Implementation Guide for Study Design Structured Document

FDA Guidance for Human Clinical Trials

Table of Contents

1 Acknowledgements

This document is based on the Health Level Seven Study Design Structured Document, and on the CDISC SDTM Implementation Guide.

2 Introduction

This document is intended to assist organizations responsible for clinical trials in reporting the design of a study. It draws on the trial design content of the SDTM standard, and shows how to represent that content using the HL7 Specification.

The study design structured document describes what is going to be done in a study. . A study in this context is any investigation performed to support the safety, effectiveness, or quality of a medical product. As such, the experimental subject of a study can be a human, other nonhuman living subjects, parts of nonhuman living subjects, groups of nonhuman living subjects, or the medical product itself. The study design structured document will transport trial design and eligibility criteria information in a standardized format. The specification is designed to allow communicating the content of a study protocol. However, it lays particular emphasis on communicating the following in a structured form: arms, epochs, subject assignment, planned encounters (visits), planned interventions, planned observations (assessments), eligibility criteria and study characteristics.

The scope of the initial release of the standard is limited to the protocol document, study plan of activities, analysis comparables and eligibility criteria. The following are out of scope: site setup, recruitment, inventory management, data management, database lock, and statistical analysis plan.

The scope of this Implementation Guide is limited to the protocol document and the trial design content defined within the SDTM Implementation Guide published by CDISC.[1] It also leverages the standard sections of a protocol as defined by the International Conference on Harmonisation Good Clinical Practice E6 Guideline[2].

Further information about the Study Design Structured Document specification is available at HL7.org.

2.1 Audience

The audience for this document is software developers and development organizations who wish to produce or receive Study Design Structured Documents.

2.2 Approach

The Study Design Structured Document specification was designed to address a wide range of possible use cases for reporting or amending study protocols. This implementation guide has been designed to support an initial test of reporting protocol information using the HL7 specification. In order to ease the implementation process, the scope of the document has been restricted to only include the unstructured protocol document and content previously defined within the trial design domains of CDISC SDTM implementation guide.

[1] Study Data Tabulation Model Implementation Guide: Human Clinical Trials, CDISC 2008.
The document also provides a reference – Section 7 – to the structure and design of a clinical trial.
[2] http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

The vocabulary items that are needed to support Study Design reporting are managed by NCI within the EVS Thesaurus. NCI EVS will provide a file for the Study Design user community to be located at: http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/fda. Material at this site will contain all pertinent CDISC terminology subsets as well as additional value sets as needed. This material is available for download 24/7 and updates to terminology will be completed by the NCI EVS team. NC EVS currently provides terminology in Excel and Text formats.

2.3 Change process

The Study Design Structured Document has been published as DSTU by HL7. It is likely that implementation experience and changes in design philosophy will lead to changes in the specification. In addition, we also expect there to be changes, possibly expansion, in the requirements to be addressed by a study design implementation guide.

Issues and new requirements should be reported to edata@fda.hhs.gov.

2.4 Abbreviated Terms

The following abbreviations appear within the document.

Abbreviated	Spelled Out
CDA	Clinical Document Architecture
CDISC	Clinical Data Interchange Standards Consortium
DSTU	Draft Standard for Trial Use
EVS	Enterprise Vocabulary Services
HL7	Health Level 7
ICH	International Committee on Harmonization
NCI	National Cancer Institute
OID	Object Identifier
SDTM	Study Data Tabulation Model
SEND	Standard for Exchange of Nonclinical Data

3 How to use this document

The Implementation Guide provides specific instructions on using the Study Design Structured Document in order to transmit the fundamental information for a planned human clinical study. It provides instruction on how to value the elements and attributes of a conformant study design document, and discusses relevant issues for managing identifiers and vocabularies.

3.1 Templates

This definition of a conformant study design document is constructed as a collection of templates. For HL7, a template is "an expression of a set of constraints on the RIM or a RIM derived model that is used to apply additional constraints to a portion of an instance of data which is expressed in terms of some other Static Model. Templates are used to further define and refine these existing models to specify a narrower and more focused scope."[3] Our templates express how the more general Study Design Structured Document specification is to be implemented for the purposes of this guide. This method of documentation is intended to ease conformance testing – we expect that instances will be tested against the constraints of these templates as a method of evaluating conformance.

[3] Formal Template Definition, Specification and Use of Reusable Constraint Templates, Normative Edition of HL7 Version 3 Standards, Health Level 7, Ann Arbor MI July 2011

In addition, the content in this document has been organized into templates in order to simplify presentation and to offer a reasonable and modular structure for the implementer. Whether or not template identifiers are needed within document instances will be an implementation decision.

3.2 Embedded Data Structures

Any HL7 Version 3 product is based on a common set of data types – of reusable data structures. This section discusses those for which further explanation will be useful to implementers.

3.2.1 Identifiers

The data element "id" is used for identifiers within HL7 Version 3, and is assigned the data type "II" – instance identifier. It is intended to allow unique identification of objects used within healthcare data processing. Uniqueness is assured through definition of both an identifier value and the namespace from which that identifier was drawn. HL7 offers a couple of identification schemes for ensuring the global uniqueness of the identifier namespace.[4] Within in this guide we are assuming the use of the Object Identifier (OID). We have also simplified the implementation of this concept to meet the specific needs of implementers and of identification in the context of study design.

We do not wish to require that implementers develop the ability to manage and assign OIDs to the relevant namespaces. However it is necessary to have some method of distinguishing identifiers since it is not always possible to rely on the document content. (This is not a practical issue for Study Design, but it is one for subject data.) Therefore a generic OID will be assigned as a designator for the kind of name space that is relevant – this is equivalent to specifying the "identifier type". The generic OIDs are used where needed, and are documented below. In addition, for those identifiers used only within the message and for which the context is always clear, the name space will not be valued. This is indicated by use of a null value indicator which signifies that a complete identifier is not being provided.

3.2.2 Coded Values

Coded values are used within this guide – as with all HL7 Version 3 products – to clearly provide the needed information (to get closer to "semantic interoperability"). You will see this in two contexts:

Structural Coherence:
HL7 has provided code sets to indicate basic structural information within a document. For example, that a structure is an observation or a substance administration, that information is being provided regarding the author of a document or the performer of an activity. These items use vocabularies provided by HL7 and are almost always constrained to a single value within implementation guides such as this.

Semantic Clarity:
Coded items constrain the set of possible included values, to allow receivers of the information to use it in more precise ways. For instance, there is a predefined set of routes of administration for medication, since different uses of the data are dependent on specific values of a particular item. These code sets are functionally meaningful, and the set of possible codes must be communicated to allow full use of the data. Within this implementation guide, those code sets (value sets) that are centrally defined, and those which are provided by study sponsors are specified in the Vocabulary section.

The data type for coded data includes properties for the code to be transmitted, for the code system used to be identified (code systems are identified with an OID), and for display text conveying the coded concept in words.

[4] 2.17 Instance Identifier, Data Types: Abstract, Normative Edition of HL7 Version 3 Standards, Health Level 7, Ann Arbor MI July 2011

3.2.3 Null Values

HL7 allows assignment of a "null value" to any attribute. A null value "means that the information does not exist, is not available or cannot be expressed in the data type's normal value set."[5]. The guide uses the null value assignment to indicate that a required data element cannot be provided, or that, in the case of identifiers, partial information is used.

3.2.4 Units of Measure

HL7 physical quantities use the HL7 PQ data type, in which units are expressed in the Unified Code for Units of Measure (UCUM; 2.16.840.1.113883.6.8), available at http://www.regenstrief.org. The guide calls on the representation of these units provided by CDISC and captured within the NCI Thesaurus.

4 Implementation Issues

4.1 Conventions

This document follows conventions used within HL7 CDA implementation guides. Relevant conventions are reiterated here.

The terms SHALL, SHALL NOT, SHOULD, SHOULD NOT, and MAY in this document are to be interpreted as described in the HL7 Version 3 Publishing Facilitator's Guide. The keyword "SHALL" implies a lower cardinality of 1 but does not disallow NULL values. If NULL values are to be excluded, it will be via an additional explicit conformance statement.

5 Study Design Structured Document

The Study Design Structured Document captures the content of a study protocol as documented by the ICH and by CDISC. It contains unstructured sections that are intended to contain text based documents as well as a structured section to contain the items that are critical for subsequent transmission of information regarding the experience of study subjects.

The Study Design Structured Document Specification is a document markup standard that specifies the structure and semantics of the documentation used to describe a planned clinical or non-clinical study. This implementation guide focuses on a subset of the data that is conveyed.

5.1 Document Header

The header contains information to identify the protocol document itself and to make clear its source, and who takes responsibility for its content. The root element of the header is the Document class. The template id for the document is: FDAroot.xx.yy.01.

Its contents are specified as follows:

1. SHALL contain exactly one [1..1] @classCode="DOCCLIN"
2. SHALL contain exactly one [1..1] @moodCode="EVN"
3. SHALL contain one to many [1..*] id
   The identifier assigned to the study design must be included. It uniquely identifies the study

[5] 2.11 DataValue (ANY), Data Types: Abstract, Normative Edition of HL7 Version 3 Standards, Health Level 7, Ann Arbor MI July 2011

design/protocol.
[SDTM: STUDYID]
In addition, there may be identifiers assigned by a registry such as ct.gov.
[SDTM: Registry Identifier]

4. SHALL contain exactly one [1..1] code@code = “Cxxxxx” (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
5. SHOULD contain zero or one [0..1] title.
   A text name for the study
   {SDTM: TSPARMCD = TITLE}
6. SHOULD contain zero or one [0..1] effectiveTime
   The date/time on which this version of the document was released.
7. SHOULD contain zero or one [0..1] confidentiality code where @code SHALL be selected from (CodeSystem: 2.16.840.1.113883.5.25 Confidentiality)
8. MAY contain zero or one [0..1] languageCode (Code System 1.0.639.3 Language Codes Alpha 3)
   The language used for the document. The entry may be left out, if the language used is English.
9. May contain zero or one [0..1] realmCode (2.16.840.1.113883.5.1124)
   Identifies a country or other administrative unit that has defined particular rules for the format or content of the structured document. The entry may be left out if the intended realm is the United States.
10. SHALL contain exactly one [1..1] setID
    An identifier that remains consistent across all revisions derived from a common original. In the first version of the document – VersionNumber = 1, setID and id will be identical.
11. Shall contain exactly one [1..1] VersionNumber
    An integer value that designates the version of the document.
12. SHALL contain exactly one [1..1] responsibleParty
    a. The responsibleParty SHALL contain exactly one [1..1] @typeCode=”RESP”
        i. The responsibleParty SHALL contain exactly one [1..1] assignedEntity
            1. The assignedEntity SHALL contain exactly one [1..1] @classCode=”ASSIGNED”
            2. The assignedEntity SHALL contain exactly one [1..1] assignedPerson
                a. The assignedPerson SHALL contain exactly one [1..1] @classCode=”PSN”
                b. The assignedPerson SHALL contain exactly one [1..1] @determinerCode=”INSTANCE”
                c. The assignedPerson SHOULD contain zero to one [0..1] name
                   A text name for the principle investigator.
                   [SDTM:]
                    i. The name MAY contain zero to one [0..1] prefix
                       A text entry with a name prefix, e.g., Dr.
                    ii. The name SHALL contain exactly one [1..1] given
                        The given name of the person.
                    iii. The name SHALL contain exactly one [1..1] family

The surname name of the person

3. The assignedEntity SHALL contain exactly one [1..1] representedOrganization
    a. The representedOrganization SHALL contain exactly one [1..1] @classCode=”ORG”
    b. The representedOrganization SHALL contain exactly one [1..1] @determinerCode=”INSTANCE”
    c. The representedOrganization SHALL contain exactly one [1..1] id
    An identifier for the study sponsor.
    d. The representedOrganization SHOULD contain zero to one [0..1] name
    A text name for the study sponsor.
    [SDTM: Appendix C3 TSPARMCD = SPONSOR]

13. SHALL contain one to many [1..*] components
    Each desired section – whose number and title may be based on advice provided by ICH – is included as a single component.
    a. The component SHALL contain exactly one [1..1] @typeCode=”COMP”
    b. The component SHALL contain exactly one [1..1] nonXMLBody
    The nonXML body will carry an unstructured section. The list of unstructured sections should be drawn from the list of possible sections included below.
        i. The nonXMLBody shall contain exactly one [1..1] @classCode=”DOCBODY”
        ii. The nonXMLBody shall contain exactly one [1..1] @moodCode=”EVN”
        iii. The nonXMLBody shall contain exactly one [1..1] text.
        The text will contain the content of the desired protocol section
14. SHALL contain exactly one [1..1] component
    a. SHALL contain exactly one [1..1] structuredBody
    The section is defined using template FDAroot.xx.yy.02.

5.2 Document Sections

The structured document will contain structured and unstructured sections. This contains the content of the protocol for the planned study.

5.2.1 Unstructured Section

The unstructured sections are expected to have content based on the following list.

1. Protocol Synopsis [1]
2. General Information [1]
3. Background Information [1]
4. Trial Objectives and Purpose [1]
5. Trial Design [1]
6. Treatment of Subjects [1]
7. Assessment of Efficacy [1]
8. Assessment of Safety [1]
9. Statistics [1]

10. Direct Access to Source Data/Documents [1]
11. Quality Control and Quality Assurance [1]
12. Ethics [1]
13. Data Handling and Recordkeeping [1]
14. Financing and Insurance [0..1] (if not addressed in a second document)
15. Publication Policy [0..1] (if not addressed in a second document)
16. Appendix [0..*]
17. Protocol Amendments [0..*]
18. Unspecified [0..*] (suggested for any additional information that doesn't fit elsewhere)

5.2.2 Structured Section

The section contains the structured content for the study design. The template id for the structuredBody content is: FDAroot.xx.yy.02.

Its contents are specified as follows:

1. SHALL contain exactly one [1..1] @classCode="DOCBODY" "
2. SHALL contain exactly one [1..1] @moodCode="EVN"
3. SHALL contain exactly one [1..1] component
    a. The component SHALL contain exactly one 1..1] @typeCode="COMP"
    b. The component SHALL contain exactly one 1..1] section
        i. The section SHALL contain exactly one [1..1] @classCode="DOCSEC" "
        ii. The section SHALL contain exactly one [1..1] @moodCode="EVN
        iii. The section SHALL contain exactly one [1..1] code/@code = "" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
        A code value to the section content is a planned study.
        iv. The section SHALL contain exactly one [1..1] title
        v. The section SHALL contain exactly one [1..1] subject
            1. The subject SHALL contain exactly one [1..1] @typeCode="SUBJ"
            2. The subject SHALL contain exactly one [1..1] plannedStudy
                a. The plannedStudy SHALL contain exactly one [1..1] @classCode="OBS"
                b. The plannedStudy SHALL contain exactly one [1..1] @moodCode="DEF"
                c. The plannedStudy SHALL contain exactly one [1..1] researchSubject
                    i. The researchSubject SHALL contain exactly one [1..1] @classCode="RESBJ"
                    ii. The researchSubject SHALL contain exactly one [1..1] subjectPersonKind
                        1. The subjectPersonKind SHALL contain exactly one [1..1] @classCode="PERS"
                        2. The subjectPersonKind SHALL contain exactly one [1..1] @determinerCode="KIND"
                        3. The subjectPersonKind SHOULD contain zero to one [0..1] quantity@value
                        The number of subjects that is planned for the study
                        [SDTM: Appendix C3 TSPARMCD = PLANSUB]
                d. The plannedStudy MAY contain zero to many [0..m] precondition
                    i. The precondition SHALL contain exactly one [1..1] @typeCode="PRCN"

ii. The precondition SHALL contain exactly one [1..1] eligibilityCriterion.
Information on inclusion and exclusion criteria for the study. Template ID = FDAroot.xx.yy,11

e. The plannedStudy SHALL contain one to many [1..m] component1
   i. The component1 SHALL contain exactly one [1..1] @typeCode="COMP"
   ii. The component1 SHALL contain exactly one [1..1] epoch.
   Information on epochs defined for the study. Template ID = FDAroot.xx.yy.03

f. The plannedStudy SHALL contain one to many [1..m] component2
   i. The component2 SHALL contain exactly one [1..1] @typeCode="COMP"
   ii. The component2 SHALL contain exactly one [1..1] arm.
   Information on arms defined for the study. Template ID = FDAroot.xx.yy.04

g. The plannedStudy SHALL contain one to many [1..m] component3
   i. The component3 SHALL contain exactly one [1..1] @typeCode="COMP"
   ii. The component3 SHALL contain exactly one [1..1] substanceAdministration.
   Information on one or more treatment substances to be administered during the study. Template ID = FDAroot.xx.yy.05

h. The plannedStudy SHALL contain one to many [1..m] component3
   i. The component3 SHALL contain exactly one [1..1] @typeCode="COMP"
   ii. The component3 SHALL contain exactly one [1..1] observation.
   Information on one or more locally defined value set to be used for validating subject data in reports from the study. Template ID = FDAroot.xx.yy.14

i. The plannedStudy SHALL contain one to many [1..m] component4
   i. The component4 SHALL contain exactly one [1..1] @typeCode="COMP"
   ii. The component4 SHALL contain exactly one [1..1] timePointEventDefinition.
   Information on elements and visits defined for the study. Element information is defined within Template ID = FDAroot.xx.yy.06
   Visit information is defined within Template ID = FDAroot.xx.yy.08

j. The plannedStudy SHALL contain one to many [1..m] subjectOf
   i. The subjectOF SHALL contain exactly one [1..1] @typeCode="SUBJ
   ii. The subjectOF SHALL contain exactly one [1..1] studyCharacteristic
   Information on characteristics/parameters defined for the study. Study characteristic information is defined within Template ID = FDAroot.xx.yy.10.

5.3 Content Data Structures

The body of the study design is comprised of several templates that are used to represent the primary functional content of the study design.

5.3.1 Study Epoch

An epoch is "an interval of time in the planned conduct of a study during which treatment is constant."[6] A subject movers from one epoch to another, and can only be in one epoch at a time. The main purpose of the epoch is to organize arms for comparison purposes. The template id for the data structure is: FDAroot.xx.yy.03.

Its contents are specified as follows:

1. The epoch SHALL contain exactly one [1..1] @classCode="ACT"
2. The epoch SHALL contain exactly one [1..1] @moodCode="DEF
3. The epoch SHALL contain exactly one [1..1] id@nullFlavor="UNK"
   The identifier is only used to provide references within the content of the study design document. A root OID to provide global uniqueness is not needed.
4. The epoch SHALL contain exactly one [1..1] id@extension
   The extension value shall be an integer, and shall be unique within the document.
5. The epoch SHALL contain exactly one [1..1] title@mediaType="text/plain"
6. The epoch SHALL contain exactly one [1..1] title
   A text description of the epoch.
   [SDTM: EPOCH]

5.3.2 Study Arm

An arm is "a sequence of epochs (time intervals during which treatment is consistent) defining the course of participation for a subject in a trial."[7] It is a path through the study which describes what activities the subject will be involved in as they pass through the study, and is typically equivalent to a treatment group in a parallel design trial. Generally, each subject is assigned to an Arm, and the design of the study is reflected in the number and composition of the individual arms. The template id for the data structure is: FDAroot.xx.yy.04.

Its contents are specified as follows:

1. The arm SHALL contain exactly one [1..1] @classCode="ACT"
2. The arm SHALL contain exactly one [1..1] @moodCode="DEF
3. The arm SHALL contain exactly one [1..1] id@nullFlavor="UNK"
   The identifier is only used to provide references within the content of the study design document. A root OID to provide global uniqueness is not needed.
4. The arm SHALL contain exactly one [1..1] id@extension
   The extension value shall be an integer, and shall be unique within the document.
5. The arm SHALL contain exactly one [1..1] code@code =”” “” (CodeSystem Arm - local)
6. The arm SHALL contain exactly one [1..1-code@displayName
   A text description of the arm.

5.3.3 Study Substance

Information on a substance to be administered during the trial, and on the manner of its administration. The template id for the data structure is: FDAroot.xx.yy.05.

Its contents are specified as follows:

1. The studySubstance SHALL contain exactly one [1..1] @classCode="SBADM"

[6] Glossary: Clinical Trails Terminology Version 2.0, CDISC. www.lau.edu.lb/chsr/forms/clinical_trials_terminology_glossary.pdf.
[7] Glossary: Clinical Trails Terminology Version 2.0, CDISC. www.lau.edu.lb/chsr/forms/clinical_trials_terminology_glossary.pdf.

2. The studySubstance SHALL contain exactly one [1..1] @moodCode="DEF"
3. The studySubstance MAY contain zero to one [0..1] effectiveTime
    a. The effectiveTime SHALL contain exactly one [1..1] @xsi:type="PIVL_TS"
    b. The effectiveTime SHALL contain exactly one [1..1] period
    Time period holds the frequency of administration. [SDTM Appendix C3 TSPARMCD = DOSFRQ]. Note that the HL7 frequency representation captures the periodicity of administrations – the scheduled time delay between two administrations.
        i. The period SHALL contain exactly one [1..1] value
        ii. The period SHALL contain exactly one [1..1] unit (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
4. The studySubstance MAY contain zero to one [0..1] routeCode@code (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
    The route by which the substance is administered.
    [SDTM Appendix C3 TSPARMCD = ROUTE]
5. The studySubstance MAY contain zero to one [0..1] doseQuantity@value
    The planned amount to be administered.
    [SDTM Appendix C3 TSPARMCD = DOSE]
6. The studySubstance MAY contain zero to one [0..1] doseQuantity@unit (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
    [SDTM Appendix C3 TSPARMCD = DOSU]
7. The studySubstance MAY contain zero to one [0..1] consumable
    a. The consumable SHALL contain exactly one [1..1] @typeCode="CSM"
    b. The consumable SHAL contain exactly one [1..1] manufacturedProduct
        i. The manufacturedProduct SHALL contain exactly one [1..1] @classCode="MANU"
        ii. The manufacturedProduct SHALL contain exactly one [1..1] manufacturedMaterial
            1. The manufacturedMaterial SHALL contain exactly one [1..1] @classCode="MMAT"
            2. The manufacturedMaterial SHALL contain exactly one [1..1] @determinerCode="KIND"
            3. The manufacturedMaterial may contain zero to one [0..1] code@code
            4. The manufacturedMaterial may contain zero to one [0..1] name
            Information on the substance to be administered. Either the name or code may be provided.
            [SDTM Appendix C3 TSPARMCD = PLANSUB]
            [SDTM Appendix C3 TSPARMCD = TRT]

5.3.4 Study Element

An element is a building block that is used to organize activity within the trial. It represents a cluster of activities that may be assigned to one or more arms within the study. Note, study design provides information about the individual elements of the study, and about an elements assignment to a particular arm. It would be possible to define a list of activities that would be expected to be performed as part of an element. However, that level of detail is beyond the scope of this implementation guide. The template id for the data structure is: FDAroot.xx.yy.06.

Its contents are specified as follows:

1. The timePointEventDefinition SHALL contain exactly one [1..1] @classCode="CTTEVENT"
2. The timePointEventDefinition SHALL contain exactly one [1..1] @moodCode="DEF"

3. The timePointEventDefinition SHALL contain exactly one [1..1] id@nullFlavor="UNK"
   Presence of the identifier is required by the schema, but is not functionally required.
4. The timePointEventDefinition SHALL contain exactly one [1..1] code@code (CodeSystem = Element Code Local)
   A code to indicate the nature of the element.
   [SDTM: ETCD]
5. The timePointEventDefinition SHALL contain exactly one [1..1] code@displayText
   [SDTM: ELEMENT]
6. The timePointEventDefinition MAY contain zero to one [0..1] effectiveTime@xsi:Type="IVL_TS"
   a. The effectiveTime SHALL contain exactly one {1..1] width@value
   b. The effectiveTime SHALL contain exactly one {1..1] width@unit
      The expected duration of the activities included within the element.
      [SDTM: TEDUR]
7. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode="PRCN"
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code="B"
      The checkpoint code "B" indicates the criterion is evaluated before the activities included within the element begin.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode="OBS"
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode="CRT"
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is an element performance rule.
      iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type="ED"
      v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType="text/plain"
      vi. The timePointEventCriterion SHALL contain exactly one {1..1] value
      A rule describing the condition under which the element is to start.
      [SDTM: TESTRL]
8. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode="PRCN"
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code="E" (
      The checkpoint code "E" indicates the criterion is evaluated in order to allow the activities within the element to end.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode="OBS"
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode="CRT"
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is an element performance rule.
      iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type="ED"
      v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType="text/plain"
      vi. The timePointEventCriterion SHALL contain exactly one {1..1] value
      A rule describing the condition under which the element is to end.
      [SDTM: TEENRL]
9. The timePointEventDefinition SHALL contain one to many [1..*] component2
   a. The component2 SHALL contain exactly one {1..1] @typeCode="COMP"

b. The component2 SHALL contain exactly one [1..1] timePointEventDefinition
Information on an element's positioning within a particular study arm. Element in Arm information is defined within Template ID = FDAroot.xx.yy.07

5.3.5 Element in Arm

The element defines a collection of activities to be performed during a study. However this collection can take place in different contexts – through being situated in different arms of the study. The "element in arm" template captures an element's assignment to an arm, as well as allowing the definition of particular rules that apply when the element occurs within the arm. The template id for the data structure is: FDAroot.xx.yy.07.

Its contents are specified as follows:

1. The timePointEventDefinition SHALL contain exactly one [1..1] @classCode="CTTEVENT"
2. The timePointEventDefinition SHALL contain exactly one [1..1] @moodCode="DEF"
3. The timePointEventDefinition SHALL contain exactly one [1..1] id@nullFlavor="UNK"
   Presence of the identifier is required by the schema, but is not functionally required.
4. The timePointEventDefinition SHALL contain exactly one [1..1] code@code (CodeSystem = Element Code Local)
   A code to indicate the nature of the element. For the element in arm, the value is used as reference to the parent element.
   [SDTM: ETCD]
5. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode="PRCN"
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code="X" (
      The checkpoint code "X" indicates the criterion is evaluated at the point the element is exited.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode="OBS"
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode="CRT"
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is a branching rule applying to the element's presence in the arm.
      iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type="ED"
      v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType="text/plain"
      vi. The timePointEventCriterion SHALL contain exactly one {1..1] value
      A rule describing the condition that, during the performance of the element, would lead a subject to be assigned to this arm of the study..
      [SDTM: TABRANCH]
6. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode="PRCN"
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code="E" (
      The checkpoint code "E" indicates the criterion is evaluated at the point that the activities within the element end.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode="OBS" "
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode="CRT"
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is an element performance rule.

iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type=”ED”
v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType=”text/plain”
vi. The timePointEventCriterion SHALL contain exactly one {1..1] value
A rule describing the next element to be performed for the subject.
[SDTM: TATRANS]

7. The timePointEventDefinition MAY contain exactly one {1..1componentOf1
   a. The componentOf1 SHALL contain exactly one {1..1] @typeCode=”COMP”
   b. The componentOf1 SHALL contain exactly one {1..1] epochReference
      i. The epochReference SHALL contain exactly one {1..1] @classCode=”ACT”
      ii. The epochReference SHALL contain exactly one {1..1] @moodCode=”EVN”
      iii. The epochReference SHALL contain exactly one [1..1] id@nullFlavor=”NI”
      iv. The epochReference SHALL contain exactly one [1..1] id@extension
      The extension includes the identifier assigned to the epoch for the element.
8. The timePointEventDefinition MAY contain exactly one {1..1componentOf2
   a. The componentOf2 SHALL contain exactly one {1..1] @typeCode=”COMP”
   b. The componentOf2 SHALL contain exactly one {1..1] sequenceNumber
      The sequence number indicates the order of the element within the arm.
      [SDTM: TAETORD]
   c. The componentOf2 SHALL contain exactly one {1..1] armReference
      i. The armReference SHALL contain exactly one {1..1] @classCode=”ACT”
      ii. The armReference SHALL contain exactly one {1..1] @moodCode=”EVN”
      iii. The armReference SHALL contain exactly one [1..1] id@nullFlavor=”NI”
      iv. The armReference SHALL contain exactly one [1..1] id@extension
      The extension includes the identifier assigned to the arm for the element.

5.3.6 Study Visit Definition

Visits are defined for a study as a way of grouping elements and activities within elements for performance by participants within the study or the study subject. The CDISC glossary notes that a visit is “A clinical encounter for a subject in a trail. Visits are frequently referred to as occurring on Day X or during Week Y; there may be gaps between visits, which can take place within an epoch or span an epoch.”[8] Note, a visit does not have to be a face to face encounter, but could be a telephone call. The template id for the data structure is: FDAroot.xx.yy.08.

Its contents are specified as follows:

1. The timePointEventDefinition SHALL contain exactly one [1..1] @classCode=”CTTEVENT”
2. The timePointEventDefinition SHALL contain exactly one [1..1] @moodCode=”DEF”
3. The timePointEventDefinition SHALL contain exactly one [1..1] id@nullFlavor=”UNK”
   The identifier is only used to provide references within the content of the study design document. A root OID to provide global uniqueness is not needed
4. The timePointEventDefinition SHALL contain exactly one [1..1] id@extension
   The extension value shall be an integer, and shall be unique within the document. It is used to identify a particular visit.
   [SDTM: VISITNUM]
5. The timePointEventDefinition SHALL contain exactly one [1..1] code@code =”visit”(CodeSystem = Element Code Local)

[8] Glossary: Clinical Trails Terminology Version 2.0, CDISC. www.lau.edu.lb/chsr/forms/clinical_trials_terminology_glossary.pdf.

A code value is needed to indicate the time point event definition refers to a visit as opposed to a particular element.

6. The timePointEventDefinition MAY contain zero to one [0..1] title@mediaType="textPlan"
7. The timePointEventDefinition MAY contain zero to one [0..1] title
   The title contains a text description of the visit.
   [SDTM: VISIT]
8. The timePointEventDefinition SHALL contain one to many [1..*] component2
   a. The component2 SHALL contain exactly one {1..1] @typeCode="COMP"
   b. The component2 SHALL contain exactly one [1..1] timePointEventDefinition
      Information on a visit's positioning within a particular study arm. Visit in Arm information is defined within Template ID = FDAroot.xx.yy.09.
9. The timePointEventDefinition MAY contain zero to one [0..1] subjectOf
   a. The subjectOf SHALL contain exactly one {1..1] @typeCode="SUBJ"
   b. The subjectOf SHALL contain exactly one {1..1] timePointEventCharacteristic
      i. The timePointEventCharacteristic SHALL contain exactly one {1..1] @classCode="OBS"
      ii. The timePointEventCharacteristic SHALL contain exactly one {1..1] @moodCode="EVN"
      iii. The timePointEventCharacteristic SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is a planned study day for the visit.
      iv. The timePointEventCharacteristic SHALL contain exactly one {1..1] value@xsi:type="INT"
      v. The timePointEventCharacteristic SHALL contain exactly one {1..1] value@value
      The planned study day for the visit.
      [SDTM: VISTDY]

5.3.7 Visit in Arm

A visit defines a contact or group of contacts with the study subject. However, the rules associated with a visit may vary depending on the arm a subject is assigned to. The visit in arm structure supports the representation of these rules. The template id for the data structure is: FDAroot.xx.yy.09.

Its contents are specified as follows:

1. The timePointEventDefinition SHALL contain exactly one [1..1] @classCode="CTTEVENT"
2. The timePointEventDefinition SHALL contain exactly one [1..1] @moodCode="DEF"
3. The timePointEventDefinition SHALL contain exactly one [1..1] id@extension
   The extension contains the same value of VISITNUM as does the "parent" visit.
4. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode="PRCN"
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code="B" ()
      The checkpoint code "B" indicates the criterion is to be evaluated at the beginning of the visit.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode="OBS"
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode="CRT"
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = "CXXXXX" (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is a performance rule applying to the visit's presence in the arm.
      iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type="ED"

v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType=”text/plain”
vi. The timePointEventCriterion SHALL contain exactly one {1..1] CONTENT
Indicate the element during which the visit starts (make this code An ETCD value)..
[SDTM: TVSTRL]

5. The timePointEventDefinition MAY contain zero to one [0..1] precondition
   a. The precondition SHALL contain exactly one {1..1] @typeCode=”PRCN”
   b. The precondition SHALL contain exactly one {1..1] checkpointCode@code=”E” (
   The checkpoint code “E” indicates the criterion is evaluated at the point that the activities within the visit end.
      i. The timePointEventCriterion SHALL contain exactly one {1..1] @classCode=”OBS”
      ii. The timePointEventCriterion SHALL contain exactly one {1..1] @moodCode=”CRT”
      iii. The timePointEventCriterion SHALL contain exactly one {1..1] code@code = “CXXXXX” (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
      The code value indicates the observation is a visit performance rule.
      iv. The timePointEventCriterion SHALL contain exactly one {1..1] value@xsi:type=”ED”
      v. The timePointEventCriterion SHALL contain exactly one {1..1] value@mediaType=”text/plain”
      vi. The timePointEventCriterion SHALL contain exactly one {1..1] CONTENT
      The element during which the visit ends –if different from the start one.
      [SDTM: TVENRL]
6. The timePointEventDefinition MAY contain exactly one {1..1componentOf2
   a. The componentOf2 SHALL contain exactly one {1..1] @typeCode=”COMP”
   b. The componentOf2 SHALL contain exactly one {1..1] armReference
      i. The armReference SHALL contain exactly one {1..1] @classCode=”ACT”
      ii. The armReference SHALL contain exactly one {1..1] @moodCode=”EVN”
      iii. The armReference SHALL contain exactly one [1..1] id@nullFlavor=”NI”
      iv. The armReference SHALL contain exactly one [1..1] id@extension
      The extension includes the identifier assigned to the arm for the visit.

5.3.8 Study Characteristic

The design for a study includes a number of relevant items that are customarily carried as a collection of name value pairs within the SDTM Trial Summary domain. Some of this information – that which can be directly modeled within the Study Design Structured Document structure – is carried elsewhere in the implementation guide. The rest is captured as a collection of study characteristics. The template id for the data structure is: FDAroot.xx.yy.10.

Its contents are specified as follows:

1. The studyCharacteristic SHALL contain exactly one [1..1] @classCode=”OBS”
2. The studyCharacteristic SHALL contain exactly one [1..1] @moodCode=”EVN”
3. The studyCharacteristic SHALL contain exactly one [1..1] code@code =””(CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
   A code to indicate the nature of the study characteristic. Note, it is expected that a predefined set of study characteristic types will be used.
   [SDTM: TSPARMCD]
4. The studyCharacteristic SHALL contain exactly one [1..1] code@displayText
   A text description of the characteristic
   [SDTM: TSPARM]

5. The studyCharacteristic SHALL contain exactly one [1..1] value
   The content of the characteristic. The data type to be used will vary with the nature of the characteristic.

5.3.9 Study Eligibility Criterion

Definition of the criteria for enrolling subjects is a feature of many study designs. These criteria are captured as eligibility criteria. The template id for the data structure is: FDAroot.xx.yy.11.

Its contents are specified as follows:

1. The eligibilityCriterion SHALL contain exactly one [1..1] @classCode="OBS"
2. The eligibilityCriterion SHALL contain exactly one [1..1] @moodCode="CRT"
3. The eligibilityCriterion MAY contain zero to one [0..1] id@nullFlavor="UNK"
   The identifier is only used to provide references within the content of the study design document. A root OID to provide global uniqueness is not needed
4. The eligibilityCriterion MAY contain zero to one [0..1] id@extension
   An identifier is needed when a criterion is a replacement of a previous criteria or criterion. In this case, the identifier will be used to indicate the version of the criterion.
   [SDTM: TIVERS]
5. The eligibilityCriterion SHALL contain exactly one [1..1] code@code =""(CodeSystem Local)
   A code to indicate the nature of the eligibility criterion.
   [SDTM: IETESTCD]
6. The eligibilityCriterion SHALL contain exactly one [1..1] code@displayText
   A text description of the criterion.
   [SDTM: IETST]
7. The eligibilityCriterion SHALL contain exactly one [1..1] value@xsi:Type="ED"
8. The eligibilityCriterion SHALL contain exactly one [1..1] value@mediaType="text/plan"
9. The eligibilityCriterion SHALL contain exactly one [1..1] value CONTENT
   The content of the criterion. Since the criteria are defined locally, it is assumed that text data will be uniformly provided.
10. The eligibilityCriterion SHALL contain exactly one [1..1] valueNegationIndicator@value
    Indicates whether the criterion provides rules for including or for excluding study subjects. If Negation = True, it is an exclusion indicator. If Negation = False, it is an inclusion indicator.
    [SDTM: IECAT (we assume that IECAT is restricted to only take on the values inclusion and exclusion.)]
11. The eligibilityCriterion MAY contain zero to many [0..*] replacementOf
    The structure supports the possibility that an amended study may designate one or more eligibility criteria as replacements for a previous one.
    a. The replacementOf SHALL contain exactly one [1..1] @typeCode="RPLC"
    b. The replacement Of SHALL contain exactly one [1..1] eligibilityCriterion.
       Information on inclusion and exclusion criteria for the study. Template ID = FDAroot.xx.yy.11

5.3.10 Study Sponsor Vocabulary

Many of the coded items that are included within subject data reports draw their values from locally defined value sets. [Such a value set may or may not draw its values from a standard code system, although the likelihood is that the code system will be sponsor defined as well.] This information is currently carried in a separate file known as define.xml. This structure makes it possible to define as many value sets as needed, and to include the allowable values for each. The template id for the data structure is: FDAroot.xx.yy.14.

Its contents are specified as follows:

1. The organizer SHALL contain exactly one [1..1] @classCode="CLUSTER"
2. The organizer SHALL contain exactly one [1..1] @moodCode="DEF
1. The organizer SHALL contain exactly one [1..1] code@code =”” “” (CodeSystem 2.16.840.1.113883.3.26.1.1 NCI Thesaurus)
   A code that indicates the nature of the value set. Section A.4.3 provides a list of the locally defined value sets currently recognized for human subject data reporting.
2. The organizer SHALL contain exactly one [1..1] code@displayName
   A text description of the locally defined valueset]

3. The organizer SHALL contain one to many [1..*] component
   a. The component SHALL contain exactly one [1..1] @typeCode="COMP"
   a. The component SHALL contain exactly one [1..1] observation
      Each observation contains a single member of the value set.
      i. The observation SHALL contain exactly one [1..1] @classCode="OBS"
      ii. The observation SHALL contain exactly one [1..1] @moodCode="DEF
      iii. The observation SHALL contain exactly one [1..1] value@xsi:type="CD"
      iv. The observation SHALL contain exactly one [1..1] value@code
          A code value defined within the local value set.
      v. The observation SHALL contain exactly one [1..1] value@displayName
         The text name associated with the code.
      vi. The observation SHALL contain exactly one [1..1] value@codeSystem
          Use the code system OID for the locally defined value set as provided above.

A Appendices

A.1: Templates

The following templates are referred to within this document. Templates have been created as a way of partitioning the definition of the document. In addition, use of templates greatly eases the task of creating this content within tooling designed for capturing CDA specifications, e.g., the MDHT tooling. Also, template identifiers in document instances may be required for some implementers.

Template ID	Name
FDAroot.xx.yy.01[9]	Study Design Structured Document
FDAroot.xx.yy.02	Study Design Structured Document Body
FDAroot.xx.yy.03	Study Epoch Definition
FDAroot.xx.yy.04	Study Arm Definition
FDAroot.xx.yy.05	Study Substance
FDAroot.xx.yy.06	Study Element Definition
FDAroot.xx.yy.07	Element in Arm
FDAroot.xx.yy.08	Study Visit Definition
FDAroot.xx.yy.09	Visit in Arm

[9] The object identifier for a template needs to be created as an FDA assigned OID. For convenience it is reasonable to include a value used to prefix all templates, and a second value to indicate study design templates.

Template ID	Name
FDAroot.xx.yy.10	Study Characteristic
FDAroot.xx.yy.11	Study Eligibility Criterion

A.2: Identifiers

Identifier	Default Namespace	Comment
Document ID, set ID	FDAroot.xx.zz.01	
Represented Organization ID	FDAroot.xx.zz.02	
Epoch ID	Unnecessary	Used for reference within the document.
Arm ID	Unnecessary	Used for reference within the document.
Element ID	FDAroot.xx.zz.03	Only used for visits. Provides a reference between the study design and reported subject data
Eligibility Criterion ID	Unnecessary	Used for reference within the document.

A.3: Vocabulary: Act Codes

Any HL7 Version 3 structure uses generic classes within HL7's RIM to represent more specific concepts that are relevant to it. This Implementation Guide uses specific act code assignments – most of these are observations – to clarify the structure of the document, but also – more specifically – to convey items that are modeled generically within the CDISC implementation guide. These code values are documented below.

A3.1 Structural Code Values

There are several places within the study design data structure in which a specific code value needs to be assigned to clarify the meaning of an act or observation. Each of these has been defined within NCI EVS, and provided with a concept ID. Here is a list of those code values.

Structural Code Values		
Attribute	**Concept ID**	**Class within the IG**
Act.code		Document (indicates a human clinical study design)
Act.code		Document Section (indicates the structured data for a human clinical study design)
Act.code		Epoch
Act.code		Arm
Observation.code		Time Point Event Criterion
Observation code		Planned Study Day (for a visit)

A3.2 Study Characteristic Code Values

A number of important information items for the study are carried within generic observation based structures within this guide. Creation of this list of value sets both reflects the design created by CDISC, and the fact that creating specific models for a disparate range of important information items can become a burdensome way to model the necessary data. The list below includes those code values that have been created to define salient features of the study – modeled in the Study Characteristic template. In some cases, the data item is supported directly within the Study Design Structured Document structure to facilitate processing by receivers. Over time, more of the content may move into this area.

Here is a list of the code values used to define Study Characteristic.[10]

Study Characteristic Code Values					
Description	**Concept ID**	**Data Type**	**Value Set**	**IG Placement**	**Comment**
Adaptive Design	C98704	ED		Study Characteristics	Indicate if the study includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study.
Added on to Existing Treatment	C49703	BL		Study Characteristics	The addition of a therapeutic product to the existing regimen in a clinical trial, where both entities remain as discrete products.
Age		PQ		Study Characteristic	Age and age unit will be captured as a single item.
Age Span	C66738	CD		Study Characteristic	
Age Unit		PQ		Study Characteristic	Age and age unit will be captured as a single item.
Clinical Study Sponsor	C70793	ED		Header	
Comparative Treatment Name	C68612	ED		Study Characteristic	A therapeutically active agent that is intended to provide reference measurements for the experimental protocol of a clinical trial. (could be managed as a study substance)
Confirmed Response Minimum Duration	C98715	PQ		Study Characteristic	The protocol specified minimum amount of time needed to meet the definition of a confirmed response to treatment.
Control Type	C49647	CD	Study Control Type	Study Characteristic	Comparator against which the study treatment is evaluated (e.g., concurrent (placebo, no treatment, dose-response, active), external (historical, published literature).
Current Therapy or Treatment	C85582	CD	Substance Code	Study Substance	The literal identifier of the therapy or medication that is currently being given per protocol. This does not include treatment that has been given in the past. (Does this belong in Subject Data?)
Diagnosis Group	C49650	CD	Diagnosis Type	Study Characteristic	Note, this could be modeled directly as an eligibility criterion.
Dose per administration	C25488	PQ		Study Substance	Dose and unit are captured as a single item.
Dose Units	C73558	PQ		Study Substance	Dose and unit are captured as a single item.

[10] The content of the table is drawn from 7.63 Trial Summary Codes, Standard for Exchange of Nonclinical Data Implementation Guides: Nonclinical Studies, CDISC, 2011

Study Characteristic Code Values					
Description	**Concept ID**	**Data Type**	**Value Set**	**IG Placement**	**Comment**
Dosing Frequency	C89081	PIVL<TS>		Study Substance	
Existing Treatment Addition	C49703	CD	Treatment Addition Type	Study Characteristic	
Exploratory Outcome Measure	C98724	ED		Study Characteristic	Exploratory measures that will be used to evaluate the intervention(s) or, for observational studies, that are exploratory of the study.
Healthy Subject Indicator	C98737	BL		Study Characteristic	Indicate if persons who have not had the condition(s) being studied or otherwise related conditions or symptoms, as specified in the eligibility requirements, may participate in the study.
Intervention Model	C98746	ED		Study Characteristic	The trial design developed to compare treatment groups.
Intervention Type	C98747	ED		Study Characteristic	The kind of product or procedure studied in a trial.
Investigational Therapy or Treatment	C41161	ED		Study Substance	
Planned Maximum Age of Subjects	C49694	PQ		Study Characteristic	Age and age unit will be captured as a single item. This could be captured as an eligibility characteristic.
Planned Minimum Age of Subjects	C49693	PQ		Study Characteristic	Age and age unit will be captured as a single item. This could be captured as an eligibility characteristic.
Pharmacological Class of Investigational Therapy	C98768	CD		Study Substance	
Planned Number of Arms	C98771	INT		Study Characteristic	The planned number of intervention groups.
Planned Number of Subjects	C49692	INT		Structured Section; Record Target	
Primary Outcome Measure	C98772	ED		Study Characteristic	The primary measurement(s) or observation(s) used to measure the effect of experimental variables in a study, or for observational studies, to describe patterns of diseases or traits or associations with exposures, risk factors or treatment. These are the outcome measures used to assess the primary objective(s).
Randomization Character		CD	Randomization Type	Study Characteristic	Indicates the manner of randomization.

Study Characteristic Code Values					
Description	**Concept ID**	**Data Type**	**Value Set**	**IG Placement**	**Comment**
Randomization Quotient	C98775	INT		Study Characteristic	The randomization quotient is the number of planned subjects to be exposed to investigational therapy, independent of dose or other factors, divided by the total number of planned subjects.
Registry Identifier	C98714	II		Header	Identification numbers assigned to the protocol by ct.gov, EudraCT, or other registries.
Route of Administration	C38114	CD	Route of Administration	Study Substance	
Secondary Outcome Measure	C98781	ED		Study Substance	Other key measures that will be used to evaluate the intervention(s) or, for observational studies, that are a focus of the study. These are the outcome measures used to assess the secondary objective(s).
Sex of Participants	C49696	CD	Sex of Participants Type	Study Characteristic	Note, this could be modeled directly as an eligibility criterion.
Stable Disease Minimum Duration	C98783	PQ		Study Characteristic	The protocol specified minimum amount of time needed to meet the definition of stable disease.
Study Stop Rules	C49698	CD	Stop Rule Type	Study Characteristic	
Study Type	C15320	ED		Study Characteristic	Describes the role the study plays in determining the interventions a subject receives.
Trial Blinding Schema	C49658	CD	Blinding Schema Type	Study Characteristic	
Trial Indication	C41184	ED		Study Characteristic	The basis for initiation of a treatment for a disease or of a diagnostic test (causal, or symptomatic, or disease-specific indication).
Trial Indication Type	C49652	CD	Indication Type	Study Characteristic	The name of a code list that contains terms to define the type of trial, e.g. cure or prevention. (NCI)
Trial is Randomized	C25196	ED		Study Characteristic	This appears to be a description as opposed to a Boolean indicator.
Trial Length		PQ		Study Characteristic	The expected duration of a subject's participation in the trial.
Trial Phase Classification	C48281	CD	Trial Phase Type	Study Characteristic	
Trial Primary Objective	C85826	ED		Study Characteristic	This may become a controlled list.
Trial Secondary Objective	C85827	ED		Study Characteristic	This may become a controlled list.
Trial Title	C49802	ED		Header	

Study Characteristic Code Values					
Description	**Concept ID**	**Data Type**	**Value Set**	**IG Placement**	**Comment**
Trial Type	C49660	CD	Trial Type	Study Characteristic	The type of clinical trial performed e.g. efficacy, safety. (NCI)

A.4 Vocabulary: Value Sets

Submission of a study design includes a number of coded elements – elements whose values are drawn from defined value set. These are organized into three categories:

- HL7 Defined
- Centrally Defined
- Sponsor Defined.

A.4.1 HL7 Defined Value Sets

These value sets are defined by the Health Level 7 Organization. For the most part they function as structural elements within the document structure. A few additional value sets provide general codes to define the context of the report.

HL7 Defined Value Sets			
Value Set Name	**Description**	**Local?**	**OID & Source**
ActClass	The set of valid act types defined by HL7.[11]	No	2.16.840.1.113883.5.6 HL7
ActMood	The set of valid act moods defined by HL7.		2.16.840.1.113883.5.1001 HL7
ParticipationType	The set of valid participation types (associations between an act and a role) defined by HL7.	No	2.16.840.1.113883.5.90 HL7
ActRelationshipType	The set of valid act relationship types (associations between two acts) defined by HL7.	No	2.16.840.1.113883.5.1002 HL7
RoleClass	The set of valid role types defined by HL7.	No	2.16.840.1.113883.5.110
EntityClass	The set of valid entity types defined by HL7.	No	2.16.840.1.113883.5.41 HL7
EntityDeterminer	The set of valid entity determiner values defined by HL7.	No	2.16.840.1.113883.5.30 HL7
Confidentiality	The set of values used to control disclosure of information.	No	2.16.840.1.113883.5.25 HL7
Language	The set of valid language codes maintained by ISO	No	1.0.639.3 ISO
HL7 Realm	The list of HL7 affiliate countries used to define the expected usage of the implementation guide.	No	2.16.840.1.113883.5.1124 HL7
Act Relationship Checkpoint	A set of codes used to indicate when, during the course of an act's performance, to check a rule that will be used to determine the next step in processing	No	2.16.840.1.113883.5.10

[11] Refer to documentation of the HL7 Reference Information Model for more information on the HL7 "structural codes. Implementers should note that these coded elements use the data type CS, and that code system information does not need to be included within a document instance.

A.4.2 Centrally Defined Value Sets

These value sets are defined centrally for use by all submitters of this Implementation Guide. They cover key concepts for which generally agreed upon codes have been created. The use of centrally defined value sets make it easier to process the data, and to compare the design of studies generated by different sponsors. The codes within these value sets are maintained within the NCI EVS. Note, a single OID – that which identifies the NCI Thesaurus is used for each of these value sets. In a document instance, the value that is passed will be an NCI concept ID. For conformance purposes, that value should be tested to ensure it is a member of the set of concepts that is valid within the named value set.

Centrally Defined Value Sets			
Value Set Name	**Concept ID**	**Description**	**OID & Source**
Units of Measure		A unit, whether of time, mass or other physical quantity that is required to add context to a measure.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Route of administration		The path taken by an administered substance to get into the body, or to come in contact with the body	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Study Characteristic		A set of codes to define possible relevant characteristics of a study. (aka trial summary parameter)	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Study Component Rule		A set of rules that specify, at least, the rules for initiating or ending an element, for branching from one element to another, or for initiating or ending a visit.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Treatment Addition Type		A set of types of treatment that may be added on to existing treatments	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Age Group Type		A set of age groupings used to organize age ranges into categories.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Randomization Type	C66742	A set of methods for randomizing the treatment of subjects within a study.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Sex of Participants Type	C66732	The collection of different combinations of sex that would be eligible to be study subjects. (*Can Administrative Gender be used?*)	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Stop Rule Type		The set of rules that define the conditions under which a study will be stopped.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Blinding Schema Type	C66735	The set of methods by which a study is blinded.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Indication Type	C66736	The set of different indications for providing mitigation of the adverse effect of a study treatment.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Study Control Type	C66785	A set of different roles that a group of subjects may perform as controls within a study. E.g., vehicle control, positive control	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Diagnosis Type	C66787	A set of diagnoses that may appear as indications for enrollment in a study.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Trial Phase Type	C66737	A set of values that describe the different phases of a trial.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Trial Type	C66739	A set of values that define the possible types of study.	2.16.840.1.113883.3.26.1.1 NCI Thesaurus
Pharmaceutical Class		The collection of drug classes that are used to characterize the study treatment	2.16.840.1.113883.3.26.1.1 NCI Thesaurus

A.4.3 Locally Defined Value Sets

In an ideal world, all the value sets used for study design would be shared across all study sponsors. However, the wide range of circumstances in which studies take place, as well as the different histories of the organizations carrying out studies make that impractical. This table lists those value sets that are locally defined. For each, the sponsor needs to define the allowable values, and to provide that set of values along with the submitted study design.

Locally Defined Value Sets		
Value Set Name	**Description**	**OID**
Substance Code	A set of codes for possible substances to be administered to the study subject	
Study Element	A set of codes for the elements cited within the planned study	
Eligibility Criteria	A set of codes to define criteria to be used for either including or excluding a subject from participation in a study	
Study Time Point	A set of codes that defines the building blocks of a study. These building blocks include the different types of element as well as the concept of a visit.	

A.4.4 Subject Data Locally Defined Value Sets

The table provides a list of locally defined value sets. These are value sets needed for evaluating coded values within subject data reports, which are defined by the study sponsor since no generally agreed upon and maintained set of values exists.

The list of the value sets that need definition to fully support subject data reporting is included within the Subject Data Implementation Guide.

A.4 Sample Messages

A sample message has been devised that uses a publicly available data set to illustrate the content of this guide.


```
<?xml version="1.0" encoding="UTF-8"?>
<Document xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns="urn:hl7-org:v3"
xmlns:ctm="http://clinicalTrialMaterial" xsi:schemaLocation="urn:hl7-org:v3 ../StudyDesignSchemas/StudyDesign.xsd"
classCode="DOCCLIN" moodCode="EVN">
	<!-- this sample message is drawn from a public SDTM  dataset - study1_sdtm_define -->
	<realmCode code="US"/>
	<typeId root="2.16.840.1.113883.1.3" extension="POCD_HD000040"/>
	<templateId root="2.16.840.1.113883.10.20.25.1"/>
	<id nullFlavor="UNK" extension="STUDY1"/>
	<code code="TBD" codeSystem="2.16.840.1.113883.6.1" codeSystemName="LOINC"/>
	<title>A 29 Day, Placebo Washout, Double Blind Randomization, Dose Escalation, Randomized Washout,
Placebo or continued active treatment,</title>
	<effectiveTime value="20120704"/>
	<confidentialityCode code="N" codeSystem="2.16.840.1.113883.5.25"/>
	<languageCode/>
	<setId nullFlavor="UNK" extension="2388747"/>
	<versionNumber>1</versionNumber>
	<responsibleParty typeCode="RESP">
		<assignedEntity classCode="ASSIGNED">
			<representedOrganization classCode="ORG" determinerCode="INSTANCE">
				<id nullFlavor="UNK" extension="GSB234455"/>
				<!-- This information does not appear in the sample SDTM data set.  -->
			</representedOrganization>
		</assignedEntity>
	</responsibleParty>
	<!-- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
		Unstructured Text Content - to handle text protocol material
		 The sample content does not include the text material for the protocol.
		 XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX-->
	<component typeCode="COMP">
		<structuredBody classCode="DOCBODY" moodCode="EVN">
			<!--   XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
	   The Planned Study Content is here.
	   XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX -->
			<component typeCode="COMP">
				<section classCode="DOCSECT" moodCode="EVN">
					<code code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1"
codeSystemName="NCI Thesaurus"/>
					<title>Planned Study Section</title>
					<text>Autogenerated Text Goes here</text>
					<subject typeCode="SUBJ">
						<plannedStudy classCode="CLNTRL" moodCode="DEF">
							<!--  XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
							The sample does not include inclusion/exclusion information
							  XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX -->
							<!-- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
									Epoch Information
									XXXXXXXXXXXXXXXXXXXXXXXXXXXXX-->
							<component1 typeCode="COMP">
								<epoch classCode="ACT" moodCode="DEF">
									<id nullFlavor="UNK" extension="1"/>
									<!-- The ID is assigned to serve as a pointer
later. -->
```

```
                                        <code code="xxx" displayName="PLACEBO
WASHOUT" codeSystem="1.22.3.1"/>
                                    </epoch>
                                </component1>
                                <component1 typeCode="COMP">
                                    <epoch classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="2"/>
                                        <code code="xxx" displayName="DOUBLE
BLIND" codeSystem="1.22.3.1"/>
                                    </epoch>
                                </component1>
                                <component1 typeCode="COMP">
                                    <epoch classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="3"/>
                                        <code code="xxx"
displayName="RANDOMIZED WASHOUT" codeSystem="1.22.3.1"/>
                                    </epoch>
                                </component1>
                                <!-- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
                                        Arm Information

        XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="1"/>
                                        <!-- The ID is assigned to serve as a pointer
later. -->
                                        <code code="HIGHHIGH"
displayName="HIGHDOSE/HIGHDOSE" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="2"/>
                                        <code code="HIGHPBO"
displayName="HIGHDOSE/PLACEBO" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="3"/>
                                        <code code="LOWLOW"
displayName="LOWDOSE/LOWDOSE" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="4"/>
                                        <code code="LOWPBO"
displayName="LOWDOSE/PLACEBO" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
                                        <id nullFlavor="UNK" extension="5"/>
                                        <code code="MIDDMIDD"
displayName="MIDDLEDOSEDOSE/MIDDLEDOSE" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <component2 typeCode="COMP">
                                    <arm classCode="ACT" moodCode="DEF">
```

```
                                        <id nullFlavor="UNK" extension="6"/>
                                        <!-- The ID is assigned to serve as a pointer
later. -->
                                        <code code="MIDDPBO"
displayName="MIDDLEDOSE/PLACEBO" codeSystem="1.22.3.2"/>
                                    </arm>
                                </component2>
                                <!-- XXXXXXXXXXXXXXXXXXXXXXXXXXX
                                    Study Substance Information -
                                    In SDTM  terms, this is drawn from the Trial Summary
domain.
                                  XXXXXXXXXXXXXXXXXXXXXXXXXXXX -->
                                <component3 typeCode="COMP">
                                    <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                        <effectiveTime xsi:type="PIVL_TS">
                                            <period value="1" unit="day"/>
                                        </effectiveTime>
                                        <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                        <doseQuantity value="0.625" unit="mg"/>
                                        <consumable typeCode="CSM" xsi:nil="true"/>
                                    </substanceAdministration>
                                </component3>
                                <component3 typeCode="COMP">
                                    <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                        <effectiveTime xsi:type="PIVL_TS">
                                            <period value="1" unit="day"/>
                                        </effectiveTime>
                                        <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                        <doseQuantity value="1.25" unit="mg"/>
                                        <consumable typeCode="CSM" xsi:nil="true"/>
                                    </substanceAdministration>
                                </component3>
                                <component3 typeCode="COMP">
                                    <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                        <effectiveTime xsi:type="PIVL_TS">
                                            <period value="1" unit="day"/>
                                        </effectiveTime>
                                        <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                        <doseQuantity value="2.5" unit="mg"/>
                                        <consumable typeCode="CSM" xsi:nil="true"/>
                                    </substanceAdministration>
                                </component3>
                                <component3 typeCode="COMP">
                                    <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                        <effectiveTime xsi:type="PIVL_TS">
                                            <period value="1" unit="day"/>
                                        </effectiveTime>
                                        <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                        <doseQuantity value="5" unit="mg"/>
                                        <consumable typeCode="CSM" xsi:nil="true"/>
                                    </substanceAdministration>
                                </component3>
                                <component3 typeCode="COMP">
```

```
                                        <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                            <effectiveTime xsi:type="PIVL_TS">
                                                <period value="1" unit="day"/>
                                            </effectiveTime>
                                            <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                            <doseQuantity value="10" unit="mg"/>
                                            <consumable typeCode="CSM" xsi:nil="true"/>
                                        </substanceAdministration>
                                    </component3>
                                    <component3 typeCode="COMP">
                                        <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                            <effectiveTime xsi:type="PIVL_TS">
                                                <period value="1" unit="day"/>
                                            </effectiveTime>
                                            <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                            <doseQuantity value="20" unit="mg"/>
                                            <consumable typeCode="CSM" xsi:nil="true"/>
                                        </substanceAdministration>
                                    </component3>
                                    <component3 typeCode="COMP">
                                        <substanceAdministration classCode="SBADM"
moodCode="DEF">
                                            <effectiveTime xsi:type="PIVL_TS">
                                                <period value="1" unit="day"/>
                                            </effectiveTime>
                                            <routeCode code="xxxx" displayName="ORAL"
codeSystem="1.22.3.3"/>
                                            <doseQuantity value="40" unit="mg"/>
                                            <consumable typeCode="CSM" xsi:nil="true"/>
                                        </substanceAdministration>
                                    </component3>
                                    <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                        Study Element Information
                                            [I have included the first six elements.]
                                            Element # 1
                                        XXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                    <component4 typeCode="COMP">
                                        <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                            <id nullFlavor="UNK"/>
                                            <code code="HWH1" displayName="High Dose
20mg D1-2" codeSystem="1.22.3.4"/>
                                            <effectiveTime xsi:type="IVL_TS">
                                                <width value="2" unit="day"/>
                                            </effectiveTime>
                                            <precondition typeCode="PRCN">
                                                <checkpointCode code="B"/>
                                                <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                                    <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                    <!-- Indicate that the observation
is an element performance rule. -->
                                                    <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind medication</value>
                                                </timePointEventCriterion>
                                            </precondition>
```

```
                                                    <precondition typeCode="PRCN">
                                                        <checkpointCode code="E"/>
                                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                            <!-- Indicate that the observation
is an element performance rule. -->
                                                            <value xsi:type="ED"
mediaType="text/plain">Prior to Dose Escalation Start</value>
                                                        </timePointEventCriterion>
                                                    </precondition>
                                                    <!-- xxxxxxxxxxxxxxxxxxxxxxxx
                                                            Element in Arm information
                                                             xxxxxxxxxxxxxxxxxxxxxxxx-->
                                                    <component2 typeCode="COMP">
                                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                            <id nullFlavor="NI"/>
                                                            <code code="HWH1"/>
                                                            <!-- Use the same ETCD value
as the element this is part of. -->
                                                            <precondition
typeCode="PRCN">
                                                                <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                                <value
xsi:type="ED" mediaType="text/plain">Dose Escalation to 40mg on Day 3 unless limited by as AE or excessive
hypotension</value>
                                                                <!-- What sort of
data type is used here?  It looks like text now. -->
        </timePointEventCriterion>
                                                            </precondition>
                                                            <componentOf1
typeCode="COMP">
                                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </epochReference>
                                                            </componentOf1>
                                                            <componentOf2
typeCode="COMP">
                                                                <sequenceNumber
value="22"/>
                                                                <!-- TAETORD.  Can
we rely on this being an integer?   No, we cannot, the sample has 2.2. -->
                                                                <armReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="1"/>
                                                                </armReference>
                                                            </componentOf2>
                                                        </timePointEventDefinition>
```

```
                                                    </component2>
                                                    <component2 typeCode="COMP">
                                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                            <id nullFlavor="NI"/>
                                                            <code code="HWH1"/>
                                                            <precondition
typeCode="PRCN">
                                                                <checkpointCode
code="E"/>

        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                    <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                                    <value
xsi:type="ED" mediaType="text/plain">Dose Escalation to 40mg on Day 3 unless limited by as AE or excessive
hypotension</value>

        </timePointEventCriterion>
                                                            </precondition>
                                                            <componentOf1
typeCode="COMP">
                                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </epochReference>
                                                            </componentOf1>
                                                            <componentOf2
typeCode="COMP">
                                                                <sequenceNumber
value="22"/>
                                                                <armReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </armReference>
                                                            </componentOf2>
                                                        </timePointEventDefinition>
                                                    </component2>
                                                </timePointEventDefinition>
                                            </component4>
                                            <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                                Study Element Information
                                                    Element # 2
                                                XXXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                            <component4 typeCode="COMP">
                                                <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                    <id nullFlavor="UNK"/>
                                                    <code code="HWH2" displayName="High Dose
40mg D3-14 E" codeSystem="1.22.3.4"/>
                                                    <effectiveTime xsi:type="IVL_TS">
                                                        <width value="12" unit="day"/>
                                                    </effectiveTime>
                                                    <precondition typeCode="PRCN">
                                                        <checkpointCode code="B"/>
                                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
```

```
                                        <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        <!-- Indicate that the observation
is an element performance rule. -->
                                        <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind Dose Escalation</value>
                                    </timePointEventCriterion>
                                </precondition>
                                <precondition typeCode="PRCN">
                                    <checkpointCode code="E"/>
                                    <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                        <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        <!-- Indicate that the observation
is an element performance rule. -->
                                        <value xsi:type="ED"
mediaType="text/plain">Prior to Randomized Washout dose start</value>
                                    </timePointEventCriterion>
                                </precondition>
                                <!-- xxxxxxxxxxxxxxxxxxxxxxxxx
                                        Element in Arm information
                                         xxxxxxxxxxxxxxxxxxxxxxxxx-->
                                <component2 typeCode="COMP">
                                    <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                        <id nullFlavor="NI"/>
                                        <precondition
typeCode="PRCN">
                                            <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                <value
xsi:type="ED" mediaType="text/plain">Randomization at the end of day 14: RW High Dose 40 mg E</value>
        </timePointEventCriterion>
                                        </precondition>
                                        <componentOf1
typeCode="COMP">
                                            <epochReference
classCode="ACT" moodCode="DEF">
                                                <id
nullFlavor="NI" extension="2"/>
                                            </epochReference>
                                        </componentOf1>
                                        <componentOf2
typeCode="COMP">
                                            <sequenceNumber
value="32"/>
                                            <armReference
classCode="ACT" moodCode="DEF">
                                                <id
nullFlavor="NI" extension="1"/>
                                            </armReference>
                                        </componentOf2>
                                    </timePointEventDefinition>
```

```
                                                    </component2>
                                                    <component2 typeCode="COMP">
                                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                            <id nullFlavor="NI"/>
                                                            <code code="HWH2"/>
                                                            <precondition
typeCode="PRCN">
                                                                <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                    <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                                    <value
xsi:type="ED" mediaType="text/plain">Randomization at the end of day 14. RW Placebo</value>
        </timePointEventCriterion>
                                                            </precondition>
                                                            <componentOf1
typeCode="COMP">
                                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </epochReference>
                                                            </componentOf1>
                                                            <componentOf2
typeCode="COMP">
                                                                <sequenceNumber
value="32"/>
                                                                <armReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </armReference>
                                                            </componentOf2>
                                                        </timePointEventDefinition>
                                                    </component2>
                                                </timePointEventDefinition>
                                            </component4>
                                            <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                                Study Element Information
                                                    Element # 3
                                                XXXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                            <component4 typeCode="COMP">
                                                <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                    <id nullFlavor="UNK"/>
                                                    <code code="HWL1" displayName="High Dose
10mg D1-2 E" codeSystem="1.22.3.4"/>
                                                    <effectiveTime xsi:type="IVL_TS">
                                                        <width value="2" unit="day"/>
                                                    </effectiveTime>
                                                    <precondition typeCode="PRCN">
                                                        <checkpointCode code="B"/>
                                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
```

```
                                        <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        <!-- Indicate that the observation
is an element performance rule. -->
                                        <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind medication</value>
                                    </timePointEventCriterion>
                                </precondition>
                                <precondition typeCode="PRCN">
                                    <checkpointCode code="E"/>
                                    <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                        <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        <!-- Indicate that the observation
is an element performance rule. -->
                                        <value xsi:type="ED"
mediaType="text/plain">Prior to Dose Escalation Start</value>
                                    </timePointEventCriterion>
                                </precondition>
                                <!-- xxxxxxxxxxxxxxxxxxxxxxxxx
                                        Element in Arm information
                                         xxxxxxxxxxxxxxxxxxxxxxxxx-->
                                <component2 typeCode="COMP">
                                    <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                        <id nullFlavor="NI"/>
                                        <code code="HWL1"/>
                                        <precondition
typeCode="PRCN">
                                            <checkpointCode
code="E"/>
                                            <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                <value
xsi:type="ED" mediaType="text/plain">Dose escalation to 20mg on Day 3 unless limited by as AE or excessive
hypotension</value>
                                            </timePointEventCriterion>
                                        </precondition>
                                        <componentOf1
typeCode="COMP">
                                            <epochReference
classCode="ACT" moodCode="DEF">
                                                <id
nullFlavor="NI" extension="2"/>
                                            </epochReference>
                                        </componentOf1>
                                        <componentOf2
typeCode="COMP">
                                            <sequenceNumber
value="21"/>
                                            <armReference
classCode="ACT" moodCode="DEF">
                                                <id
nullFlavor="NI" extension="1"/>
                                            </armReference>
```

```
                                                                    </componentOf2>
                                                                </timePointEventDefinition>
                                                            </component2>
                                                            <component2 typeCode="COMP">
                                                                <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                                    <id nullFlavor="NI"/>
                                                                    <code code="HWL1"/>
                                                                    <precondition
typeCode="PRCN">
                                                                        <checkpointCode
code="E"/>
                    <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                            <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                            <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                                            <value
xsi:type="ED" mediaType="text/plain">Dose escalation to 20mg on Day 3 unless limited by as AE or excessive
hypotension</value>
                    </timePointEventCriterion>
                                                                    </precondition>
                                                                    <componentOf1
typeCode="COMP">
                                                                        <epochReference
classCode="ACT" moodCode="DEF">
                                                                            <id
nullFlavor="NI" extension="2"/>
                                                                        </epochReference>
                                                                    </componentOf1>
                                                                    <componentOf2
typeCode="COMP">
                                                                        <sequenceNumber
value="21"/>
                                                                        <armReference
classCode="ACT" moodCode="DEF">
                                                                            <id
nullFlavor="NI" extension="2"/>
                                                                        </armReference>
                                                                    </componentOf2>
                                                                </timePointEventDefinition>
                                                            </component2>
                                                        </timePointEventDefinition>
                                                    </component4>
                                                    <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                                        Study Element Information
                                                            Element # 4
                                                        XXXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                                    <component4 typeCode="COMP">
                                                        <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                            <id nullFlavor="UNK"/>
                                                            <code code="HWL2" displayName="High Dose
20mg D3-14 E" codeSystem="1.22.3.4"/>
                                                            <effectiveTime xsi:type="IVL_TS">
                                                                <width value="12" unit="day"/>
                                                            </effectiveTime>
                                                            <precondition typeCode="PRCN">
                                                                <checkpointCode code="B"/>
```

```
                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                            <!-- Indicate that the observation
is an element performance rule. -->
                                            <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind medication</value>
                                        </timePointEventCriterion>
                                    </precondition>
                                    <precondition typeCode="PRCN">
                                        <checkpointCode code="E"/>
                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                            <!-- Indicate that the observation
is an element performance rule. -->
                                            <value xsi:type="ED"
mediaType="text/plain">Prior to Randomized Washout dose Start</value>
                                        </timePointEventCriterion>
                                    </precondition>
                                    <!-- xxxxxxxxxxxxxxxxxxxxxxxxx
                                            Element in Arm information
                                             xxxxxxxxxxxxxxxxxxxxxxxxx-->
                                    <component2 typeCode="COMP">
                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                            <id nullFlavor="NI"/>
                                            <code code="HWL2"/>
                                            <precondition
typeCode="PRCN">
                                                <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                    <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                    <value
xsi:type="ED" mediaType="text/plain">Randomization at the end of day 14: RW High Dose 20mg E</value>
        </timePointEventCriterion>
                                            </precondition>
                                            <componentOf1
typeCode="COMP">
                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                    <id
nullFlavor="NI" extension="2"/>
                                                </epochReference>
                                            </componentOf1>
                                            <componentOf2
typeCode="COMP">
                                                <sequenceNumber
value="31"/>
                                                <armReference
classCode="ACT" moodCode="DEF">
                                                    <id
nullFlavor="NI" extension="1"/>
```

```
                                                                    </armReference>
                                                                </componentOf2>
                                                            </timePointEventDefinition>
                                                        </component2>
                                                        <component2 typeCode="COMP">
                                                            <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                                <id nullFlavor="NI"/>
                                                                <code code="HWL2"/>
                                                                <precondition
typeCode="PRCN">
                                                                    <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                        <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                                        <value
xsi:type="ED" mediaType="text/plain">Randomization at the end of day 14: RW Placebo</value>
        </timePointEventCriterion>
                                                                </precondition>
                                                                <componentOf1
typeCode="COMP">
                                                                    <epochReference
classCode="ACT" moodCode="DEF">
                                                                        <id
nullFlavor="NI" extension="2"/>
                                                                    </epochReference>
                                                                </componentOf1>
                                                                <componentOf2
typeCode="COMP">
                                                                    <sequenceNumber
value="31"/>
                                                                    <armReference
classCode="ACT" moodCode="DEF">
                                                                        <id
nullFlavor="NI" extension="2"/>
                                                                    </armReference>
                                                                </componentOf2>
                                                            </timePointEventDefinition>
                                                        </component2>
                                                    </timePointEventDefinition>
                                                </component4>
                                                <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                                    Study Element Information
                                                        Element # 5
                                                    XXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                                <component4 typeCode="COMP">
                                                    <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                        <id nullFlavor="UNK"/>
                                                        <code code="LWH1" displayName="Low Dose
1.25mg D1-2" codeSystem="1.22.3.4"/>
                                                        <effectiveTime xsi:type="IVL_TS">
                                                            <width value="2" unit="day"/>
                                                        </effectiveTime>
                                                        <precondition typeCode="PRCN">
                                                            <checkpointCode code="B"/>
```

```
                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                            <!-- Indicate that the observation
is an element performance rule. -->
                                            <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind medication</value>
                                        </timePointEventCriterion>
                                    </precondition>
                                    <precondition typeCode="PRCN">
                                        <checkpointCode code="E"/>
                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                            <!-- Indicate that the observation
is an element performance rule. -->
                                            <value xsi:type="ED"
mediaType="text/plain">Prior to Dose Escalation Start</value>
                                        </timePointEventCriterion>
                                    </precondition>
                                    <!-- xxxxxxxxxxxxxxxxxxxxxxxxx
                                            Element in Arm information
                                             xxxxxxxxxxxxxxxxxxxxxxxxx-->
                                    <component2 typeCode="COMP">
                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                            <id nullFlavor="NI"/>
                                            <code code="LWH1"/>
                                            <precondition
typeCode="PRCN">
                                                <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                    <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                    <value
xsi:type="ED" mediaType="text/plain">Dose escalation to 1.25mg on Day 3 unless limited by as AE or excessive
hypotension</value>
        </timePointEventCriterion>
                                            </precondition>
                                            <componentOf1
typeCode="COMP">
                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                    <id
nullFlavor="NI" extension="2"/>
                                                </epochReference>
                                            </componentOf1>
                                            <componentOf2
typeCode="COMP">
                                                <sequenceNumber
value="22"/>
                                                <armReference
classCode="ACT" moodCode="DEF">
```

```
                                                                    <id
nullFlavor="NI" extension="3"/>
                                                                </armReference>
                                                            </componentOf2>
                                                        </timePointEventDefinition>
                                                    </component2>
                                                    <component2 typeCode="COMP">
                                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                            <id nullFlavor="NI"/>
                                                            <code code="LWH1"/>
                                                            <precondition
typeCode="PRCN">
                                                                <checkpointCode
code="E"/>

        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                    <!-- Indicate
that the observation is a transition rule applying to the element's presence in an arm. -->
                                                                    <value
xsi:type="ED" mediaType="text/plain">Dose escalation to 1.25mg on Day 3 unless limited by as AE or excessive
hypotension</value>

        </timePointEventCriterion>
                                                            </precondition>
                                                            <componentOf1
typeCode="COMP">
                                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </epochReference>
                                                            </componentOf1>
                                                            <componentOf2
typeCode="COMP">
                                                                <sequenceNumber
value="22"/>
                                                                <armReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="4"/>
                                                                </armReference>
                                                            </componentOf2>
                                                        </timePointEventDefinition>
                                                    </component2>
                                                </timePointEventDefinition>
                                            </component4>
                                            <!-- XXXXXXXXXXXXXXXXXXXXXXXXXX
                                                Study Element Information
                                                    Element # 6
                                                XXXXXXXXXXXXXXXXXXXXXXXXXX-->
                                            <component4 typeCode="COMP">
                                                <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                    <id nullFlavor="UNK"/>
                                                    <code code="LWH2" displayName="Low Dose
1.25mg D3-14E" codeSystem="1.22.3.4"/>
                                                    <effectiveTime xsi:type="IVL_TS">
                                                        <width value="12" unit="day"/>
```

```
                                                    </effectiveTime>
                                                    <precondition typeCode="PRCN">
                                                        <checkpointCode code="B"/>
                                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                            <!-- Indicate that the observation
is an element performance rule. -->
                                                            <value xsi:type="ED"
mediaType="text/plain">First dose of Double Blind medication</value>
                                                        </timePointEventCriterion>
                                                    </precondition>
                                                    <precondition typeCode="PRCN">
                                                        <checkpointCode code="E"/>
                                                        <timePointEventCriterion
classCode="OBS" moodCode="CRT">
                                                            <code code="CXXXXXX"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                            <!-- Indicate that the observation
is an element performance rule. -->
                                                            <value xsi:type="ED"
mediaType="text/plain">Prior to Randomized Washout dose Start</value>
                                                        </timePointEventCriterion>
                                                    </precondition>
                                                    <!-- xxxxxxxxxxxxxxxxxxxxxxxxx
                                                        Element in Arm information
                                                         xxxxxxxxxxxxxxxxxxxxxxxxx-->
                                                    <component2 typeCode="COMP">
                                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                            <id nullFlavor="NI"/>
                                                            <code code="LWH2"/>
                                                            <precondition
typeCode="PRCN">
                                                                <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                    <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                                    <value
xsi:type="ED" mediaType="text/plain">Randomization at the end of day 14: Lowe Dose 1.25mg</value>
        </timePointEventCriterion>
                                                            </precondition>
                                                            <componentOf1
typeCode="COMP">
                                                                <epochReference
classCode="ACT" moodCode="DEF">
                                                                    <id
nullFlavor="NI" extension="2"/>
                                                                </epochReference>
                                                            </componentOf1>
                                                            <componentOf2
typeCode="COMP">
                                                                <sequenceNumber
value="32"/>
```

```
                                                    <armReference
classCode="ACT" moodCode="DEF">
                                                        <id
nullFlavor="NI" extension="3"/>
                                                    </armReference>
                                                </componentOf2>
                                            </timePointEventDefinition>
                                        </component2>
                                        <component2 typeCode="COMP">
                                            <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF">
                                                <id nullFlavor="NI"/>
                                                <code code="LWH2"/>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="X"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a branching rule applying to the element's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">andomization at teh end of day 14: RW Placebo</value>
        </timePointEventCriterion>
                                                </precondition>
                                                <componentOf1
typeCode="COMP">
                                                    <epochReference
classCode="ACT" moodCode="DEF">
                                                        <id
nullFlavor="NI" extension="2"/>
                                                    </epochReference>
                                                </componentOf1>
                                                <componentOf2
typeCode="COMP">
                                                    <sequenceNumber
value="32"/>
                                                    <armReference
classCode="ACT" moodCode="DEF">
                                                        <id
nullFlavor="NI" extension="4"/>
                                                    </armReference>
                                                </componentOf2>
                                            </timePointEventDefinition>
                                        </component2>
                                    </timePointEventDefinition>
                                </component4>
                                <!-- XXXXXXXXXXXXXXXXXXXXXXXX
                                        Study visit Information
                                            XXXXXXXXXXXXXXXXXXXXXXXX-->
                                <!-- Visit #1 -->
                                <component4 typeCode="COMP">
                                    <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                        <id nullFlavor="UNK" extension="1"/>
                                        <code code="Visit" codeSystem="1.22.3.4"/>
                                        <!-- We need a code for visit in the code system.
-->
```

```
                                        <title mediaType="text/plain">Screening</title>
                                        <!-- XXXXXXXXXXXXXXXXXXXX
                                             Visit within Arm Information
                                             Note, in the example this extra nesting
is not needed because there is no arm referred to.
                                             XXXXXXXXXXXXXXXXXXXXXXX-->
                                        <component2 typeCode="COMP">
                                            <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                <id nullFlavor="UNK"
extension="1"/>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">Days prior to Double Blind Randomization</value>
        </timePointEventCriterion>
                                                </precondition>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">Prior to frst dose of Double Blind Randomization</value>
        </timePointEventCriterion>
                                                </precondition>
                                                <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                                    <!-- As noted, the ARM
designation is blank.  -->
                                            </timePointEventDefinition>
                                        </component2>
                                        <!-- Study visit Information -->
                                        <subjectOf typeCode="SUBJ">
                                            <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                                <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                <!-- Planned Study Day -->
                                                <value xsi:type="INT" value="-
7"/>
                                                    <!-- VISITDY -->
                                            </timePointEventCharacteristic>
                                        </subjectOf>
                                    </timePointEventDefinition>
                                </component4>
```

```
                                        <!-- Visit #2 -->
                                        <component4 typeCode="COMP">
                                            <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                <id nullFlavor="UNK" extension="2"/>
                                                <code code="Visit" codeSystem="1.22.3.4"/>
                                                <title mediaType="text/plain">Day 1</title>
                                                <!-- XXXXXXXXXXXXXXXXXXXX
                                                    Visit within Arm Information
                                                    XXXXXXXXXXXXXXXXXXXXXXX-->
                                                <component2 typeCode="COMP">
                                                    <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                        <id nullFlavor="UNK"
extension="2"/>
                                                        <precondition
typeCode="PRCN">
                                                            <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                                <value
xsi:type="ED" mediaType="text/plain">First Dose of Double Blind Medication</value>
        </timePointEventCriterion>
                                                        </precondition>
                                                        <precondition
typeCode="PRCN">
                                                            <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                                <value
xsi:type="ED" mediaType="text/plain">Prior to Dose Escalation Start</value>
        </timePointEventCriterion>
                                                        </precondition>
                                                        <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                                    </timePointEventDefinition>
                                                </component2>
                                                <!-- Study visit Information -->
                                                <subjectOf typeCode="SUBJ">
                                                    <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                                        <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Planned Study Day -->
                                                        <value xsi:type="INT"
value="1"/>
                                                    </timePointEventCharacteristic>
                                                </subjectOf>
                                            </timePointEventDefinition>
```

```
                                        </component4>
                                        <!-- Visit #3 -->
                                        <component4 typeCode="COMP">
                                            <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                                <id nullFlavor="UNK" extension="3"/>
                                                <code code="Visit" codeSystem="1.22.3.4"/>
                                                <title mediaType="text/plain">Day 3</title>
                                                <!-- XXXXXXXXXXXXXXXXXXXX
                                                    Visit within Arm Information
                                                    XXXXXXXXXXXXXXXXXXXXXXX-->
                                                <component2 typeCode="COMP">
                                                    <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                        <id nullFlavor="UNK"
extension="3"/>
                                                        <precondition
typeCode="PRCN">
                                                            <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                                <value
xsi:type="ED" mediaType="text/plain">The third day after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                                        </precondition>
                                                        <precondition
typeCode="PRCN">
                                                            <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                                <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                                <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                                <value
xsi:type="ED" mediaType="text/plain">2 days after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                                        </precondition>
                                                        <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                                    </timePointEventDefinition>
                                                </component2>
                                                <!-- Study visit Information -->
                                                <subjectOf typeCode="SUBJ">
                                                    <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                                        <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Planned Study Day -->
                                                        <value xsi:type="INT"
value="3"/>
                                                    </timePointEventCharacteristic>
                                                </subjectOf>
```

```
                                    </timePointEventDefinition>
                                </component4>
                                <!-- Visit #4 -->
                                <component4 typeCode="COMP">
                                    <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                        <id nullFlavor="UNK" extension="4"/>
                                        <code code="Visit" codeSystem="1.22.3.4"/>
                                        <title mediaType="text/plain">Day 7</title>
                                        <!-- XXXXXXXXXXXXXXXXXXXX
                                            Visit within Arm Information
                                            XXXXXXXXXXXXXXXXXXXXXXX-->
                                        <component2 typeCode="COMP">
                                            <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                <id nullFlavor="UNK"
extension="3"/>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="B"/>
                                                    <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">The 7th day after visit 2 (Day 1)</value>
                                                    </timePointEventCriterion>
                                                </precondition>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="E"/>
                                                    <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">6 days after visit 2 (Day 1)</value>
                                                    </timePointEventCriterion>
                                                </precondition>
                                                <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                            </timePointEventDefinition>
                                        </component2>
                                        <!-- Study visit Information -->
                                        <subjectOf typeCode="SUBJ">
                                            <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                                <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                <!-- Planned Study Day -->
                                                <value xsi:type="INT"
value="7"/>
                                            </timePointEventCharacteristic>
```

```
                                        </subjectOf>
                                    </timePointEventDefinition>
                                </component4>
                                <!-- Visit #5 -->
                                <component4 typeCode="COMP">
                                    <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                        <id nullFlavor="UNK" extension="5"/>
                                        <code code="Visit" codeSystem="1.22.3.4"/>
                                        <title mediaType="text/plain">Day 15</title>
                                        <!-- XXXXXXXXXXXXXXXXXXXX
                                            Visit within Arm Information
                                            XXXXXXXXXXXXXXXXXXXXXXX-->
                                        <component2 typeCode="COMP">
                                            <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                <id nullFlavor="UNK"
extension="3"/>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">The 15th day after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                                </precondition>
                                                <precondition
typeCode="PRCN">
                                                    <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                        <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                        <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                        <value
xsi:type="ED" mediaType="text/plain">14 days after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                                </precondition>
                                                <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                            </timePointEventDefinition>
                                        </component2>
                                        <!-- Study visit Information -->
                                        <subjectOf typeCode="SUBJ">
                                            <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                                <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                <!-- Planned Study Day -->
                                                <value xsi:type="INT"
value="15"/>
```

```
                                        </timePointEventCharacteristic>
                                    </subjectOf>
                                </timePointEventDefinition>
                            </component4>
                            <!-- Visit #6 -->
                            <component4 typeCode="COMP">
                                <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                    <id nullFlavor="UNK" extension="6"/>
                                    <code code="Visit" codeSystem="1.22.3.4"/>
                                    <title mediaType="text/plain">Day 22</title>
                                    <!-- XXXXXXXXXXXXXXXXXXXX
                                        Visit within Arm Information
                                        XXXXXXXXXXXXXXXXXXXXXXX-->
                                    <component2 typeCode="COMP">
                                        <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                            <id nullFlavor="UNK"
extension="3"/>
                                            <precondition
typeCode="PRCN">
                                                <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                    <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                    <value
xsi:type="ED" mediaType="text/plain">The 22nd day after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                            </precondition>
                                            <precondition
typeCode="PRCN">
                                                <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                    <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                    <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                    <value
xsi:type="ED" mediaType="text/plain">21 days after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                            </precondition>
                                            <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                            <!-- As noted, the ARM
designation is blank.  -->
                                        </timePointEventDefinition>
                                    </component2>
                                    <!-- Study visit Information -->
                                    <subjectOf typeCode="SUBJ">
                                        <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                            <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
```

```
                                                    <!-- Planned Study Day -->
                                                    <value xsi:type="INT"
value="22"/>
                                                </timePointEventCharacteristic>
                                            </subjectOf>
                                        </timePointEventDefinition>
                                    </component4>
                                    <!-- Visit #7 -->
                                    <component4 typeCode="COMP">
                                        <timePointEventDefinition classCode="CTTEVENT"
moodCode="DEF ">
                                            <id nullFlavor="UNK" extension="7"/>
                                            <code code="Visit" codeSystem="1.22.3.4"/>
                                            <title mediaType="text/plain">Day 29 OR
EARLY WITHDRAWAL</title>
                                            <!-- XXXXXXXXXXXXXXXXXXXX
                                                Visit within Arm Information
                                                XXXXXXXXXXXXXXXXXXXXXXX-->
                                            <component2 typeCode="COMP">
                                                <timePointEventDefinition
classCode="CTTEVENT" moodCode="DEF ">
                                                    <id nullFlavor="UNK"
extension="3"/>
                                                    <precondition
typeCode="PRCN">
                                                        <checkpointCode
code="B"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                            <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                            <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                            <value
xsi:type="ED" mediaType="text/plain">The 29th day after visit 2 (Day 1)</value>
        </timePointEventCriterion>
                                                    </precondition>
                                                    <precondition
typeCode="PRCN">
                                                        <checkpointCode
code="E"/>
        <timePointEventCriterion classCode="OBS" moodCode="CRT">
                                                            <code
code="CXXXXXX" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                            <!-- Indicate
that the observation is a visit performance rule applying to the visit's presence in an arm. -->
                                                            <value
xsi:type="ED" mediaType="text/plain">28 days after visit 2 (Day 1)</value>
                                                            <!-- What sort of
data type is used here?  It looks like text now. -->
        </timePointEventCriterion>
                                                    </precondition>
                                                    <componentOf2
typeCode="COMP" xsi:nil="true"/>
                                                </timePointEventDefinition>
                                            </component2>
                                            <!-- Study visit Information -->
                                            <subjectOf typeCode="SUBJ">
```

```
                                        <timePointEventCharacteristic
classCode="OBS" moodCode="EVN">
                                            <code code="C83450"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                            <!-- Planned Study Day -->
                                            <value xsi:type="INT"
value="29"/>
                                        </timePointEventCharacteristic>
                                    </subjectOf>
                                </timePointEventDefinition>
                            </component4>
                            <!-- XXXXXXXXXXXXXXXXXXX
                                Study Summary Information
                                 XXXXXXXXXXXXXXXXXXXXXXX-->
                            <subjectOf typeCode="SUBJ">
                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                    <code code="AGESPAN" displayName="Age
Span" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                    <value xsi:type="ED">Pediatrics</value>
                                </studyCharacteristic>
                            </subjectOf>
                            <subjectOf typeCode="SUBJ">
                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                    <code code="DESIGN"
displayName="Description of Trial Design" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI
Thesaurus"/>
                                    <value xsi:type="ED">Double-Blind Pediatrics
randomized to low, middle, and hig dose, Dose Escalation on Day 3, Randomize Washout on Day 14 to placebo or
continued active treatment</value>
                                </studyCharacteristic>
                            </subjectOf>
                            <subjectOf typeCode="SUBJ">
                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                    <code code="INDIC" displayName="Indication"
codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                    <value xsi:type="ED">Hypertensive
Medication</value>
                                </studyCharacteristic>
                            </subjectOf>
                            <subjectOf typeCode="SUBJ">
                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                    <code code="LENGTH" displayName="Trial
Duration" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                    <value xsi:type="IVL_TS">
                                        <width value="29" unit="day"/>
                                    </value>
                                </studyCharacteristic>
                            </subjectOf>
                            <subjectOf typeCode="SUBJ">
                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                    <code code="RANDOM"
displayName="Randomized" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                    <value xsi:type="BL" value="true"/>
                                </studyCharacteristic>
                            </subjectOf>
                            <subjectOf typeCode="SUBJ">
```

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                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="SEXPOP" displayName="Sex of
Participants" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXXX"
displayName="Both" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TBLIND" displayName="Trial
Blinding Schema" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXX"
displayName="DOUBLE BLIND" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TBLIND" displayName="Trial
Blinding Schema" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXX"
displayName="RANDOMIZED WASHOUT" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI
Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TDIGRP"
displayName="Diagnosis Group" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXX"
displayName="Subjects Diagnosis with Hypertensive Children" codeSystem="2.16.840.1.113883.3.26.1.1"
codeSystemName="NCI Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TINDTP" displayName="Trial
Indication Type" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXX"
displayName="TREATMENT" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TPHASE" displayName="Trial
Phase Classification" codeSystem="1.22.3.3"/>
                                            <value xsi:type="CD" code="CXXXXX"
displayName="Phase 1 Trial" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                        </studyCharacteristic>
                                    </subjectOf>
                                    <subjectOf typeCode="SUBJ">
                                        <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                            <code code="TRT" displayName="Reported
Name of Test Product" codeSystem="1.22.3.3"/>
```

```
                                                    <value xsi:type="ED"
mediaType="text/plain">DRUGA</value>
                                                </studyCharacteristic>
                                            </subjectOf>
                                            <subjectOf typeCode="SUBJ">
                                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                                    <code code="TTYPE" displayName="Trial Type"
codeSystem="1.22.3.3"/>
                                                    <value xsi:type="CD" code="CXXXXX"
displayName="SAFETY" codeSystem="2.16.840.1.113883.3.26.1.1" codeSystemName="NCI Thesaurus"/>
                                                </studyCharacteristic>
                                            </subjectOf>
                                            <subjectOf typeCode="SUBJ">
                                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                                    <code code="WTSPAN" displayName="Weight
Span" codeSystem="1.22.3.3"/>
                                                    <!-- Note, the code does not appear on the list I
have published in the SDTM IG.  -->
                                                    <value xsi:type="IVL_PQ">
                                                        <low value="50" unit="kg"
inclusive="false"/>
                                                    </value>
                                                </studyCharacteristic>
                                            </subjectOf>
                                            <subjectOf typeCode="SUBJ">
                                                <studyCharacteristic classCode="OBS"
moodCode="EVN">
                                                    <code code="WTSPAN" displayName="Weight
Span" codeSystem="1.22.3.3"/>
                                                    <!-- Note, the code does not appear on the list I
have published in the SDTM IG.  -->
                                                    <value xsi:type="IVL_PQ">
                                                        <high value="50" unit="kg"
inclusive="true"/>
                                                    </value>
                                                </studyCharacteristic>
                                            </subjectOf>
                                            <!--XXXXXXXXXXXXXXXXX
                                                Inclusion/Exclusion Information
                                                The sample data set does not include any.
                                                XXXXXXXXXXXXXXXXXXXXX-->
                                        </plannedStudy>
                                    </subject>
                                </section>
                            </component>
                        </structuredBody>
                    </component>
</Document>
```