Food and Drug Administration

Phase 2 –Testing of the HL7 Study Design Structured Document Standard for Study Protocol Information

Test Report

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- Ceutical Laboratories, Inc.
- Thin Spring
- Sanofi
- Center for Drug Evaluation and Research

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1   INTRODUCTION

1.1   PURPOSE

This Study Design Test Report provides a summary of the results of testing of the HL7 Study Design Structured Document (SDSD) standard.

1.2   BACKGROUND

FDA has sponsored the development of a structured document standard describing how HL7 V3 foundation models can be used to represent study protocol information in a standardized machine-readable format for submission to FDA. The standard has passed the initial HL7 ballot as a Draft Standard for Trial Use (DSTU).

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 study design test files.

2   GOALS

The goals of the Study Design testing were:

o   To use simple testing tools (xForm, Style sheet) to create, edit, view, and save valid Study Design files for review by US FDA.
o   To identify and utilize controlled vocabularies. Vocabularies are necessary to support creation of Study Design files, requiring the use of controlled terms, and where appropriate make the necessary additions and/or modifications to these terminologies and value sets.
o   To identify business processes and/or technical issues that may negatively affect efforts to implement HL7 V3 for Study Design
o   To identify issues, and (if feasible) propose potential remedies
o   To determine whether such issues will impact the further use of HL7 V3 for Study Design, and if so to communicate these issues with the HL7 Study Design Standards team accordingly.
o   To confirm a collective (if only general) understanding of how the process and technology will function together.

3   APPROACH

The project team recruited internal testers from CDER organizational components that receive and review study protocol information. Other Centers were aware of the testing

but did not participate formally. Industry volunteers came from the HL7 Study Design project team (Stage II) within the Regulated Clinical Research Information Management (RCRIM) work group and from the structured product labeling (SPL) vendor community. The latter was selected given the similarities between SPL and the Study Design Structured Document standard (both are HL7 V3 structured documents). Because an xForm was available for testing, no technical experience with XML or HL7 V3 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 I) and an evaluation form (see Appendix II).

Tester volunteers received the HL7 V3 Study Design implementation guide, the standard HL7 V3 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   PARTICIPANTS

The following organizations participated in the testing and provided test files:
- Ceutical Laboratories, Inc.
- Thin Spring
- Sanofi
- Center for Drug Evaluation and Research

5   RESULTS

The results of each individual test file are described below. There are a total of 7 test files submitted. All were valid against the HL7 schema. Comments from both creators and reviewers of the test files are captured.

5.1   CEUTICAL LABORATORIES, INC

The tester provided a single test file: SIMPLETESTPROTOCOL.xml

Tester Comment [1.1]
I am still not 100% clear in a lot of areas pertaining to language like "Epochs, Study arms, etc." This made it tough to interpret the written design into a format that would be useable in the Xform and an accurate representation of the protocol design. It

would seem that it might be useful to include a step in the entire process of file creation wherein the information in the written document can be entered into a table and codes would be defined before they were being entered in the Xform. That table could then be used to easily create the valid XML file. Pulling codes and values (as well as other information/data) from a table would be easier than interpreting them directly from the written document and adding them to the Xform on the fly, especially for someone with little familiarity of the language used in these study designs. Another option would be using language that is more similar in the Xform and the written document so less interpretation is necessary.

Action Item: Provide help text in xForms on what Epochs, Study Arms, Elements are so it makes it easy to understand and interpret for the user.

Tester Comment [1.2]

I found it difficult to edit a previously created XML document using the software. I am certain that I am simply skipping an important step in the process; however, updating the Xform with new codes was not accomplished. I also had a difficult time when creating a new study. Early in the testing period I was able to save a number of invalid files that would generate an error report. At some point in the process I became unable to save an invalid file. After that, many times I had attempted to create a new study only to find that I was unable to save the study. At that point I would receive an error message on the screen in a white box. The message stated that the system detected an error while submitting the form "most likely caused by missing a required field or invalid field format..." It seems like I may have messed up some of the configuration or left out a step somewhere that caused this. Unfortunately, it did not highlight a field to indicate the location of the error and try as I may, I could not identify the error, fix it and save/update my test file successfully. The work around for this was simply to enter all the required code sets first disregarding whether or not it was a scientifically accurate file. The test file I provided is that file and it apparently has all the necessary code sets to be a valid XML. This is probably a user error on my part, but it seems that the time it takes to enter and define all the necessary code sets is directly dependent upon the complexity of the protocol design. In other words; the more complex the design, the more time it takes to enter and define all the code sets. Attempting to save all the code sets and then create and save a new study without all the necessary sets to make a valid XML would, in my testing, end up in a failed save attempt. It was very difficult to create a partial new study. I know that in the fast paced industry environment I work in, it is often necessary to switch tasks while in the middle of a task. For this reason, being able to save a partial study so that I can return and continue to enter the remainder of the necessary code sets at a later time is crucial. I

am certain that this capability is built into the software because I was able to perform this operation earlier in the testing period. Also, after working with Elias and Bindu I was able to save a zip file and email it to myself in order to begin working on the same design from another system. For most of the testing period, the saving of a partial/incomplete file was a complicated and frustrating matter. Increasing the user friendliness of this particular capability or more explicitly defining this process would have helped me a lot.

Action Item: Implementation of the schematron will facilitate the understanding of validation errors. Update xForm to easily allow saving incomplete/invalid files.

Tester Comment [1.3]

As I had mentioned in a previous email the validation page was difficult to decipher whenever it was generated. The validation report with the Study Design XForm would be much more useful if the line number and the code error were displayed so that I could immediately go to that particular section and fix/troubleshoot the error(s).

Action Item: Implementation of the schematron will facilitate understanding of the validation errors

Tester Comment [1.4]

I would estimate that I worked several hundred hours trying to create a scientifically accurate and technically valid XML document using my interpretation of the written document. I would continually get lost in the process and overwhelmed by how complex it quickly became and then when finally attempting to save I would receive the error that I had mentioned above. Being unable to save, I'd basically just lose my work and start over again the next time. So in those several hundred hours I was able to successfully create 1 valid XML file from scratch. But that file took only about 30 minutes to create. It is the one test file I am able to provide to you along with this evaluation. Again, this file makes almost no sense from a scientific standpoint; however, it is a valid XML file (0 errors in the XML language).

Action Item: Increase the time in which a user can save any data that has been entered thus far. It would also be useful to allow users to save incomplete files to complete the study at a later time.

Tester Comment [1.5]

Other than the general operation of the software, code sets was probably the most confusing aspect of the software. It was especially difficult to manage code sets for editing files. I attempted to edit a number of files and had a difficult time getting the newly defined code to show up in just the place I wanted it to within the Xform.

Action Item: The application should be modified to allow a new code set to be available for the user in the dropdown value list when a code set is added to the list of existing local code sets.

Tester Comment [1.6]

The eligibility criteria were difficult for me to assign and translate into a usable format for the Xform. However, once I began looking at the study file that had been distributed to the testing team and comparing the actual XML code to the written study design document I could understand why each code and value was assigned.

Action Item: Help text to be provided to enhance understanding.

Tester Comment [1.7]

I still have a difficult time identifying and interpreting the study epoch information from the written document. This is probably as a result of not being very familiar with the language used in clinical study protocol designs. However, if I were working on a team in an actual real-life design and submission to FDA, the previously mentioned form could be filled out by a team member more familiar with the language of these clinical trials and then I would easily be able to create the valid corresponding XML file using the Xform.

Action Item: Help text to be provided to enhance understanding.

Tester Comment [1.8]

The information about substance type, dosage form, dosage amount and frequency was rather easy to interpret and use. I believe that this is mostly because the majority of this information and corresponding code sets is centrally and not locally defined. Additionally I have used this type of information in other submission that I have built for drugs in XML format.

Action Item: NONE

Tester Comment [1.9]

Just as with many other areas, I had a difficult time interpreting the written document into a format that I could enter in the Xform and easily comprehend.

Action Item: Help text to be provided to enhance understanding.

Tester Comment [1.10]

The matrix certainly helps in visualizing what is happening in the study. Just the same, managing the code set and entering the information so that the matrix display is accurate is still very difficult for me.

Action Item: The xform was updated to manage code sets better. When a new Study design file is uploaded, the application allows the user to add all the code sets that are new and are not already present in the available code sets thereby eliminating the need to manually enter all the code sets before uploading a new test file. Also, the matrix display needs to be updated for ease of understanding of the study design file.

Tester Comment [1.11]

Defined code sets are easier to identify in the written document and then include in the Xform.

Action Item: NONE

Tester Comment [1.12]

I had little difficulty working with the unstructured protocol text. The only feature I was unable to find was spellcheck. I assume that the text I entered here could be checked for spelling within a separate word document and then pasted within the unstructured protocol test, but it would be easier for me if it was included in the software package. Again, it may be but I was unable to locate and use it.

Action Item: Add an additional feature for spell check.

5.2   THIN SPRING

The tester provided a single test file: ThinSpring 20130731

Tester Comment [2.1] – Installation:

- The Java installation steps didn't work. I had to manually install the 64 bit version of Java 7.

- Step 4.5 of the installation instructions, Window firewall blocked allowing access to files eXist database needed. Tried to start the eXist database and it errored. Rebooted the computer and then start the eXist database and it errored.
- Reinstalled the eXist database without first uninstalling the first try. Became stuck on step 7
- Unistalled eXist database, rebooted computer. Installed eXist database successfully.

Action Item: Installation Guide should include steps to first uninstall eXist database before re-installing.

Tester Comment [2.2] – General Navigation

- It would be helpful if the description of each Action icon could appear with a mouse over of each instead of the one help window. I had to bring that up often at first.
- It would be helpful to be able to open and view the study in a separate window as I'm working on editing the structured and or unstructured sections.

Action Item: Provide help text action icons. Further research will be done to see if a separate window can be launched to view the study in the style sheet.

Tester Comment [2.3] – Code Sets

- Had to hit back button twice to get back to Code Set list after finishing each local code set.

  Action Item: research to be done to ensure that the user does not have to hit the back button twice to get back to the code set list after finishing the editing of each local code set.

- Allows the creation of duplicate code identifiers

  Action Item: Duplicate code identifiers should not be allowed.

- When I imported the test design file none of the local code sets associated with that study loaded so it was then difficult to edit the structured data of that imported file. Difficulty getting the local code sets to match the terminology used in the imported study.

Action Item: The code was updated to manage code sets better. When a new Study design file is uploaded, the application allows the user to add all the code sets that are new and are not already present in the available code sets thereby eliminating the need to manually enter all the code sets before uploading a new test file.

- For new study it would be helpful if the codes associated with that study could be saved for possible reuse in future studies. And/or some of these could link to industry standard terms.

  Action Item: Same as above

- When starting a new study, I could not clear or reset all of the local code sets. Each had to have at least one code left over from the previous study that I had to overwrite with an edit to make applicable to the new study.

  Action Item: Same as above

- Importing a study and then trying to edit the structured data leads to unexpected/confusing screen options. See example below after importing test study file. If I tried to change the epoch sequence and add epochs after adding them to the local epoch code sets, it would not let me save the changes but just displays a general error message.

  Action Item: No action item needed as changes were made to have the capability for the application to read through a new study and give the user an option to add any code sets that are not already present in the local code sets. Should the user decide to not add the code sets to the local code sets, the application has the capability to store the code sets pertaining to the study in local tables that are specific to the study and will not hinder the display of the study either in the application or in the style sheet.

Tester Comments [2.4] – Editing Structured Content

- It would be helpful to be able to store local lookup tables for Sponsor Ids, investigators, etc.

  Action Item: The application can have the ability to store local lookup tables for sponsor IDs, investigators.

- It would be helpful to be able to save a study file after just entering the basic structured content header information and then come back and finish the study design specifics.

  Action Item: The application should have the capability to allow a user to save a study file even after just entering the basic information.

- The version field, the xml file version only allow a numeric value. It would be helpful to be able to enter other user version numbers in different formats and associate them with the xml file version. For example a user study version format "VIII (j)" which uses Roman numberals for the main version and a lower case letter for a version suffix in parenthesis.

  Action Item: Rules should be defined for the version number.

- Lead investigater information – should be able to add a middle initial and name suffix.

  Action Item: The application should be modified to include the middle initial and name suffix for the lead investigator,

- It would be helpful to be able to create and save unstructured content before I am done with the structured content.

  Action Item: The application should have the capability to allow a user to save a study file even after just entering the basic information.

- Where look up codes exist in optional data entry fields, eg. Route of Administration, it would be helpful to type the first letter of the code and go directly to that section of the look up list.

  Action Item: This is a feature of the browser and it currently works as stated. When the drop-down menu appears, typing the first a letter jumps to the first entry with that letter

- It would be helpful to see what is in each study cell without having to click on "edit cell" before I try to edit the cell. User guide could do a better job of explaining the logic behind how cells are related to epochs, elements and a visits.

Action Item: User guide should be updated to include explanation of the various terms such as epochs, arms, elements, visits etc to better help the industry in understanding the relationships between each of the terms.

- When saving the structured content, even with all red asterisked fields completed, it is still possible to get validation errors. The error message is general and not specific enough to tell the user what they did wrong and how to fix it. Trial and error is required to fix study design issues before it will save.

   Action Item: Implementation of the schematron will help in understanding the error as the error message would be more specific and easy to understand.

5.3   SANOFI

The tester provided two test files: Sanofi-sample1-FDAStudyDesignPilot201307.xml Sanofi-sample2-FDAStudyDesignPilot-201307.xml

Tester Comment [3.0]
We were able to install the xForm successfully. We were also able to successfully update an existing installation. The instructions for uploading an external XML file were also helpful.
We had one instance (a quick try) where we were unsuccessful in the installation of the xForm.
Action Item: NONE

Tester Comment [3.1]
We had some issues in creating valid Study Design files with the original version of the xForm. We documented the issues and provided them to the FDA. Once the updated xForms were installed, we had no issues creating valid Study Design files.

Action Item: NONE

Tester Comment [3.2]
We were able to Edit/View/Save Study Design files. However, the latest version of the xForm does a check of the required fields before saving the XML. If a required field is missing, a message is displayed but the XML file is not saved. This requires the user to fill out each section of the xForm before anything can be saved. We would prefer that an XML file be generated even when the required field message is displayed.

Action Item: The application should have the capability to allow a user to save a study file even after just entering the basic information.

Tester Comment [3.3]
We had no issue with the validation of the XML output generated.

Action Item: None

Tester Comment [3.4]
Significant time was required (i.e., days) to identify content and map it. Also, code sets had to be created, etc. Data entry was in the range of 3-5 hours per protocol (entry of multiple rules across visits took a large chunk of time).

Action Item: None

Tester Comment [3.5]
We often wound up providing the same value for the "Value" and "Description" fields in the code sets.
"Unit of Measure" Central code set needs to be expanded. For instance we needed to have 'µg' included.

Ensure alignment with CDISC controlled terminology

Action Item: Add 'µg' to Unit of Measure which is a central code set. Code Sets should be aligned with CDISC controlled terminology

Tester Comment [3.6] – Substance Administration
One study involved Dose Titration. The xForms tips guide stated "Please ignore titration information, if there is a titration phase", so we only entered the last dosing values.
A second study had a dose-adjustment element where the dose and frequency could be changed during the study. We entered the substance name and the route of administration but did not provide values for dose or frequency. Should we have entered multiple doses/frequencies for the substance?
What is the correct way to handle these two situations?
"Unit of Measure" Central code set needs to be expanded. For instance we needed to have 'µg' included.

Action Item: Any additional information beyond the drug name (dose, frequency, route of administration, should be considered optional. These fields can be used only if they make sense to do so. Otherwise, detailed dosing information should be provided as unstructured text in the appropriate section.

Tester Comment [3.7]
What is the difference between Element End Rules in the Study Elements section and the Element End Rules in the Study Cells - Element to Epoch/Arm Assignment section?

Section 5.1.7 of the User Guide reads "A study element may be assigned an expected duration." However, the xForm requires a duration.

Action Item: The user guide should be updated to include the definitions and relationships of epochs, arms, visits etc for ease of understanding.

Tester Comment [3.8]
The Study Cells – Element to Epoch/Arm Assignment screen was tedious. If there are 30 visits that need to be assigned to the treatment epoch in two different arms, it can be quite time consuming. Having a multi-select capability so that a user could select multiple visits to assign to an element at one time would be helpful.

The interface for entering Checkpoints and Rules for each of the visits could be improved. Being able to see only one visit's rules at a time was limiting.

Action Item: Research to be done to see if the assignment screen can be made more user friendly.

Tester Comment [3.9]
The Study Characteristics section was designed well. Easy to use.

Action Item: NONE

Tester Comment [3.10]
Generally copy/paste from MS Word seemed to go well
It may be useful to have a specific section (outside of the unstructured protocol text) to capture content that couldn't be expressed sufficiently in the structured content (e.g., the adjusted dosing).
Action Item: None.

Tester Comment [3.11]

1. We are not convinced that sufficient testing has been done to approve this standard for use and would recommend further testing with a variety of differing study designs and including the reviewers/users of the content "down-stream". We question how many of the 20 Use Cases identified in the HL7 Study Design Structured Document Topic (see May 2013 ballot page) have been tested as a part of this pilot and how many remain to be tested?

Action Item: We agree. An operational pilot would be needed to provide additional experience.

2. We are concerned that variable dose regimens in terms of timing, frequency, and dose are not adequately addressed in the model and/or user guide. Also, we may select a different approach if we knew better how the agency planned to use the structured data.

Action Item: We agree. Any additional structured dosing information beyond the drug name (dose, frequency, route of administration), should be considered optional. These fields can be used only if they make sense to do so. Otherwise, detailed dosing information should be provided as unstructured text in the appropriate section.

3. It would be beneficial to have a clear statement of the FDA goals associated with the use case for the initial implementation.

Action Item: We agree, but this is beyond the scope of the current testing, which is focused on assessing the standard.

4. We believe that there needs to be discussion of use cases regarding how this standard would work in different protocol life-cycle scenarios.

Action Item: See previous comment.

5. A comprehensive set of standardized vocabularies with defined terms should be provided in order that reviewers not have to master many definitions for similar term sets.

Action Item: These will be provided for the operational pilot phase.
6. Industry should be knowledgeable of and ideally have access to any tools FDA develops to view the input and to any transformations FDA makes from the

input. This is critical to ensuring that FDA staff are receiving the same message that industry believes it is communicating.

Action Item: We appreciate the comment and will take it under consideration.

7. Within the xForm there is an ability to use a stylesheet to view both the structured and unstructured content. Is there a stylesheet available that could be used outside of the xForm so that other staff could view the generated xml without having to install the xForm?

Action Item: The intent is to have a stylesheet that can be used independently of the xForm.

8. We are wondering what attempts have been made to include input from the study investigator community into this effort. It would be problematic to have to produce the protocol differently for review by the agency versus use by the study investigation team. This type of input should be sought as a part of moving forward with this standard.

Action Item: We appreciate the comment and will take it under consideration.

5.4 CENTER FOR DRUG EVALUATION AND RESEARCH

The tester provided four test files:
I1F-MC-RHAG.xml
I1F-MC-RHAZ.xml
laxoSmithKline-2.xml July 01.xml
NIDA_CTN_0001_b.xml

Tester Comment [4.0]
Comment #1: Initially unable to install eXist, but successful on switch from IE to Firefox browser
Comment #2: NONE
Comment #3: Installation instructions were very clear and installation proceeded without difficulty.
Action Item: NONE

Tester Comment [4.1]

Comment #1: Initially unable to "save" file with "General Study Information" but found it necessary to fill in all required areas in other sections (that have asterisks (*)) with at least one item – then the new file could be "saved" with the file name

Comment #2: None

Comment #3: Troubleshooting the validation error report was challenging for those without a strong technical background or xml experience.

Action Item: Implementation of schematron for validation should increase the understandability of errors without needing a strong technical background or XML experience. The application should allow the user to save an incomplete file.

Tester Comment [4.3]

Comment #1: None

Comment #2: None

Comment #3: Saving a file outside the database could be a bit more intuitive. For example, an "Export Study File" feature next to the Import Study File link on the home page would be a welcome enhancement.

Action Item: Add instructions on how a study design file can be exported to be saved outside of the eXist database. Further research needs to be done to see if the application can have a link or button that can be clicked on to have the file exported from the application.

Tester Comment [4.4]

Comment #1: Validation is automatic each time one "saves" an entry. Rarely does an entry not save. If one has entered a lot of information, it may be difficult to find exactly what the error is even with looking at the Page Line in the xml file. In some instances, I had to delete the entry and enter in small pieces, validating each small piece. In this process, I have found that it is possible to get "invalid" entry with a lot of data entry but "valid" each time entered if identical information is entered in smaller chunks.

Also, the xForm may automatically log out when the session is long, even when the computer is not idle. If one has entered a lot of data, they may not be saved and require reentry. It becomes advisable to always keep saving during the work.

Action Item: The application should have the capability to auto save work and also the user should be able to save the study file without completing all the information

Comment #2: None

Comment #3: It would be nice if the report were more user friendly, and were interactive (e.g. clicking on the error would take the user to the referenced line in the xml or the relevant data field in the xForm)

Action Item: see 2.2

Tester Comment [4.5]

Comment #1: Time taken to create the test file: 2-3 days depending on the complexity of the study and whether there is already a mature protocol familiar to the tester. Looking for information from the protocol to fill in the fields would take longer for one who needs this search, especially for missing information.
Comment #2: None
Comment #3: None
Action Item: None

Tester Comment [4.6]

Comment #1: Managing Code Sets-
1. The "local" code sets are in fact unique for a study but currently once entered, they apply to all studies on file. In order to manage entry into the xForm, I had to delete the outdated codes when doing the second study. However, if I needed to go back to work on the first, I have to reenter the specific code to be used. Alternatively, I do not delete anything and just enter new codes of the second study, which will cause much confusion. Suggest making "local" more study-specific, allowing existence of different "local" codes for different studies.

Action Item: All code sets for multiple studies can be present in the local code sets. Code sets need not be deleted once a study is completed. The local code set is a library of local codes that are available for all studies. The application has been modified to ensure that studies that contain code sets that do not have the codes present in the local code sets will still display as any other study. The user has the option to store the code sets that are not present in the local code sets to the local code sets and if the user chooses to not store the code sets, they will then be stored in a local table pertaining to the study.

2. The codes for study characteristics can be difficult to understand. For instance, for "healthy subject indicator", when only patients are to be enrolled, is it "no" or "not applicable"? C85582 for current therapy or treatment is too ambiguous – is it referring to the investigative product or is it about a concomitant drug/treatment that is needed together with the test drug? It would be superfluous for the test drug because there is already a local code for the study substance.

Action Item: Help text should be provided to help understand study characteristics.

3. The User Guide instruction for "Study Elements" is not helpful, and the examples given "screening element" and "follow-up element" are more like epochs. An element is an activity or group of activities taken as building block. I believe it requires clarification as to how granular the building block should be. It cannot be so gross to embrace an epoch, because the building blocks should be exclusive of each other, and if an entire epoch is used as the "element", then there should be no other "element" within the same Study Cell. On the other hand, making it very granular would be extremely cumbersome, with each Cell containing too many things. More guidance is needed on this. Scientifically speaking, an element should be pure vs a compound which contains more than one element. Thus, conceptually a group of activities may not be regarded as an element, but it is also recognized that listing detailed activities separately can be very onerous. It is also recognized that CDISC's SDTM has "Trial Elements" that frequently spans across an epoch. SDTMIG (v 3.1.2) section 7.3.4.1 has stated that it is a matter of judgment to determine how granular an "element" needs be in terms of finely dividing the time, and for our purpose, the User Guide can provide more guidance.

Action Item: User guide needs to be updated to provide more guidance on the various data elements.

4. Entry of eligibility criteria can be tricky as sometimes there could be subcriteria and conditions not amenable to simple pigeonholing into one single item, e.g., pregnancy prevention methods, criteria depending on age or sex, condition a AND condition b vs condition a OR condition b vs condition a AND/OR condition b, etc.

5. Study arm entry: (a) This can be problematic for dose escalating studies. The different cohorts to be dose-escalated are not really arms, but there is no better way to designate them. (b) Also, for a study on efficacy with non-responders switching to investigative drug, it is difficult to designate an "arm" for such switches. It is possible for assignment to a new arm from the re-randomization of responders, especially when this re-randomization occurs as the dividing line between epochs. If reassignment to new treatment occurs within an epoch (e.g., rescue with investigational drug allowed in long-term extension epoch), this may create more of an issue with number of subjects in the "arms".

Action Item: Same as 4.6.3.

Comment #2: None

Comment #3: This is a very useful method to manage locally defined codesets. Navigating between the xForm and the manage codeset screen was a bit awkward and could be streamlined. Changes to the local codeset were not always immediately reflected in the corresponding drop-down list in the xForm (is there a reliable method to update the drop-down list?)

Action Item: When codes are updated to the local code sets, the codes should immediately take effect and show up the drop down list of values in the xForms.

Tester Comment [4.7]
Comment #1: General Study Information –
The content in this section is noncontroversial, although protocols do not usually provide a sponsor ID. I had to look up the DUNS# of the sponsor via a search. I have no investigator information from the sponsor submission, thus leaving the relevant cells on investigator blank. Also, I have not tested different versions of the protocol, but believe that they may need different file names with the same study identifier.

Action Item: NONE
Comment #2: None
Comment #3: Hint for Release date could be clarified to say "the date the document version was released or finalized." and moved just below Version. Sponsor ID hint could be clarified to say "Sponsor identifier. This could be sponsor-defined or could be the sponsor's DUNS (Dun and Bradstreet) identifier.". Label for Principal Investigator could be changed to Principal or Coordinating Investigator.
Action Item: Modify the hint for the release date and move it below the version. Also the hint for Sponsor ID needs to be updated along with the label change for Principal Investigator.

Tester Comment [4.8]
Comment #1: Eligibility Criteria –
Entry of eligibility criteria is straightforward once these criteria have been entered into the code system. As discussed above, if one is doing more than one study, then the dropbox will show irrelevant criteria unless the criteria of other study(ies) have been deleted first.
Comment #2: None
Comment #3: [1] Describing eligibility criteria as locally-defined codesets is fine for now, but in the future, eligibility criteria should be expressed as machine-readable logic to interpret observations performed at screening. For example, an inclusion criterion for 'Age >= 15' could be expressed as "IF Age(at screening) >= 15 THEN enroll. [2] ability to replace an eligibility criterion in a future document version is of

questionable usefulness. It's a feature that possibly could be dropped to simplify implementation of the first release. One could simply delete an old criterion and add the new one to the list in a new version. A tool-based comparison between versions can identify what has changed.

Action Item: Schematron is being developed in order for the eligibility criteria to be expressed in a machine-readable logic.

Tester Comment [4.9]
Comment #1: Study Epochs –
The concept of "epoch" is dependent on the periods a subject goes through in a clinical trial. There are no issues on entering study epoch information to the xForm. For a dose-escalation study, there are actually several overlapping stages for the different cohorts. These are not epochs for the purpose of the xForm, but there is no good way to represent the escalation process.

Action Item: Capturing titration information in a structured format was out of scope for the first release and will be captured as a requirement for a future release.
Comment #2: None
Comment #3: We need controlled terminology for epochs, at least the common ones (e.g. screening, randomization, treatment, follow-up). The sequence number of the epoch should determine the order the epoch appears in the study cells section of the xForm (currently, the order is determined by the order the epochs appear in this section).

Action Item: The xForm should be modified to allow the order in which the epoch appears in the study cells section of the xForm to determine the Sequence number of the epoch.

Tester Comment [4.10]
Comment #1: Substance Administration –
1. No issues encountered, except for frequency: currently the entry is for x times / time frame (hours, months, etc.), and when the dose frequency is x times per y weeks, as in Study RHAZ I entered, there is no accurate way to do it. For Q2W, I used 2 times/month, for Q4W, I used 1 time/month, and for Q12W, I used 4 times/year. These then are approximations due to lack of a number to fill in preceding the time unit (hours, months, etc.)

Action Item: None

2. For topical products, the dose may be hard to ascertain, especially when the treated lesion size changes, and so one may actually have to leave blank the dose; another issue would be that the dose unit does not include items like drop, thin film, etc., and the terms mg, g, mL, etc., are not practical in use for such products.

Comment #2: None

Comment #3: A hint (and the user's guide) should reflect that every substance administered per protocol should be entered in this section. This includes the investigational drug, any protocol-specified comparator and background therapy. For each substance, we need the ability to flag whether it is the investigational drug, and active comparator (control), or background treatment.

Action Item: A hint is to be provided for the substance administration and the User Guide is to be updated to indicate that every substance administered per protocol should be entered in the substance administration section.

Tester Comment [4.11]

Comment #1: See above for comments on "Study Element" entry in the vocabulary. I used the activities within an epoch as elements. However, it is a requirement to put in the "order" of the elements within the epoch when one does the Study Cells. Since these are recurrent activities in different visits, and their recurrence varies, it is in fact not appropriate to be placing orders among them. I used the logical order of doing these activities within a visit for that purpose. I also did not include all the activities, as an exhaustive list would be too long, and already the Study Cell tables are of incredible width with the current number of elements and visits. More guidance would be needed.

Comment #2: None

Comment #3: We need controlled terminology for the common study elements, or possibly machine-verifiable rules for creating element names from other protocol structured data elements.

Action Item: The scope of the testing did not include the capturing of individual activities for the release.

Tester Comment [4.12]

Comment #1: Study Cells –

1. For blinded studies, the elements within an epoch are the same (except for the intervention being studied). Thus, unless the name of the study drug (or dose, if the study is also testing the dose) to be administered is entered, the cells in a column will all contain the information. This is the case I encountered because I used the same name for the element for IP administration without specifying product or dose. It is a lot of repetitive work to enter cells for many arms of each epoch with the same information when the epoch contains many elements. Even if the IP administration

elements have been distinguished between different arms, the other elements are the same across arms in the same epoch. It would be much more efficient if copy/paste function between cells is possible, and so only the relevant changes characterizing the arms are needed.

2. The study cells are rigid. If there is early termination, there is no suitable way to accommodate the information.

3. The cells would not allow for flexibility. In Study RHAZ, the PK blood sampling goes by cohorts. They are not study arms. Each cohort has PK blood sampling at different visits. There is no way to accommodate this information.

Comment #2: None

Comment #3: When there are many epochs (I think those with 5 or more), the rows of the study matrix wrap around to a 2nd row, making it difficult to understand the matrix. Additional epochs should stay on the same row.

Action Item: This has been fixed in the XForms. The epochs no longer wrap around, but they extend horizontally ensuring that the matrix looks OK.
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Tester Comment [4.13]

Comment #1: Study Characteristics –

1. The study characteristics are easy to use.

2. Not all items apply to each protocol. For instance, for a new protocol, study data cutoff date, data cutoff date description, and study start/end dates are unknown. Trial length is a hypothetical question, as it hinges on enrollment, and so not practical for a new protocol; a more realistic question is about length for subject participation. For safety and tolerability studies, usually there is no specific primary or secondary outcome measure but an overall adverse event profile weighed against potential benefit; this may also apply to studies on the pharmacokinetics (PK) of a product, where the PK profile is the research of interest, instead of a clinical outcome.

3. For actual study subject number, it is not possible to fill in when a new protocol is created.

Action Item: The application should be modified to remove certain TSPARM entries for a new protocol.

Comment #2: Done

Comment #3: The drop down list for each study characteristic that has controlled terminology is terrific and is a huge timesaver, since the value sets are not immediately known for each concept.

Action Item: None

Tester Comment [4.14]

Comment #1: Unstructured Protocol text-

1. The unstructured protocol text does not allow pasting diagrams, and so study schema involving diagrams (ICH E6 section 6.4.2; xForm unstructured text section 5) cannot be properly shown.

Action Item: Instructions should be included in the user guide to guide to user to include diagrams as the application does have the capability to include diagrams.

2. The unstructured text paste the symbols $\geq$ and $\leq$ out of place and not preceding the relevant numbers.

Action Item: Research should be done to check why the copy paste of symbols is not working as it should and needs to be fixed.

3. Some Tables can be pasted but others cannot. In the Appendix section (unstructured text section 17) I pasted the Table for clinical laboratory tests for each study, and the contents have been thrown out of place. However, the Schedule of Events Tables are preserved.

4. The unstructured protocol text section uses the ICH E6 format. Protocols written not following that format would present difficulties especially when certain information is absent. One has to search throughout the document to be sure that the information is missing.

Comment #2: None

Comment #3: Sometime for unexplained reasons, large blocks of text entered in the text editor (using the Edit button) does not appear in the section after the editor is closed. When clicking the "save" button, a user-unfriendly message appears making it unclear whether the text has been successfully saved. The Firefox limitation to cutting and pasting was an issue. At the end of each section, it would be useful to have a hyperlink "back to the top" such as the one available in the structured section. It would also be useful to be able to expand/collapse each section. A future version of the xForm should support multiple sections for amendments, appendices, and unspecified sections.

Action Item: The application should provide the ability for the user to move from the section to the top by having a hyperlink "back to the top" in the unstructured section. The copy/paste issue should be resolved and the xForm should support more sections for unspecified sections.

Tester Comment [4.15]

Every study has a timeline. Study day 1 is typically the first day of the first treatment epoch. Negative study days are used to describe activities that occur in epochs earlier

than the first treatment epoch (e.g. screening, baseline, run-in). We are capturing adequate information to place visits on the study timeline, since we are capturing the study day that a visit begins.

We know how long epochs last: the sum of the durations of all the elements contained within the epoch. But, we are unable to place the epochs on the timeline because we don't know when the epochs begin. Specifically, we don't know which is the first treatment epoch. If we did, we could assign it a start day = 1 and generate start days for all the other epochs based on their durations. Then we would know where each visit occurs within each epoch.

Action Item:
1. Create a new study characteristic called first treatment epoch. The permissible values come from the user-defined code set for epochs.
2. The system will then assign the start day of that epoch to 1.
3. All other study epoch start dates can be derived using epoch durations.

6 DISCUSSION

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

Goal: To create a valid Study Design file for review by US FDA
Goal: To use simple testing tools (xForm, Style sheet) to create, edit, view, and save Study Design Files

The testing successfully achieved these goals. 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 Study Design files. The xForm did require testers to install eXist database and Java which are both open-source tools. Some testers had difficulty in installing the eXist database but once given a little direction were able to install successfully and start creating the study design files. Another limitation was the lack of familiarity with the CDISC protocol representation model (arms, epochs, elements, etc.).

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

The Study Design uses both local and centrally maintained code sets. The local code sets allow the user to enter their own criteria pertaining to the study that they are working on. The centrally defined code sets are the codes that are defined by various terminology maintenance organizations and will not be editable by the users. We conducted the testing using the same SDTM controlled terms available for some of these concepts.

Goal: To identify business processes and/or technical issues that may negatively affect efforts to implement HL7 V3 for Study Design
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 design file exchange, we were also interested in identifying, at a high level, potential roadblocks to piloting and implementation.
XSLTforms were used in the development of the study design. It uses eXist database which is an open-source database and Java that is being used predominantly across the FDA. No additional software is required.
On the FDA side, there was uniform excitement in being able to receive study 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. 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 Study Design Structured Document 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 and the SPL vendor community but this resulted in only three participating organizations besides FDA. 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).

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. This could be accomplished in the future by updating the Agency's PDUFA IT Plan.

7   RECOMMENDATIONS

The following summarizes the actionable items identified during testing.

7.1   GENERAL CHANGES FOR CONSIDERATION

No changes are identified.

7.2   CHANGES TO THE STANDARD (RMIM)

No changes are identified.

7.3   CHANGES TO THE SCHEMA

No changes are identified.

7.4   CHANGES TO THE IMPLEMENTATION GUIDE

Comment	Action
2.4	Rules should be defined for the version number.
2.4	The Implementation Guide should be modified to include the middle initial and name suffix for the lead investigator.
4.15	The study characteristic for the first treatment epoch needs to be present to define the timeline of the study

7.5   CHANGES TO THE VOCABULARY

4.15	The study characteristic for the first treatment epoch needs to be defined and present to place epochs on the timeline of the study

7.6   CHANGES TO THE XFORM

Comment	Action
1.1	xForms should be updated to include help text so it is easy for the users to understand study design terms such as epochs, arms etc
1.2	Implementation of the schematron will facilitate the understanding of validation errors. Update xForm to easily allow saving incomplete/invalid files.
1.4	Increase the time in which a user can save any data that has been entered thus far. It would also be useful to allow users to save incomplete files to complete the study at a later time.
1.5	The application should be modified to allow a new code set to be available for the user in the dropdown value list when a code set is added to the list of existing local code sets
1.12	Add an additional feature for spell check.
2.2	Provide help text action icons. Further research will be done to see if a separate window to view the study in the style sheet.
2.3	research to be done to ensure that the user does not have to hit the back button twice to get back to the code set list after finishing the editing of each local code set.
2.3	Duplicate code identifiers should not be allowed.
2.4	The application can have the ability to store local lookup tables for sponsor IDs, investigators.
2.4	The application should have the capability to allow a user to save a study file even after just entering the basic information.
3.5	Add 'µg' to Unit of Measure which is a central code set. Code Sets should be aligned with CDISC controlled terminology
4.6	When codes are updated to the local code sets, the codes should immediately take effect and show up the drop down list of values in the xForms.
4.13	The application should be modified to remove certain TSPARM entries for a new protocol.
4.14	Research should be done to check why the copy paste of symbols is not working as it should and needs to be fixed.
4.14	The application should provide the ability for the user to move

	from the section to the top by having a hyperlink "back to the top" in the unstructured section. The copy/paste issue should be resolved and the xForm should support more sections for unspecified sections.
4.15	The study characteristic for the first treatment epoch needs to be defined and present to place epochs on the timeline of the study

7.7   CHANGES TO THE STYLESHEET

4.15	Once the study characteristic for the first treatment epoch is added to the xForm, the style sheet should derive the study epoch start dates using the epoch durations.

7.8   CHANGES TO THE INSTALLATION GUIDE

2.1	Installation Guide should include steps to first uninstall eXist database before re-installing

8   NEXT STEPS

It is recommended that the project team make the changes described in section 7.

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 submissions using this format into normal workflows.