Subject Accrual Status data? (assume the "delete" function is not possible once the data have been sent). We should always be able to keep previous information.

There were questions raised about process since the data were being created/viewed within a tool (xForm). Clearly information life-cycle issues (e.g., how to update a previously submitted record) would need to be clarified before using this message in production.

I would suggest the option to additional/ new information.

FDA Note: The tester is correct, the xForm delete function should be removed. Regarding lifecycle management, the preliminary thinking is that new information would replace or append older information using the eCTD submission file lifecycle management functionality. That is, the message would always be part of an eCTD submission.

Action Item: [xForm] Remove the delete button for Accrual Status information (see also 2.8)

Tester Comment [6.5]

Who is the intended person to enter this investigator data (the user referenced in the guideline), Industry or Investigator? If it is industry, Identifier (required field) will be unique to the company, but are there any plans to standardize among all using 1572 (databank) this identifier?

FDA Note: The intent is for the sponsor to provide the information in the message. In the future, it seems perfectly reasonable for the investigator fields to be auto-populated from information the investigator provide upstream. There are currently no plans to use a unique investigator identifier, although we recognize great benefit to moving in this direction. See also 2.10.

Action Item: None.

Tester Comment [6.6]

Again, there is an option to delete the following entries in the Investigator tab:

- Investigator CV or Statement of Qualifications,
- Licenses / Degrees
- Investigator

I would suggest we just be able to add changes and keep the history.

FDA Note: We agree.

Action Item: [xForm] Remove the ability to delete previously entered information under the Investigator tab.

Tester Comment [6.7]

Yes more investigator types are needed, since more staff may be involved in the direct care of the patient:

- Nurse
- Research Fellows

- Residents

(NOTE: Anyone who would need to complete a Financial Disclosure form)
FDA Note: current federal regulations do not require sponsors to identify these roles to FDA; a designation of 'sub-investigator' to make it clear they are not the principal investigator at the site, is sufficient. We are reluctant to add additional roles to investigator type at this time as it may be interpreted as a new reporting requirement.

Action Item: None. Defer to a future release if new reporting requirements emerge.

Tester Comment [6.8]

For the test investigator status data we deferred to Active, but it is difficult to differentiate between

- Cancelled vs. Terminated vs. Suspended

Pending could be used while study site is being evaluated but this is a lot of rework going into making changes to initial entries.

FDA Note: We agree. See 1.3.

Action Item: See 1.3

Tester Comment [6.9]

The license/degree type options seem okay for now but we need a clear understanding of how the options should be applied.

FDA Note: We appreciate the feedback. See also 4.5

Action Item: [xForm] Provide clarity on how license/degree type should be selected. See also 4.5.

Tester Comment [6.10]

As above, for the test license/degree status data we deferred to Active, but it is difficult to differentiate between

- Cancelled vs. Terminated vs. Suspended

Pending could be used while study site is being evaluated but this is a lot of rework going into making changes to initial entries.

FDA Note: We agree. See 2.13

Action Item: See 2.13.

Tester Comment [6.11]

As above, for the test service provide status data we deferred to Active, but it is difficult to differentiate between

- Cancelled vs. Terminated vs. Suspended
- Pending could be used while study site is being evaluated but this is a lot of rework going into making changes to initial entries.

Also the idea of deleting a Service provider. I would rather replace with new information and be able to keep the old service provider information

FDA Note: We agree and propose simplifying service provider status codes. See 2.14. When updating information, the sponsor may generate a new message with the old service provider still present, and status=inactive and provide the new service provider status=active

Action Item: See 2.14

Tester Comment [6.12]

Need clarification on provider role for study vendor types (eClinical vendor is that an IVRS serve vendor)? Perhaps addition of independent reader – see it in some (e.g. oncology or cardiology) studies. The option for the use of "other" can result in loss of information or miscoding of information if the category choices are not clear.

FDA Note: We agree. Initially, we plan to add additional roles. See 2.15.

Action Item: See 2.15

Tester Comment [6.13]

General statement on the option to "remove from site vs. just add new information as an update and keeping the previous information as different status.

FDA Note: We agree. The broader issue of life-cycle management of this information will need to be addressed separately. Please also see 6.4

Action Item: [General] FDA will need to publish separate instructions on how to handle information that changes over time, using active/inactive codes in the message and the eCTD submission file life-cycle features (e.g. "replace" and "append" previously submitted information).

Tester Comment [6.14]

Yes it is reasonable that the standard supports more than one physical location for a site, since it is common to have "satellite" sites.

FDA Note: This confirms the feedback we've received from other testers.

Action Item: See 2.17.

Tester Comment [6.15]

Subject Protection approval; is that the IRB/EC in place?

I would think this would be good in a situation where the IRB length is not as long as the study time point but would defer to my clinical colleagues if this would be a benefit.

FDA Note: If we understand the comment correctly, this is similar to 2.19

Action Item: See 2.19.

Tester Comment [6.16]

Again, I would not delete subject protection approval information rather update/ add information.

Action Item: [xForm] Remove the ability to delete previously entered subject protection approval information.

Tester Comment [6.17]

Is there a “stop date” associated with the renewal of the IRB contract?

FDA Note: From a regulatory perspective, we are only interested in the date an IRB withdraws approval to a site, and not the end of the IRB renewal contract.

Action Item: See 2.19

Tester Comment [6.18]

The 1572 shows both the investigator and sub-investigator, is this appropriate?

In the 1572 form, should the “Curriculum Vitae” box be checked if there is a file referenced? Otherwise how does this box get checked?

Also, should the form have a different field to reference a “statement of qualification” so that these boxes get appropriately marked?

How does section 8 of the form 1572 get completed?

Will the Principle Investigator’s signature and date of their signature be collected?If yes, how?

FDA Note: There is an error in the xForm. The xForm should not generate a separate 1572 for sub-investigators. See 2.27. There is also somewhat of a disconnect between the xForm and the 1572 in that submission of the completed 1572 to FDA is not required, yet much (but not all) of the information contained within the 1572 is useful to submit to fulfill the reporting regulations described in 21 CFR 312.23. The checkbox information in section 2 need not be reported. The information in section 8 also need not be reported, because protocol information is submitted separately to the IND. See comment 3.2. Similarly, the principal investigator signature and signature date are not needed for submission. See comment 2.22.

Action Item: See 2.27.

5.0 DISCUSSION

The discussion focuses on the goals of the testing and additional issues that arose during testing.

Goal: To create a valid Study Participation message for review by US FDA

Goal: To use simple testing tools (xForm, Style sheet) to create, edit, view, and save HL7 Study Participation messages

The testing successfully achieved these goals. Although three of the six test files did not validate initially, simple corrections resulted in valid files (e.g. removal of illegal characters). Testers achieved the creation of the test files through the use of an xForm. The biggest advantage of this approach was that testers did not need any experience either with HL7 standards or XML. This demonstrates that the complexity of v3 messaging can be hidden from the end user with proper tooling (in this case, open source technology – xForm). One tester (the NCI) successfully created their test file programmatically without the xForm from their internal databases.

Once installed, the xForm allowed testers to create, edit, view, and save HL7 Study Participation messages. The xForm did require testers to install MozzIE. MozzIE is an open-source plug-in for Microsoft Internet Explorer that enables the display of XHTML + Xforms using the Mozilla Gecko Rendering Engine.[3] Some testers had difficulty getting the xForms to work with their hardware/software environment, which clearly limits its usefulness outside of a testing scenario. At FDA, MozzIE was later found to have certain security risks so that installation on FDA workstations was no longer allowed. FDA I.T. staff was able to install MozzIE on a computer in a sequestered environment that was then made available to FDA testers via a Citrix connection. These findings made it clear that the installation of a plug-in is not desirable for future testing using xForms. The testing team subsequently became aware of new technology, XSLTForms, that can render xForms in any browser without the use of a plug-in. The plan is to use XSLTForms for future testing. The disadvantage is that the existing xForm is not compatible with XSLTForms, and would have to be re-engineered. However, the main goal of the xForm was to support testing, which we were able to complete.

The style sheet was useful in displaying in a human readable format the information contained in FDA form 1572. However, the xForm generated a 1572 for both principal investigators and sub-investigators. A 1572 is not needed for sub-investigators. This needs to be fixed in any future xForm version.

Goal: To identify and utilize controlled vocabularies sufficient to conduct the testing.

We conducted the testing with an initial set of draft controlled terms and value sets and specifically sought feedback from testers on the most

[3] See http://sourceforge.net/projects/mozzie/ (last accessed 12/7/2012)

appropriate concepts to use in the future. The feedback was successful in identifying concepts for future piloting. These are documented in the Recommendations section below.

Goal: To identify business process and/or technical issues that may negatively affect efforts to implement HL7 Study Participation
Goal: To confirm a collective (if only general) understanding of how the process and technology will function together.

Although the main goal of testing was to assess the standard's capability to support study participation information exchange, we were also interested in identifying, at a high level, potential roadblocks to piloting and implementation.

For test file creators, one notable roadblock is the fact that the information supported by the standard is not managed within a single system or a single organizational component. This limits the potential for automation of business processes used to generate the files for submission. It should be noted that this roadblock exists regardless of the format used for submission. That is to say, it exists whether the information is provided in PDF or XML. By moving towards a machine-readable standard for submission, we believe this will enable the automation of upstream processes to generate the files for submission.

Another roadblock is the technical issue associated with the use of the xForm itself. This has been described previously, but it is clear that the use of the MozzIE plug-in was problematic. We plan to address this in future testing via the use of a different open-source technology called XSLTforms; however it remains to be seen whether xForms have any role at all in a production environment. We believe long-term efficiencies are gained when the files can be created programmatically directly from internal systems that contain the information.

On the FDA side, there was uniform excitement in being able to receive study participation information in a machine-readable format, but this will require additional infrastructure and processes to receive, validate, store, and retrieve the information. Currently, clinical investigator information is manually entered in internal databases. It is recognized that there is great potential for automation of these data management business processes, leading to increased efficiencies.

Goal: To provide a proof of concept of HL7 Study Participation to the broader stakeholder community

We believe the testing has accomplished this goal. Most importantly it demonstrated that a simple data entry tool can facilitate the creation of XML test files without the need to understand the HL7 standard or XML.

Limitations of the Testing

CDER is very grateful for the individuals and organizations that participated in the testing, but ideally we would have preferred more testers. We sought volunteers through the RCRIM and Stage II communities but this resulted in a limited test community. FDA may be able to solicit more testers in the future by issuing a public notice, either in the Federal Register, on www.fda.gov, or some other means.

Despite the limited number of testers and test files, many of the results across test files were similar, suggesting that the important issues and action items have been identified. However, we believe additional experience with the standard should be gained through a second round of testing by broadening stakeholder participation through a operational pilot. (see Section 8, Next Steps).

5.0 RECOMMENDATIONS

The following summarizes the actionable items identified during testing.

7.1 GENERAL CHANGES FOR CONSIDERATION

Comment	Action
6.13	FDA will need to publish separate instructions on how to handle information that changes over time, using active/inactive codes in the message and the eCTD submission file life-cycle features (e.g. “replace” and “append” previously submitted information).

7.2 CHANGES TO THE STANDARD (RMIM)

Comment	Action
1.4	Consider for future release of the standard: capturing type of degree, board certification, and license.
1.5	Change RMIM to associate investigator with the site (StudyActivitiesAtSite), with two codes: principal, sub-investigator. Add optional association with the Study, one code: coordinating investigator. Also update the Implementation Guide to reflect these changes.

Comment	Action
1.6	Change RMIM to allow 1…n physical locations for StudyActivityAtSite
1.9	Change the RMIM and schema so SubjectProtectionApproval.id element is optional.
2.6	Consider for future release: capturing the date the clinical investigator confirmed their information (i.e. the date the 1572 was signed).
2.7	Add Study Title as an optional field.
2.8	Remove RegistrationEvent Act and DataCollection Act; replace with AccrualStatus Act as a component of the Study Act.
2.23	Check with modeler to see what versioning capabilities are currently supported and consider adding this feature (if absent).
3.7	Investigator contact information should be optional
3.20	Discuss with modeler on eliminating Subject Protection Approval ID or assigning a system-generated GUID in the I.G. See also 1.9.
4.1	As previously noted, the subject protection approval ID should either be removed, optional, or auto-generated by the system (e.g. GUID). See 1.9 and 3.20.
5.7	Make investigator email address optional.
5.20	Consider for a future release: the ability to associate an investigator with multiple studies.
5.23	Consider for future release: adding versioning capability.

7.3 CHANGES TO THE SCHEMA

It is understood that the schema will be re-generated based on the RMIM changes described above. In addition, the following actions are noted.

Comment	Action
1.8	Fix the schema to match the RMIM by adding the commissioningOrganization element of EthicalCommittee.
1.9	Change the RMIM and schema so SubjectProtectionApproval.id element is optional.
3.7	Investigator contact information should be optional

7.4 CHANGES TO THE IMPLEMENTATION GUIDE

Comment	Action
1.1	Change Implementation Guide to capture name in parts.
1.2	Change the I.G. to use optional DUNS numbers for sponsors, CROs, and healthcare organizations associated with the Investigators.
1.4	Change Appendix 2 example with UT Southwest Medical School to remove “MD” from extension.
1.5	Change RMIM to associate investigator with the site (StudyActivitiesAtSite), with

Comment	Action
	two codes: principal, sub-investigator. Add optional association with the Study, one code: coordinating investigator. Also update the Implementation Guide to reflect these changes.
2.5	Make explicit that the StudyID is the SDTM StudyID.
2.6	Make explicit the meaning of Report Cutoff Date
2.19	Provide clearer meaning of the three available dates for subject protection approval date and start/end of approval interval.
3.5	Ensure that I.G. states that contact information for sub-investigators is not needed, including telephone and email.
3.7	I.G. should include a business rule that contact information is required for principal investigators
3.9	Include definition for license/degree end date.
3.20	Discuss with modeler on eliminating Subject Protection Approval ID or assigning a system-generated GUID in the I.G. See also 1.9.
4.1	As previously noted, the subject protection approval ID should either be removed, optional, or auto-generated by the system (e.g. GUID). See 1.9 and 3.20.
5.1	Provide instructions how to enter international addresses.
5.3	Clarify the meaning of the report cutoff date.
5.7	Add 2nd line to investigator address to capture optional organization information
5.7	Make investigator email address optional.
5.9	See 1.3. Clarify the meaning of Active and Inactive for investigator status. In general, an “Active” investigator means that they are actively involved (and responsible, in the case of the principal investigator) for study-related activities at the site. “Inactive” means they are no longer involved (or responsible) for study-related activities at the site.
5.10	Make License/Degree type entry optional (since it’s not required to be an investigator). It is therefore optional to identify any license, degree, or certification for the investigator.
5.12	Clarify the definition of a service provider.

7.5 CHANGES TO VOCABULARY

Comment	Action
1.3	Propose two codes for investigator statusCode: Active and Inactive and develop definitions.
2.8	Propose using terminology for accrual status that aligns with clinicaltrials.gov (see proposed terms in comment 2.8)
2.13	Propose two codes for license/degree status: Active and Inactive, until clearer requirements emerge.
2.14	Propose two codes for service provider status: Active and Inactive, until clearer

Comment	Action
	requirements emerge.
2.15	Consider these additional service provider codes: ECG reader; Imaging reader.
3.9	Delete term for Board Eligibility for License/degree type.
3.16	Clarify that a service provider at a site means the service provider is used by the site, not necessarily that they are on-site.
4.5	Add new term “License” to License/Degree type value set.
5.10	For license/degree type, use three codes: license, degree, certification

7.6 CHANGES TO THE XFORM

Comment	Action
n/a	Re-engineer xForms to use XSLTForms technology; avoid use of MozzIE plug-in
2.2	Make hints clearer
2.3	Display all required fields by default.
2.4	Fix xForm so all service providers appear in the drop down list, including those without a DUNS number.
2.5	Make explicit that the StudyID is the SDTM StudyID.
2.6	Make explicit the meaning of Report Cutoff Date
2.16	Clarify what information is needed for site location.
2.18	Rename the label of Ethical Committee to Institutional Review Board/Ethical Committee
2.19	Provide clearer meaning of the three available dates for subject protection approval date and start/end of approval interval.
2.20	Fix xForm so that the subject approval date field is stored in the XML file
2.21	Ensure that the 1572 style sheet displays service provider and qualifications information accurately.
2.22	Make it clear that a signed or digital signature is not needed for FDA submission.
2.27	Modify xForm to allow user selection of which 1572 forms to generate/preview. It should not generate a 1572 for a sub-investigator.
3.1	Update xForm so the service provider role assigned at the study level is the default role selected at the site level (but can be changed to a different role if necessary).
3.7	Fix xForm to store telephone information correctly: null for no phone number and only one + sign for country code if entered that way.
3.9	Label for license/degree end date could be more descriptive. Date revoked (?)
3.10	Modify xForm so selection of DUNS number for Service Provider, once entered, should not be necessary.
3.14	Fix xForm to allow association of investigators to sites using the full investigator name.

Comment	Action
3.17	Investigate why the same IRB is not displayed for the second site, and correct.
3.18	Fix xForm so 1572 is not generated for an inactive investigator.
3.23	Add validate on save functionality.
4.1	Add self-validation feature to reject missing required data.
4.8	Fix print feature so formatting is corrected. CV and “other statement” checkboxes should translate to the printed form.
5.1	Add self-validation feature to reject illegal characters upon entry or upon save. See 3.23.
5.2	Provide instructions how to enter international addresses.
5.3	Clarify the meaning of the report cutoff date.
5.7	Add 2nd line to investigator address to capture optional organization information
5.7	Make investigator email address optional.
5.9	See 1.3. Clarify the meaning of Active and Inactive for investigator status. In general, an “Active” investigator means that they are actively involved (and responsible, in the case of the principal investigator) for study-related activities at the site. “Inactive” means they are no longer involved (or responsible) for study-related activities at the site.
5.12	Clarify the definition of a service provider.
5.18	Enhance printing capability to also print the attachment(s).
5.23	Consider future enhancements to the xForm to support additional use cases as described in 5.23 comment.
6.1	Add in the documentation that Internet Explorer option “Enable third-party browser extensions” must be checked for xForms to work properly
6.4	Remove the delete button for Accrual Status information (see also 2.8)
6.6	Remove the ability to delete previously entered information under the Investigator tab.
6.9	Provide clarity on how license/degree type should be selected. See also 4.5.
6.16	Remove the ability to delete previously entered subject protection approval information.

8.0 NEXT STEPS

It is recommended that the project team update the project plan to incorporate these next steps.

- Make the changes described in section 7

- Submit the changes to the RMIM and I.G. to HL7 as normative ballots
- Register new controlled terms and value sets with NCI Enterprise Vocabulary Services (EVS)
- Conduct another round of BRIDG harmonization
    - Identify gaps with current BRIDG release
    - Submit gaps to the BRIDG semantic coordination committee (SCC)

Once these steps are complete, the testing team recommends a second round of testing encompassing a wider stakeholder community in the form of an operational pilot.

APPENDIX A: TESTING PLAN

HL7 Study Participation and Patient Narrative/CDA DSTU — Testing Plan

Overview (Scope, Goals, Approach, Governance & Expectations)

Introduction –

As part of FDA's ongoing study data standards research and development activities, FDA is planning to test the use of the HL7 Study Participation standard (currently a Draft Standard for Trial Use – DSTU) and the HL7 Clinical Document Architecture, Release 2 (CDA R2) normative standard. Please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm269946.htm for more information.

Scope –

The scope of the testing will be limited to test files provided to the US Food and Drug Administration. By limiting the scope, our intent is to gain hands-on experience at a very focused, detailed level to identify potential issues in preparation for a future implementation of HL7 Study Participation and Patient Narratives/CDA for regulatory submissions to the US FDA. The testing will proceed in two phases.

- Phase 1 Testing will test the use of the Study Participation DSTU standard to support the exchange of information about key entities that participate in a trial:
  - Investigators and their qualifications (electronic FDA Form 1572, Investigator C.V.)
  - Other service providers (e.g. contract research organizations, central labs)

- Phase 2 Testing will test the use of CDA Release 2 to support the exchange of Patient Narrative information from a clinical trial, based on the Patient Narrative/CDA DSTU Implementation Guide.

Goals –

Phase 1 Goals:

- To create a valid Study Participation message for review by US FDA.
- To use simple testing tools (xForm, Style sheet) to create, edit, view, and save HL7 Study Participation messages.

- To identify and utilize controlled vocabularies sufficient to conduct the testing. Vocabularies are necessary to support creation of HL7 Study Participation messages. This will require the application of such controlled vocabularies using realistic (not fabricated) values, and where appropriate making the necessary additions and/or modifications to these terminologies and value sets.
- To identify business process and/or technical issues that may negatively affect efforts to implement HL7 Study Participation
    - To carefully and thoroughly diagnose issues, and (if feasible) propose potential remedies
    - To determine whether such issues will impact the further use and development of HL7 Study Participation, and if so to communicate these issues with the HL7 Study Data Standards (Stage II) team accordingly.
- To confirm a collective (if only general) understanding of how the process and technology will function together.
- To provide a proof of concept of HL7 Study Participation to the broader stakeholder community who will be critical to supporting full implementation of HL7 Study Participation. Furthermore, to confirm (or to reasonably predict) the feasibility of implementing HL7 Study Participation for use by sponsors of clinical trials in submitting data to the FDA.

Phase 2 Goals Will Include:

- To create a valid CDA documents containing Patient Narrative information for US FDA.
- To use simple testing tools (xForm, Style sheet) to create, edit, view, and save Patient Narrative/CDA documents.
- To identify and utilize controlled vocabularies sufficient to conduct the testing. Vocabularies are necessary to support creation of Patient Narrative/CDA documents. This will require the application of such controlled vocabularies using realistic (not fabricated) values, and where appropriate making the necessary additions and/or modifications to these terminologies and value sets.
- To identify business process and/or technical issues that may negatively affect efforts to implement Patient Narrative/CDA
    - To carefully and thoroughly diagnose issues, and (if feasible) propose potential remedies
    - To determine whether such issues will impact the further use of Patient Narrative/CDA, and if so to communicate these issues with the HL7 Study Data Standards (Stage II) team accordingly.
- To confirm a collective (if only general) understanding of how the process and technology will function together.
- To provide a proof of concept of Patient Narrative/CDA to the broader stakeholder community who will be critical to supporting full implementation of Patient Narrative/CDA. Furthermore, to confirm (or to reasonably predict) the feasibility of implementing CDA for Patient Narrative information for use by sponsors of clinical trials in submitting data to the FDA.

Approach –

- The Test Team will consist of
    - **Volunteers** from the HL7 Study Data Standards project team (Stage II). Because FDA is providing xForms to facilitate the creation of valid test files, no technical experience in the standard is required; however, technical expertise among some volunteers is welcomed. The use of the testing tools is also not required, but we hope testers will find them useful.
    - **Test Team Lead:** will provide broad oversight during testing.
    - **Technical Lead:** will identify and provide the xForms and style sheets to successfully perform testing, and will identify, review, and apply necessary controlled vocabularies. The technical lead will also clarify and explain the contents of the Implementation Guides, and make any modifications to the guides as a result of the testing.

- Each phase will last a total of two months, and will be staggered, during which
    - Test team volunteers will create and submit test files to FDA members
    - FDA will evaluate the test files both for format/structure and content
    - Test team volunteers will be encouraged to share test files with other, non- FDA team members, in the spirit of promoting community learning to help us achieve our goals. This is not required, as we recognize some of the dummy data provided in the test files might be sensitive.
- Testing will promote strong communication, including:
    - Setting and sharing expectations/plans at all levels
    - Bringing individual testing experience back to the team as a whole
    - Sharing information with HL7 Study Data Standards (Stage II) Team
    - Documentation and public publication of issues, resolutions, lessons learned
- Testing will promote flexibility:
    - Be willing to be flexible, as the testing gets underway, a different approach or strategy may emerge as desirable
    - Expect plans to evolve and change. We will treat initial plans as general guidelines and will enhance them as we go.

- Please continually offer suggestions on how to work more effectively as a team.

Governance –

- The testing team lead will be responsible for keeping this project moving forward. He/she will seek *and leverage* the collective knowledge and advice of the group to evaluate and reach decisions. Where a decision is required, the testing team lead will accept responsibility for making a decision.
- This team will largely operate as a democracy; however there may be situations where consensus is split or a decision is unpopular, requiring escalation to the HL7 Study Data Standards Stage II Team (first), and then to RCRIM, if necessary, for further discussion and vote.

Expectations—

- Hands-on participation. The project will need every participant to be an active contributor to the effort.
- Ideally, we seek Involvement from sponsors of clinical trials, and software vendors.
- Willingness to share, where possible, test data with the entire group.
- Testing will facilitate the refinement of the Study Participation standard and the Study Participation and Patient Narrative/CDA implementation guides.

Success Criteria/Metrics—

- Testers are able to create, edit, view, and save HL7 Study Participation messages and Patient Narrative/CDA Documents
- FDA can view HL7 Study participation messages and Patient Narrative/CDA documents
- All necessary information identified by FDA subject matters experts (Bioresearch Monitoring (BIMO) staff/Office of Scientific Investigations (OSI)/reviewers) is contained in the displayed messages and documents

High Level Project Timeline –

Commencement of testing is dependent on the availability of the testing tools (xForms and Style Sheets).

- Phase 1 – Study Participation

- We expect availability of the xForm and style sheet for Study Participation to be available around April 15, 2012.
- We will schedule a webinar demonstration of the tools shortly thereafter
- We will begin the two-month test period shortly thereafter. The exact start date will be determined by the test team, to best align with volunteers' schedule.

- Phase 2 – Patient Narrative/CDA
  - We expect the xForm and style sheet for Patient Narrative/CDA to be available around June 1st, 2012
  - We will schedule a webinar demonstration of the tools shortly thereafter
  - We will begin the two-month test period shortly thereafter. The exact start date will be determined by the test team, to best align with volunteers' schedule. Testing will not begin until the Phase 1 testing period has ended.

APPENDIX B: EVALUATION FORM

Study Participation xForm
General Instructions and Evaluation Sheet

Study Participation Testing will proceed along these high level steps:

1. Install the xForm

Please see the Xforms Quick Install Guide.doc located at [LINK].

2. Create test files

Create test files using the xForm. Detailed instructions for using the tool are located in the \Project Documents\User Manual folder.

You may use actual study data or dummy data. Please indicate in the evaluation sheet which you used, and whether the test files can be shared outside of FDA.

3. Complete Evaluation Sheet

The evaluation sheet is on the next page of this document.

4. Submit test files

Each test file will have one or more associated PDF files of investigator CVs and/or statement of qualifications. Please zip one test file and all associated PDFs into a single zip file. There are numerous freeware available on the internet for this purpose. Email the zipped file to crystal.allard@fda.hhs.gov along with a completed evaluation sheet.

Study Participation Evaluation Sheet

Submitter: **Date:**

Submitting Organization:

Email: **Phone:**

Name of Test File:

Can Test File Be Shared Outside FDA: Yes ☐ **No** ☐

General Comments:
Please comment on your ability to create, edit, view, save test files.
Study Information Tab
Comments:
Study Title is not supported in the standard, because Study Title exists in other parts of the submission and can be retrieved using the STUDYID. Is this acceptable?
Subject Accrual Status: What Status Codes would you like to see in the drop-box?
Data Collection Status of Study: What Status Codes would you like to see in the drop-box?
Investigator Tab
Comments:

Investigator Type: Two types are supported: Principal Investigator and Sub-Investigator (taken from ICH E6). Are these acceptable? Are there any others that are needed?
Investigator Status: What status codes would you like to see in the drop-box?
License/Degree Type: What type codes would you like to see in the drop-box?
License/Degree Status: What status codes would you like to see in the drop-box?
Service Provider
Comments:
Provider Status: What status codes would you like to see in the drop-box?
Provider Role for Study: Are the current role codes reasonable? What additional role codes would you like to see in the drop-box?

Site
Comments:
Location(s) The standard supports more than one physical location for a site. Is this reasonable?
Subject Protection Approval ID Is an ID for the approval needed or desirable?
Subject Protection Approval Dates Three dates are supported: the approval date, and the start and end dates of the approval interval. Are these reasonable? We assume that a stop date is entered only if subject protection approval is withdrawn.
Preview 1572
Comments:
Additional Comments

APPENDIX C: Test Report Approval

The undersigned acknowledge they have reviewed the **HL7 Study Participation Draft Standard for Trial Use Test Report** and agree with the approach it presents. Changes to this **Test Report** will be coordinated with and approved by the undersigned or their designated representatives.

Signature/ Date:	
Print Name:	Crystal Allard
Role:	Project Manager