Center for Drug Evaluation and Research

CLINICAL TRIALS PATIENT NARRATIVE

USING CLINICAL DOCUMENT ARCHITECTURE (CDA) RELEASE 2

TEST REPORT

FINAL

JUNE 2013

TABLE OF CONTENTS

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ACKNOWLEDGEMENTS

The Food and Drug Administration gratefully acknowledges the contributions of those individuals and organizations that participated in the testing.

Johnson and Johnson

Sanofi

Center for Drug Evaluation and Research, Office of New Drugs

1.0 INTRODUCTION

1.1 PURPOSE

This report contains the results of testing the use of the Clinical Document Architecture (CDA) standard, Release 2, a Health Level Seven (HL7) version 3 standard, for the exchange of patient narrative information of subjects in a clinical trial. The patient narrative is a summary document that describes a subject's clinical experience resulting from participation in a clinical trial. The purpose of the testing was to determine if the CDA standard is capable of capturing and exchanging patient narrative information, for submission to the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA).

1.2 BACKGROUND

CDER has developed an implementation guide (IG) describing how CDA R2 can be used to represent patient narrative information in a machine-readable format for submission to CDER. This IG has passed initial ballot in HL7 as a Draft Standard for Trial Use (DSTU).

In current practice, sponsors of clinical investigations generate patient narratives on some investigative subjects. These summary documents enhance a reviewer's understanding of the subject's clinical experience during the trial. The triggers for generating a narrative vary, but may include death, a serious adverse event, or an adverse event leading to discontinuation from the study.

CDER currently receives patient narratives either in paper format or PDF. These formats are adequate for manual, human review, but they do not easily support more modern analytical techniques, e.g., integrating patient narrative information with other clinical data such as a tool-generated patient profile or other analyses. It is also desirable to pool patient narrative information across subjects and studies to mine the information using modern information mining tools that rely on natural language processing techniques. Receiving patient narratives in a machine-readable format will enable more advanced and efficient review processes.

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 patient narrative test files. In a recent FDA public meeting on Solutions for New Study Data Exchange Standards (November 5, 2012),[1] 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

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

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.

2.0 GOALS

The goals of the Patient Narrative testing were:

- To create a valid Patient Narrative files for review by US FDA.
- To use simple testing tools (xForm, Style sheet) to create, edit, view, and save Patient Narrative files.
- To identify and utilize controlled vocabularies. Vocabularies are necessary to support creation of Patient Narrative files. 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 CDA R2 for patient narratives
    - To identify issues, and (if feasible) propose potential remedies
    - To determine whether such issues will impact the further use of CDA R2 for patient narratives, 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 on the use of CDA R2 for patient narratives to the broader stakeholder community. Furthermore, to confirm (or to reasonably predict) the feasibility of implementing CDA R2 for use by sponsors of clinical trials in submitting patient narrative information to CDER.

3.0 APPROACH

The project team recruited internal testers from CDER organizational components that receive and review patient narrative information. Other Centers were aware of the 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 CDA R2 was required. However, those with more technical expertise were welcome to generate the test files programmatically from their internal information systems. The project team developed a test plan (see Appendix 1) and an evaluation form (see Appendix 2).

Tester volunteers received the CDA R2 patient narrative implementation guide, the standard CDA R2 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

Three organizations participated in the testing and provided test files:

- Johnson and Johnson
- Sanofi
- Center for Drug Evaluation and Research, Office of New Drugs

5.0 RESULTS

The results of each individual test file are described below. There was a total of 17 test files submitted. All but two were valid against the CDA schema. The errors in the two invalid files were easily correctible (details provided below). Comments from both the creators and reviewers of the test files are captured.

5.1 JOHNSON AND JOHNSON

Johnson and Johnson provided two test files:

StudySubjectData_aaaaa-1234-567.xml and

StudySubjectData_PN-C0XYZT00-1234-567.xml

The first file is valid against the CDA schema. The second file failed to validate because of a null value in the <EthnicGroupCode> element. Entering a valid value (e.g. Not Hispanic or Latino) easily corrected the validation error.

Tester Comment [1.1]

In order to use the xform in our Windows7 environment, I had to change the security setting on the IE browser. This was very problematic and a security risk. Another tester was able to install and create a narrative with xform in an XP environment without any issue.

Action Item: [xForm] Future xForm version should not impose the need to lower browser security settings.

Tester Comment [1.2]

Effort was made to transfer information from existing patient narrative format to the xform. A number of data elements (eg., document identifier, Medra codes,

investigator name, reporter name, etc. are typically not contained in the narratives that are generated by the system.

FDA Note: We recognize that moving to a more structured format for patient narrative information results in the inclusion of additional information not typically captured in paper or PDF, but feel the additional information adds value to either or both data management and review processes.

Action Item: None

Tester Comment [1.3]

I attempted to include data from tabular component of our typical report. Tabular information (e.g., conmeds, etc) was not handled well in xform narrative box and was not included in the final file.

Action Item: [I.G., xForm] Add the instructions (I.G.) and ability (xForm) to incorporate tabular and other formatted information in the narrative block.

Tester Comment [1.4]

While it was relatively easy to generate an individual report manually with the xform, I do not think that this is a sustainable approach going forward. The preferred approach would be to allow for these narratives to be generated programmatically, using controlled terminology and fields, without needing to access the xform for document set identifiers and/or drop down lists. A preferred approach would be to have a stable XML schema that we can upload standard narrative formatted XML to.

FDA Note: We agree.

Action Item: [General] Acknowledge that xForm is not a viable solution for a production environment. Process efficiencies will be gained if xml documents can be generated programmatically from internal systems.

Tester Comment [1.5]

Role of authenticator needs additional discussion from both process and technical level.

FDA Note: We agree and has been the subject of discussion within Stage II and elsewhere. We think the most practical approach is not to have an authenticator, since the patient narrative is part of a regulatory submission, and an authenticator for the patient narrative itself is not needed.

Action Item: [I.G.] Remove the use of legal authenticator from the I.G.

[xForm] Combine Sponsor and Legal Authenticator into one field called Sponsor, which is stored in the xml as the custodian.

Tester Comment [1.6]

Document Title can be anything descriptive, but the xForm defaults to “Patient Narrative Report.” Is this reasonable? Tester response: Yes.

Action Item: None

Tester Comment [1.7]

Document Identifier: Note that this is required and is tester/sponsor-defined. The document ID changes if the content changes (e.g. a new version would have a new document ID. Should the xForm support the generation of a global unique identifier (GUID) instead? (similar to SPL)

Tester Response: Typically patient narratives are identified solely by the subject id. May need to consider additional naming conventions. Would prefer that the identifier be generated within our system versus having the identifier generated within the XForm. This would require less configuration.

Action Item: [I.G. and xForm] The document ID can be system-generated (e.g. GUID) or user-provided rather than provided by the xForm user. The xForm should have the option to generate a GUID or the user can enter their own ID.

Tester Comment [1.8]

Document Set Identifier: Note that the xForm provides the option to generate a global unique identifier (GUID). The Set ID remains constant across multiple versions.

Tester Response: This feature will be problematic for the volume of narratives that are generated programmatically. Using xforms to generate the document set identifier will require reconfiguration of system used to generate narratives in order to access the xform to generate the document set identifier. A preferred approach would be to have document set identifier created programmatically by the creator without needing to access the xforms?

FDA Note: We agree. This is related to comment 1.4 recognizing that efficiencies are greatest when the xml and the identifiers are generated programmatically.

Action Item: See 1.4

Tester Comment [1.9]

Confidentiality Code: Is this useful? Should be retained or assigned a default value? What values are useful?

Tester Response: Not clear as to the value of the code for reporting patient narratives. However, this would not be an issue if the system assigns a default value versus having the value set by the xforms

FDA Note: We agree confidentially code doesn't seem useful in the context of a submission. Confidentially of the entire application is the same and need not be reported in a patient narrative document.

Action Item: [I.G. and xForm] Remove the implementation of Confidentiality code. If required by the schema, assign a default value of "Normal" in the I.G. for all narratives.

Tester Comment [1.10]

The inclusion of Medra (sic) code and term are typically not included in patient narratives. However, this information is available in the reporting dataset and could be added.

FDA Note: This information is useful to clearly identify the AE that resulted in the narrative. Ideally the patient narrative could reference the AE information in the dataset and not repeat the information. This is currently not possible so acknowledge this is an interim "work around."

Action Item: None

Tester Comment [1.11]

It is not always the case that a single adverse event will trigger the need for a patient narrative. Either we need to provide a means of identifying multiple events that trigger a narrative or have a very explicit guidance in an implementation guide to help determine what event will be reported.

FDA Note: We agree. We think developing rules to determine which single AE event to report is problematic. We prefer your first suggestion.

Action Item: [I.G. and xForm] Allow reporting multiple AEs as the reason for the narrative

Tester Comment [1.12]

Reason for Narrative: What reason codes would you like to see in the drop-box?
Tester Response: The list should be limited to adverse event, death and other for patient narratives. We may want to consider subcategories for adverse events, Serious adverse event, Adverse event leading to discontinuation, Adverse event "of interest" It would be preferred if the reason codes be generated by the system that programmatically creates the patient narrative rather than selecting a value from a drop down list.

FDA Note: We agree, although we think Adverse Event of Interest can simply be reported as an adverse event. We have seen sponsors use the term "Adverse Dropout" for a discontinuation due to an adverse event. We also agree with the last comment regarding generating the reason codes programmatically, and is related to comment 1.4.

Action Item: [Vocabulary] Limit "Reason for Narrative" value set to Adverse Event, Death, and Other. Consider also Serious Adverse Event and Adverse Dropout (definition: discontinuation due to an adverse event). See also 1.4.

Tester Comment [1.13]

Please comments on the various roles in this tab (Participants). Note that CDA requires the document have at a minimum an author and a custodian (i.e. sponsor). Also note that FDA needs to identify the investigator and the sponsor.
Tester Response: For the test, the names entered for author, legal authenticator, investigator were set to be the same. The name of the reporter is

typically not included patient narratives prepared for clinical study reports. This information would need to be accessed from safety reporting system. While the information is provided by the investigator or staff at the investigational site, designating an authenticator who "signs" each individual patient narrative, as a distinct document, may be problematic from both a process and technical level. Investigators are responsible for the review and approval of CRF information.

FDA Note: Given that CDA requires an author and a custodian and FDA needs to know the investigator and the sponsor, the most pragmatic solution is to store the investigator in the author element and the sponsor in the custodian element, even though the investigator may not in reality be playing the author role. This should be explained as such in the I.G. and the labels in the xForm should simply say Investigator and Sponsor. The legal authenticator role is not needed.

Action Item: [I.G. and xForm] Store the investigator name in the Author field and the Sponsor in the custodian field. Provide explanation in the I.G. why it is being done this way. Provide labels in the xForm for Investigator and Sponsor only. See also 1.5

Tester Comment [1.14]

Did not include organization id; legal authenticator id; sponsor id . Are these ids intended to be DUNS numbers?

FDA Note: For organizations and businesses, yes. However they should be optional for this use case.

Action Item: [I.G. and xForm] State that the IDs in the participants tab for organizations and businesses are DUNS numbers, but they are optional.

Tester Comment [1.15]

The printed form shows the author as a "study nurse". This should not be assumed. Just identify the reporter.

FDA Note: We agree.

Action Item: [xForm] Fix printing so only the investigator and sponsor are shown. See also 1.13.

5.2 SANOFI

Sanofi provided three test files:
StudySubjectData_001234-126201004-1.xml
StudySubjectData_005678-124501002-1.xml
StudySubjectData_009989-123001002-1.xml

All three files are valid.

Tester Comment [2.1]

Study Identifier: The IG indicates that ID (within the serviceEvent) has both a root and extension that are required. The XForm masks the creation of these two components of the study identifier.

FDA Note: The I.G. page 23 states that the id shall contain the root OID 2.16.840.1.113883.4.548.2 and the extension is the SDTM Study ID. Therefore the xForm need only collect one field, the Study ID.

Action Item: None

Tester Comment [2.2]

Document Title can be anything descriptive, but the xForm defaults to “Patient Narrative Report.” Is this reasonable? Yes

Action Item: None

Tester Comment [2.3]

Document Identifier: Note that this is required and is tester/sponsor-defined. The document ID changes if the content changes (e.g. a new version would have a new document ID. Should the xForm support the generation of a global unique identifier (GUID) instead? (similar to SPL) Response: Would there be a check to prevent the same number from being repeated by mistake? Our systems generate a unique “form ID number”. Is the use of a GUID required? See ID comments at the end of this form.

FDA Note: We see the possibility of creating a business rule that checks that the set ID + document ID combination is unique within the system. The use of a GUID would not be required

Action Item: [I.G.] see 1.7

Tester Comment [2.4]

Document Set Identifier: Note that the xForm provides the option to generate a global unique identifier (GUID). The Set ID remains constant across multiple versions. This is not marked as “required”, yet what happens if you don’t use it and then need to send a new version? It seems that it would be wise to generate this ID from the start even though it isn’t required.

FDA: We agree the SetID should be required.

Action Item: [I.G.] Make sure SetID is required and is a GUID.

Tester Comment [2.5]

Similarly, version number would need to be maintained for the same reason (see 2.4)

FDA Note: We agree.

Action Item: [I.G.] Make sure version number is required.

Tester Comment [2.6]

The IG indicates that the setID and versionNumber “SHALL” be present (suggesting that they are required) however the XForm does not indicate that they are required fields.

FDA Note: We agree this is a problem and will be corrected in a future xForm version

Action Item: [xForm] Make sure SetID and Version numbers are required for data entry.

Tester Comment [2.7]

Confidentiality Code: Is this useful? Should be retained or assigned a default value? What values are useful? Not really sure why some information would be more confidential than other information, this is not my expertise. It is not clear to industry how this value should be used. Note that section 3.1.8 of the IG indicates that this is a required field (per CDA) however the XForm does not indicate that it is required.

Action Item: [I.G.] See 1.9.

Tester Comment [2.8]

Subject Identifier: 1. The IG (section 3.2.1) indicates that ID (within the patientRole) is required. This element has both a root and extension that are assumed to be required. The XForm masks the creation of these two components of the subject identifier.

FDA Note: The rootID is a fixed OID, so the xForm need not collect it. See also 2.1. However, the USUBJID should be associated with the entity, not the patient role.

Action Item: [I.G.] The SDTM USUBJID should be associated with the ID of the Patient entity class (the subject enrolled in the trial). The SDTM SUBJID should be the ID of the patientRole class. The SUBJID is not required for this implementation.

Tester Comment [2.9]

Subject Identifier: It is assumed that the GenderCode, RaceCode and ethnicGroupCodes are all consistent with the coding used within CDISC SDTM data structures. If they are not then they should be aligned although the question would come up regarding why this information should be provided in two different ways.

FDA Note: We agree GenderCode, RaceCode, and ethnicGroupCodes should be the same between CDA and SDTM. The xForm uses the codes from NCI EVS, where CDISC codes reside.

Action Item: none

Tester Comment [2.10]

There should be clarity regarding how to collect age values to ensure consistency with similar information collected within the CDISC SDTM structures (or there should be clarity regarding the potential differences between them – e.g., is the age associated with the narrative the age at the time of the event).

FDA Note: Since the patient narrative is a stand-alone document, the reported AGE should be age of the patient at the time the triggering event for the narrative occurred, which may differ from the AGE reported in the SDTM data.

Action Item: [I.G.] Clarify that the AGE is the age of the patient at the time the reason for the narrative occurred, which may differ from the AGE reported in the SDTM data.

Tester Comment [2.11]

It may be noted that there is no mention of potential validation rule or expectation that the value in Actual Arm should be equal to the Actual Arm for the same patient in the CDISC SDTM data set. Is this expected?

FDA Note: Yes, the Actual Arm should match the Actual Arm in the SDTM datasets.

Action Item: [I.G.] Clarify that the Actual Arm is the SDTM Actual Arm (ACTARM) described in Version 1.3

Tester Comment [2.12]

There may be multiple values associated with “Reason for Narrative” (although only 1 primary reason). Sponsors are at times asked by reviewers to associate secondary or alternative reasons for narratives.

FDA Note: We agree.

Action Item: [I.G. and xForm] Allow multiple reasons for a narrative.

Tester Comment [2.13]

For test files, we entered the same individual for both author and investigator.

Action Item: see 1.13

Tester Comment [2.14]

assignedAuthor: a. The XForm hides the management of the root attribute while exposing the extension attribute of the ID element. Are both required? The XForm generates a root value. Also, 2. assignedAuthor: b. Section 3.2.2 of the IG leaves flexibility with regard to exactly who it is that the sponsor may choose to place in this element. Should there be an attribute that indicates the role of the individual represented in this element?

FDA Note: The I.G. uses an OID for the root value and the optional user-defined extension. See also 1.13.

Action Item: [I.G. and xForm] The assigned author should be the investigator and the id extension should be the sponsor-assigned investigator ID (SDTM INVID). See also 1.13.

Tester Comment [2.15]

assignedAuthor representedOrganization b. The xml text shown in Figure 12 of the IG in section 3.2.2 shows a representedOrganization however the text of this section provides no direction about it. Additionally, the XForm comments associated with the ID element indicate that this is the site ID. Depending on the role/person selected it may or may not make sense to place the site ID in this position. Further instruction may be needed regarding the values required here and expected consistency of values in both the root and extension attribute. See comments at the end of this form.

FDA Note: We agree. See 1.13. With this approach, it makes sense to store SiteID information in representedOrganization.

Action Item: [I.G.] See 1.13

Tester Comment [2.16]

representedCustodianOrganization: The XForm hides the management of the root attribute while exposing the extension attribute of the ID element. Are both required? The XForm generates a root value.
representedCustodianOrganization: Further instruction may be needed regarding the values required here and expected consistency of values in both the root and extension attribute.
legalAuthenticator: The XForm hides the management of the root attribute while exposing the extension attribute of the ID element. Are both required? The XForm generates a root value.
FDA Note: The intent is to use standard OIDs for the root, and the user of the xForm enters the value for the extension. For this reason, the xForm intentionally does not expose the management of the root attribute to the user.
Action Item: None

Tester Comment [2.17]

legalAuthenticator: Does CDA or the FDA require the Legal Authenticator if the narratives are not “signed” (see first paragraph of IG section 3.2.4)?

FDA Note: We do not require a legal authenticator.

Action Item: [I.G.] Remove legalAuthenticator information

Tester Comment [2.18]

Our current narratives typical contain tabular data. It would be helpful if the agency clarified the need for tabular data representations in narratives.

FDA Note: We agree that providing instructions for tabular data and other formatted data would be helpful.

Action Item: [I.G.] provide instructions for providing tabular data and other formatted data in the narrative text block.

Tester Comment [2.19]

The report tab does not display the Investigator even though one was added.

Action Item: [xForm] Display the Investigator information in the report tab.

Tester Comment [2.20]

The Narrative Summary / Clinical Trial Experience Section on the Report Tab does not maintain formatting (line breaks, spacing) even though the formatting is captured in the XML file.

Action Item: [xForm] Maintain formatting in the report tab when formatting information is contained in the xml.

Tester Comments [2.21]

Would it make sense to add specific data entry fields/tabs for other required information such as: relationship (between event and IMP), intensity of event, timing of event relative to IMP administration, action taken with IMP (stopped), relevant labs, relevant countermeasures (concomitant medications), relevant medical history, investigator and sponsor opinion of causality, outcome, seriousness of event (SAE), AE leading to treatment discontinuation, preferred term, hospitalization, unblinding for RA/PV purposes, etc.

FDA Note: We agree this additional structured information is desirable but we are concerned that it would complicate the initial implementation.

Action Item: [I.G.] Defer additional structured data entry fields for a future release.

Tester Comment [2.22]

Generally would like to better understand expectations of the IDs throughout the narrative report, in life cycle events and beyond. Specifically would like to understand how their generation may be constrained and the degree to which a sponsor would have to actively manage/coordinate or track each ID. Consider these examples: 1. Document ID (required) a. Will this be required to reference a specific narrative report in the future? It seems that it may be too early to be able to know how an ID like this may be used “down stream”.

1. Document ID (required) b. The IG notes in section 3.1.3.1 that, “It is expected that the CDA rules for guaranteeing identifier uniqueness – the consistent use of object identifiers (OIDs) will be followed.” This may be a constraint that sponsors are not familiar with managing. 1. Document ID (required) c. Note that the XForm hides the potential complexity of managing both the root and extension attributes of the ID element.

2. Document Set ID a. Per note in “Document Tab” section, this may effectively be required so that a relationship can be maintained between versions that are not anticipated. Additionally the IG (section 3.1.10) indicates it is required.

2. Document Set ID b. Sponsors will have to understand and manage the constraints for both the root and extension attributes.

3. VersionNumber a. Similar to Set ID above, the version number would need to be managed within the SetID and Document ID framework.

4. Study ID (ID within serviceEvent) a. Sponsors will have to understand and manage the constraints for both the root and extension attributes.

4. Study ID (ID within serviceEvent) b. It is assumed that any submission of narratives for a specific study would need to have consistency between these root and extension attributes.

4. Study ID (ID within serviceEvent) c. Is there an expectation that there would be consistency between the extension study ID and the value of study ID within CDISC data sets?

5. Subject ID a. Sponsors will have to understand and manage the constraints for both the root and extension attributes for subject ID.

5. Subject ID b. It is assumed that any submission of narratives for a specific subject would need to have consistency between these root and extension attributes.

FDA Note: In general it is too early to tell how the various IDs will be used for information management downstream. Because each narrative report will be associated with an application, we don’t think there is a need for truly globally unique identifiers in most cases.

Action Item: [General] During piloting and early implementation, more specific information about managing identifiers will be needed.

[xForm and I.G.]: Make it clear that the Study ID is the SDTM STUDYID.

5.3 CDER OFFICE OF NEW DRUGS

The Office of New Drugs provided 12 test files.
StudySubjectData_DSXS 0914-053.xml
StudySubjectData_DSXS 0914-075.xml
StudySubjectData_MBL 0502 US-4407.xml
StudySubjectData_MBL 0502 US-4502.xml
StudySubjectData_MBL 0502 US-4503.xml
StudySubjectData_ZLB03_03CR-2002.xml
StudySubjectData_ZLB03_03CR-11004.xml
StudySubjectData_ZLB03_03CR-12003.xml
StudySubjectData_ZLB03_03CR-13001.xml
StudySubjectData_ZLB03_03CR-18005.xml
StudySubjectData_ZLB03_03CR-18009.xml
StudySubjectData_ZLB03_03CR-20004.xml

Eleven of the 12 files were valid. The file StudySubjectData_ZLB03_03CR-2002.xml is not valid, because the reason for the narrative was an adverse event yet no adverse event or code was provided. Entering an adverse event and code in the xForm resulted in a valid file.

Tester Comment [3.1]
Tester General Comment #1. No issues in creating, editing, viewing or saving test files while open.
Tester General Comment #2. Upon closing, the saved files are in xml, and cannot be opened directly except by using the “open” button in the XForm. At first I did not do this and could not correct errors in the original file, resulting in the creation of a new test file for error correction. This issue is resolved now.
Tester General Comment #3. Although it should be possible to print an adobe file from the xml file (as stated in the Report tab), viewing the saved files in xml is problematic, as they cannot be opened due to style sheet problem; attempts at opening meet with error message as follows:

- Cannot view XML input using XSL style sheet. Please correct the error and then click the Refresh button, or try again later, and
- Access is denied. Error processing resource 'file:///c:/xforms/xsl/fda_cda.xsl'

It is also noted that although the Report tab states that the User Guide is to be referred to for more information on displaying the style sheets, I have not been able to find such information.
FDA Note: We agree that opening the xml file should automatically render the content using the referenced style sheet.
Action Item: [General] In an operational environment, ensure that opening (i.e. double-clicking) the xml file automatically renders the content in the browser using the referenced style sheet.

Tester Comment [3.2]
Tester Comment on Document Tab. For study identifier, I use the study number provided in the clinical study report. Is it necessary to look up clinicatrials.gov? Older studies may not be in the system.
Action Item: See 2.22

Tester Comment [3.3]
Evalution Question: Document Identifier: Note that this is required and is tester/sponsor-defined. The document ID changes if the content changes (e.g. a new version would have a new document ID. Should the xForm support the generation of a global unique identifier (GUID) instead? (similar to SPL). Tester Response: Fine but not essential. The question is whether there is any advantage to having the GUID. Any GUID must facilitate searches across databases, e.g., same subject with sequential AEs, etc. Random generation of a number does not seem to be helpful.
Action Item: See 1.7.

Tester Comment [3.4]
Evaluation Question. Document Set Identifier: Note that the xForm provides the option to generate a global unique identifier (GUID). The Set ID remains constant across multiple versions. Tester Response #1. This question appears to suggest the GUID is the same as the Set ID. However, this tab says at the outset: “A replacement document gets a new globally unique StructuredDocument.id value, and uses the same value for StructuredDocument.setId as the parent document being replaced, and increments the value of StructuredDocument.versionNumber by 1.” Please clarify the intent of this question.
FDA Note: The question was intended to determine what is the best strategy for generating SetID and the Document ID as the document evolves in its natural lifecycle.
Action Item: See 1.7

Tester Comment [3.5]
Tester Response #2 to Evaluation Question in 3.4. Neither the Document ID nor the Set ID is shown in the Report tab or the report printout. If they are viewed as being important, shouldn’t these IDs be shown?
FDA Note: Typical patient narratives that are currently received don’t display this information, but it could be displayed if users find it useful.
Action Item: [xForm] Consider displaying setID and document ID in the Report tab.

Tester Comment [3.6]
Tester Reponse #3 to Evaluation Question in 3.4. The change in the “Version” number is not automatic, and a replacement document needs to be saved under another file name or else the original document will be erased.
Action Item: [xForm] Provide save feature so that new versions trigger a new filename.

Tester Comment [3.7]
Evaluation Question. Confidentiality Code: Is this useful? Should be retained or assigned a default value? What values are useful? Tester Response. I have not found this useful and have maintained “normal” in all documents. If this is to be of any use, the User Guide should instruct what circumstances are for using “restricted” or “very restricted”.
Action Item: see 1.9

Tester Comment [3.8]
Tester Comment #1 on the Subject Tab. In User Guide Section 5.3, there is a “Site Identifier” field in this tab which is not currently seen. I have not put the site information into the subject identifier field. Is this acceptable?
FDA Note: Site information is not a currently identified requirement for a narrative.

Action Item: [xForm] Remove reference to site identifier information in the User Guide.

Tester Comment [3.9]
Tester Comment #2 on Subject Tab. “Gender” in this tab shows up as “Sex” in the Report tab. These are different concepts. What exactly is being requested?
FDA Note: The requested information is Sex.
Action Item: [xForm] Change “Gender” label to “Sex.”

Tester Comment [3.10]
Tester Comment #3 on Subject Tab. Birth Time is really for birth date, as the field is for yyyymmdd. Actual time of birth may be more critical for studies on neonates.
Action Item: [xForm] Change “Birth Time” label to “Birth Date.”

Tester Comment [3.11]
Tester Comment #4 on Subject Tab. I was unable to get hold of the birth dates for study [xx] subjects. In the other studies, although this parameter is not in the tabulations, I could find the information in the CRFs.
FDA Note: Birth date information is optional.
Action Item: None

Tester Comment [3.12]
Tester Comment #5 on Subject Tab. For ethnic group, study [xx] does not have the information and so I select “not reported”, assuming that “unknown” is for cases where the CRF actually reports on not knowing the ethnicity.
FDA Note: This seems reasonable.
Action Item: None

Tester Comment [3.13]

Tester Comment #1 on subject Narrative Tab. Out of the three studies from which I used subject narratives, two do not provide MedDRA code information and I put in NA for the AE code cells. In the one where coding is available, I used the LLT codes and terms, although other codes were also provided in the datasets.

FDA Note: For testing purposes, this is acceptable. In a production environment, a validation error will result if the MedDRA code is missing.

Action Item: None.

Tester Comment [3.14]

Tester Comment #2 on Subject Narrative Tab. There are cases in which withdrawal of treatment may be due to multiple AEs. Since the new cells opened up after clicking “adverse event” allow only one code and one code description, one has to choose the most significant AE to record and leave others, which

potentially may be equally important AEs, unrecorded. In such a case (MBL 0502 US-4503) I listed all the relevant AEs in the code description cell.

Action Item: See 1.11.

Tester Comment [3.15]

The cell for summary narrative, as with other cells in the XForm, does not allow for the use of superscripts such as 10 to the power 6, which appears as 106. On the other hand, it does allow for special characters that I have tried, such as é, Î, ô, ®, ★ and ↓. Bulleting can be pasted on the XForm, but does not preserve the overhang margin formatting from the original, i.e., margin spacing obliterated after the first line. Moreover, the bullets do not appear properly in the printout (printout (a) not showing new line for each bullet, presumably because line breaks are not allowed, and (b) the tab spacing between bullet and text becoming only one space between them). Tables cannot be created in or pasted into the Summary Narrative cell.

Action Item: See 2.18.

Tester Comment [3.16]

Evalution Question. Reason for Narrative: What reason codes would you like to see in the drop-box? Tester Response #1. The drop-box contains many codes but the most useful is actually “adverse event”. Most narratives in clinical study reports are written for adverse events. I made one file for “lack of efficacy”, but in the studies I looked at for this evaluation, either the other items in the drop-box do not apply, or if they do, there were no narratives in the clinical study reports. I did not make attempts to create new ones not present originally in the clinical study reports. That would require extracting data from multiple datasets for each subject and unless I have a program to do that, it would be very time consuming. Of course alternatively, the narrative can be derived from information in the CRF; this still would be time consuming as one has to go through multiple pages to sort out the data. Tester Reponse #2. It is not clear whether “completed”, “recovery”, etc are of any use.

FDA Note: We acknowledge the value set for “Reason for Narrative” should be smaller.

Action Item: See 1.12.

Tester Comment [3.17]

Tester Response #3 to Question in 3.16. A subject’s narrative may fit multiple categories in the drop-box. Is there a hierarchy for choosing the items in the list? If not, should multiple XForms be created in choosing different categories for the same subject? If yes, how can one capture the information that there are multiple reasons for having the narrative of that subject, and what those reasons are?

Action Item: See 2.12

Tester Comment [3.18]

Tester Response #4 to Question in 3.16. “Adverse event” can be made more granular. AE alone does not merit making a narrative. There are important categories that are often associated with creation of narratives: serious AE, AE leading to withdrawal, special AEs being monitored for certain product classes (e.g., local application site reactions for topical agents), etc. Some of the files I created were for withdrawals due to AEs, but I had to simply use AE as the reason. Also, there is a “lack of efficacy” file in which the lack of efficacy manifests as signs and symptoms of disease worsening. By using “lack of efficacy”, these AEs are only seen in the Summary Narrative cell, and may not be captured under “reason”.

Action Item: See 1.12.

Tester Comment [3.19]

Tester Response #5 to Question in 3.16. The use of different MedDRA codes for the same condition may be misleading. For instance, there are different codes for “anaemia” and “anemia” in the files I created. This has even occurred with “anaemia” under PT and “anemia” under LLT. For all purpose in the XForm, I use the LLT name. Tester Response #6 to Question in 3.16. Also, the coding depends on how granular the case report tabulation (CRT) has provided the information. Some of the CRTs from which I got the data use anaemia or anemia for coding, whereas other AEs associated with the anaemia/anemia suggest hemolytic anaemia/anemia which would require different codes. In another instance, the AE description is “vascular dizziness” whereas the coding description under PT and LLT were “dizziness”.

FDA Note: The intended code should be the MedDRA PT

Action Item: [I.G. and xForm] Clarify that the AE code should be the MedDRA PT code.

Tester Comment [3.20]

Tester Response to #7 to Question in 3.16. The use of older versions of AE codes in older studies vs newer versions in more recent studies can also cause problems.

Action Item: [I.G.] Provide instructions for capturing the version of the dictionary that was used to code the AE.

Tester Comment [3.21]

Tester Comment on “Planned Arm” Removal. Regardless of the above, this tab with request for “arm” information is fitting for uncontrolled or parallel group controlled studies, and unsuitable for studies comparing subject anatomic locations (bilateral application of topical products) or time periods (cross-over).

FDA Note: We recognize this limitation. At the present time, the work-around is to describe in the narrative text the actual relationship between the adverse event and the exposure.

Action Item: [General] Consider for a future release a more structured approach to capture the relationship between the exposure and the adverse event.

Tester Comment [3.22]

Tester Comment #1 on the Participants Tab. The ID numbers of author, sponsor, and legal authenticator are obscure in the studies I used. I used the author of the clinical study report as the author if this information was available, and put in NA when not. In one case, the author and legal authenticator happen to be the same person. Tester Comment #2 on the Participants Tab. In another case, the date of the clinical study report completion, which I took as the date for the author, was after the date for the authenticator signing for the clinical study. Since the User Manual does not explain what “Time” means for those cells under author or legal authenticator, this item is up to interpretation. In most cases, I believe the author of the narrative (said to be the study nurse coordinator in the “Report” tab) is unknown, and so is the time of write-up. It is entirely possible for the legal authenticator to have authenticated the narrative prior to signing for the study report. However, there is lack of clarity as to what “Time” is being requested, and the accuracy of such “Times”.

FDA Note: See 1.13, 1.14, and 2.17. We agree “Time” is not needed.

Action Item: See 1.13,1.14 and 2.17. [I.G.] Remove the need to report time from author and custodian elements.

Tester Comment [3.23]

Tester Comment #1 on the Report Tab. It would be nice to allow for the special features, but not essential. I have not seen the use of tabular data or figures in most narratives in clinical study reports. On the other hand, superscripts and subscripts are essential for presenting certain lab data.

FDA Note: We agree.

Action Item: See 2.18.

Tester Comment [3.24]

Tester Comment #2 on the Report Tab. The distortion of bulleting in the Subject Narrative cell and the removal of line breaks in the printout should be remedied.

Action Item: [xForm] Correct the distortion of the bulleting in the Subject Narrative cell and the removal of line breaks in the printout.

Tester Comment [3.25]

Tester Comment #3 on the Report Tab. There is a potential bug in using the “Print Report” button in the Report tab. For several times, when I tried to print,

this appears: “The instructions at (a set of numbers and letters) referred memory at (another set of numbers and letters). The memory could not be “read”. Click OK to terminate the program. Click on Cancel to debug the program.” This message is followed by the buttons OK and Cancel. Clicking either one crashes the program and the XForm disappears. I had to create the XForm again several times due to this problem.

Action Item: [xForm] Fix the Print Report feature in the Report tab.

Tester Comment [3.26]

Tester Comment #4 on the Report Tab. The report tab and printout show the authenticator as signatory of the XForm and “investigator”. This is not correct. The investigator information in the “Participants” tab is not made use of.

FDA Note: The only information we intend to display on a future revision to the report is the investigator name and the sponsor name.

Action Item: [xForm] Fix the report so that it only shows the Investigator name and the Sponsor name. The signatory feature should be removed.

Tester Comment [3.27]

Tester Additional Comment #1. In the User Guide, Section 3.3, it is stated that direct import of information from messages would be recommended in preparing the XForm. I am not able to use this as I do not have a useable program for this purpose.

FDA Note: We recognize this limitation during testing. Manual data entry was the only expected method to populate the xForm.

Action Item: [xForm] Clarify the User Guide, section 3.3 to recognize that manual data entry is expected when using the xForm.

Tester Comment [3.28]

Tester Additional Comment #2. The question about how long it takes to create a test file gives variable answers. Some files are more complex than others. Searching for information and organizing as well as reconciling inconsistencies take up most of the time. Filling in the XForm itself is easy if the information is ready at hand. It also takes time to verify accuracy of the data entered. An estimate of 15 to 60 minutes for each file has been given above. In some instances, as stated earlier, the program crashed due to a bug at the print report stage, and the XForm completely disappeared.

FDA Note: We appreciate the information.

Action Item: None.

6.0 DISCUSSION

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

Goal: To create a valid Patient Narrative files for review by US FDA

Goal: To use simple testing tools (xForm, Style sheet) to create, edit, view, and save Patient Narrative Files

The testing successfully achieved these goals. Although two of the 17 test files did not validate initially, simple corrections resulted in valid files (e.g. addition of an ethnicity code in one file and addition of an adverse event in the second file). 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 version 3 can be hidden from the end user with proper tooling (in this case, open source technology – xForm).

Once installed, the xForm allowed testers to create, edit, view, and save CDA/patient narratives. 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.[2] 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 the patient narrative in a human readable format.

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

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

The patient narrative uses a small subset of structured information that has already been defined by the CDISC SDTM (e.g. StudyID, SiteID, Unique Subject ID, sex, race, ethnicity, Adverse Event). We conducted the testing using the same SDTM controlled terms available for some of these concepts. The new concept for which we needed controlled vocabulary was "Reason for Narrative." Initially, we borrowed available SDTM controlled terms for reasons for study discontinuation, as we surmised that the reasons for creating a narrative would be similar. This was a reasonable approach for testing, as it allowed us to narrow this value set further for future piloting: Adverse Event, Death, and Other. Consider also Serious Adverse Event and Adverse Dropout (definition: discontinuation due to an adverse event). Consider adding a free text field when "Other" is selected as the reason.

Goal: To identify business processes and/or technical issues that may negatively affect efforts to implement CDA R2 for Patient Narrative information

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 patient narrative information exchange, we were also interested in identifying, at a high level, potential roadblocks to piloting and implementation.

One notable 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 patient narrative information in a machine-readable format, but this will require additional infrastructure and processes to receive, validate, store, retrieve, and more importantly, integrate the information with other review tools. Currently, patient narratives arrive in PDF format. It is recognized that there is great potential for automation of data management and review processes, leading to increased efficiencies.

Goal: To provide a proof of concept of using CDA R2 for Patient Narratives 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 only three participating organizations. 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 in an operational pilot. (see Section 8, Next Steps).

Another limitation was the testing failed to adequately describe to testers the roll or planned use of the patient narratives in this new format by the Agency and how the new format will facilitate review and approval. In addition, testers would like to know how this project fits into the Agency's overall I.T. plan so that they can prioritize involvement based on perceived value.

7.0 RECOMMENDATIONS

The following summarizes the actionable items identified during testing.

7.1 GENERAL CHANGES FOR CONSIDERATION

Comment	Action
1.4	Acknowledge that xForm is not a viable solution for a production environment. Process efficiencies will be gained if xml documents can be generated programmatically from internal systems.
2.22	During piloting and early implementation, more specific information about managing identifiers will be needed.
3.1	In an operational environment, ensure that opening (i.e. double-clicking) the xml file automatically renders the content in the browser using the referenced style sheet.
3.21	Consider for a future release a more structured approach to capture the relationship between the exposure and the adverse event.

7.2 CHANGES TO THE STANDARD (RMIM)

No changes to the standard (RMIM) are needed.

7.3 CHANGES TO THE SCHEMA

No changes to the schema are needed.

7.4 CHANGES TO THE IMPLEMENTATION GUIDE

Comment	Action
1.3	Add the instructions (I.G.) and ability (xForm) to incorporate tabular and other formatted information in the narrative block.
1.5	Remove the use of legal authenticator from the I.G.
1.7	The document ID can be system-generated (e.g. GUID) or user-provided rather than provided by the xForm user.
1.9	Remove the implementation of Confidentiality code. If required by the schema, assign a default value of “Normal” in the I.G. for all narratives.
1.11	Allow reporting multiple AEs as the reason for the narrative
1.13	Store the investigator name in the Author field and the Sponsor in the custodian field. Provide explanation in the I.G. why it is being done this way.
1.14	State that the IDs in the participants tab for organizations and businesses are DUNS numbers, but they are optional.
2.4	Make sure SetID is required and is a GUID.
2.5	Make sure version number is required.
2.8	The SDTM USUBJID should be associated with the ID of the Patient entity class (the subject enrolled in the trial). The SDTM SUBJID should be the ID of the patientRole class. The SUBJID is not required for this implementation.
2.10	Clarify that the AGE is the age of the patient at the time the reason for the narrative occurred, which may differ from the AGE reported in the SDTM data.
2.11	Clarify that the Actual Arm is the SDTM Actual Arm (ACTARM) described in Version 1.3
2.12	Allow multiple reasons for a narrative.
2.14	The assigned author should be the investigator and the id extension should be the sponsor-assigned investigator ID (SDTM INVID).
2.17	Remove legalAuthenticator information
2.18	provide instructions for providing tabular data and other formatted data in the narrative text block.
2.21	Defer additional structured data entry fields for a future release.
2.22	Make it clear that the Study ID is the SDTM STUDYID.

Comment	Action
3.19	Clarify that the AE code should be the MedDRA PT code.
3.20	Provide instructions for capturing the version of the dictionary that was used to code the AE.
3.22	Remove the need to report time from author and custodian elements.

7.5 CHANGES TO VOCABULARY

Comment	Action
1.12	Limit “Reason for Narrative” value set to Adverse Event, Death, and Other. Consider also Serious Adverse Event and Adverse Dropout (definition: discontinuation due to an adverse event).

7.6 CHANGES TO THE XFORM

Comment	Action
1.1	Future xForm version should not impose the need to lower browser security settings.
1.3	Add the instructions (I.G.) and ability (xForm) to incorporate tabular and other formatted information in the narrative block.
1.5	Combine Sponsor and Legal Authenticator into one field called Sponsor, which is stored in the xml as the custodian.
1.7	The document ID can be system-generated (e.g. GUID) or user-provided rather than provided by the xForm user. The xForm should have the option to generate a GUID or the user can enter their own ID.
1.9	Remove the implementation of Confidentiality code. If required by the schema, assign a default value of “Normal” in the I.G. for all narratives.
1.11	Allow reporting multiple AEs as the reason for the narrative
1.13	Store the investigator name in the Author field and the Sponsor in the custodian field. Provide explanation in the I.G. why it is being done this way. Provide labels in the xForm for Investigator and Sponsor only.
1.14	State that the IDs in the participants tab for organizations and businesses are DUNS numbers, but they are optional.
1.15	Fix printing so only the investigator and sponsor are shown.
2.6	Make sure SetID and Version numbers are required for data entry.
2.12	Allow multiple reasons for a narrative.
2.14	The assigned author should be the investigator and the id extension should be the sponsor-assigned investigator ID (SDTM INVID).

Comment	Action
2.19	Display the Investigator information in the report tab.
2.20	Maintain formatting in the report tab when formatting information is contained in the xml.
2.22	Make it clear that the Study ID is the SDTM STUDYID.
3.5	Consider displaying setID and document ID in the Report tab.
3.6	Provide save feature so that new versions trigger a new filename.
3.8	Remove reference to site identifier information in the User Guide.
3.9	Change “Gender” label to “Sex.”
3.10	Change “Birth Time” label to “Birth Date.”
3.19	Clarify that the AE code should be the MedDRA PT code.
3.24	Correct the distortion of the bulleting in the Subject Narrative cell and the removal of line breaks in the printout.
3.25	Fix the Print Report feature in the Report tab.
3.26	Fix the report so that it only shows the Investigator name and the Sponsor name. The signatory feature should be removed.
3.27	Clarify the User Guide, section 3.3 to recognize that manual data entry is expected when using the xForm.

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
- Register new controlled terms and value set for “Reason for Narrative” with NCI Enterprise Vocabulary Services (EVS)

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. An operational pilot should explore and evaluate changes to people (e.g. training), business processes, and technology (e.g. authoring tools, review tools) for both submitters and FDA staff in integrating narrative submissions using this format into normal workflows. The pilot should also explore and resolve any potential lifecycle issues associated with patient narrative requests from reviewers.

In addition, the project team should work closely with the Agency’s PDUFA information management working group to ensure that future versions of the PDUFA I.T. plan adequately describes this project regarding both its

role in the Agency's overall I.T. strategy and also it's business value to the pre-market review and approval process.

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

Patient Narrative 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.

Patient Narrative Evaluation Sheet

Submitter: _____ **Date:** _____

Submitting Organization: _____

Email: _____ **Phone:** _____

Name of Test File: _____

How was the file created?
Programatically from internal database(s)/system(s) ☐
Manual data entry using the xForm ☐

How long did it take to create the test file? _____

Can Test File Be Shared Outside FDA: Yes ☐ **No** ☐
(e.g. with other testers)

General
Please comment on your ability to create, edit, view, save test files.
Document Tab
Comments:
Document Title can be anything descriptive, but the xForm defaults to "Patient Narrative Report." Is this reasonable?
Document Identifier: Note that this is required and is tester/sponsor-defined. The document ID changes if the content changes (e.g. a new version would have a new document ID. Should the xForm support the

generation of a global unique identifier (GUID) instead? (similar to SPL)
Document Set Identifier: Note that the xForm provides the option to generate a global unique identifier (GUID). The Set ID remains constant across multiple versions.
Confidentiality Code: Is this useful? Should be retained or assigned a default value? What values are useful?
Subject Tab
Comment:
Subject Narrative Tab
Comments:
Reason for Narrative: What reason codes would you like to see in the drop-box?
Planned Arm: Please note that ballot reconciliation in RCRIM removed Planned Arm, as this information is provided elsewhere and is not needed to evaluate the narrative summary. It has been removed from the implementation guide.

Participants Tab
Please comments on the various roles in this tab. Note that CDA requires the document have at a minimum an author and a custodian (i.e. sponsor). Also note that FDA needs to identify the investigator and the sponsor.
Report Tab
Comments: Please note that the xForm supports free text only. Please comment on the need to support other types of information in this field: e.g. tabular data, figures.
Additional Comments

Thank you for your time and effort!!