Pain Therapeutic Area User Guide Supplement to the Study Data Tabulation Model Implementation Guide

Prepared by

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Notes to Readers

- This is the Pain user guide for Human Clinical Trials corresponding to the CDISC Study Data Tabulation Model and the Study Data Tabulation Model Implementation Guide for Human Clinical Trials and domain models.
- This work was funded in part by the ACTTION Public-Private Partnership with FDA.
- See Appendix C for Representations and Warranties, Limitations of Liability, and Disclaimers.

Revision History

Date	Version	Summary of Changes
2012-03-02	0.1	Draft Pain-specific User Guide – Public Review.
2012-08-07	1.0	Pain-specific User Guide for provisional use.

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1 INTRODUCTION

1.1 PURPOSE

This Pain-specific User Guide (SDTMUG-PAIN) v1.0 is to be used as a Therapeutic Area Supplement to the CDISC Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG). The SDTMUG-PAIN document was prepared by the Analgesic Clinical Trial Translations Innovations, Opportunities, and Networks (ACTTION) (http://www.acttion.org) group with participation from volunteer members of the Submissions Data Standards (SDS) team of the Clinical Data Interchange Standards Consortium (CDISC). It is intended to guide the organization, structure, and format of standard pain clinical trial tabulation datasets submitted to a regulatory authority such as the US Food and Drug Administration (FDA).

This guide describes the explicit implementation of a subset of the SDTMIG domains with rules and examples as they should be applied to represent data typically captured on case report forms (CRFs) for clinical trials relevant to the study of pain. The SDTMUG-PAIN V1.0 should be used in close concert with the current version of the SDTMIG and the CDISC Study Data Tabulation Model (SDTM). Both of these CDISC documents are available at http://www.cdisc.org/sdtm.

This document does not replace, supersede, nor otherwise override any rules or requirements of the current SDTM and SDTMIG. Knowledge of this document alone is not a substitute for knowledge of SDTM nor is it sufficient to produce complete, SDTM-compliant regulatory submissions of clinical trials data for pain studies. CDISC SDTMIG domains not referenced in the SDTMUG-PAIN should be used as necessary based on the requirements of the protocol. Other domains required for most studies include Demographics (DM), Exposure (EX), Lab (LB), Concomitant Medications (CM), Substance Use (SU), Adverse Events (AE), Disposition (DS), ECG (EG), Vital Signs (VS), Inclusion/Exclusion (IE) and others.

To be successful in implementing the SDTMUG-PAIN, users who are not previously knowledgeable of the CDISC SDTM standards must:

- Read the SDTM and SDTMIG first. These describe the conceptual framework of the SDTM models and include the basics of representing data according to CDISC standards. It is not possible to understand the SDTMUG-PAIN without a command of the information in the SDTMIG.
- Find CDISC controlled terminology and learn how it interacts with SDTM models by reading about it in Chapter 4 of the SDTMIG.
- Read the SDTMUG-PAIN to understand the general approach for utilizing the SDTM for representing data in pain studies.
- Consult the separate Pain-specific Supplements to the SDTMIG that have been prepared for specific Pain instruments, which are available on the CDISC website at http://www.cdisc.org/content2909. In some cases a sample instrument annotated with SDTM variables is also available for public domain instruments and those approved for this purpose by copyright holders.

This standards development process looks backward to the extent that it must to support legacy studies, but it also looks forward to support future studies of emerging treatments, diagnostics, and disease models. Therefore, the current version of the SDTMUG-PAIN should not be regarded as the complete and final set of data standards required for every Pain/Analgesic research study, but as a starting point for an inventory of standards that will improve and grow through iterative review and revision under the leadership of ACTTION with its partners CDISC and the FDA.

1.2 BACKGROUND

The mission of the Pain Data Standards initiative is to create a foundation for future research aligned with the FDA Critical Path Initiative and supported by the ACTTION public-private partnership. In November 2010, ACTTION, together with industry representatives and clinical experts, established the STandardized ANalgesic DAtabase for Research, Discovery, and Submissions (STANDARDS) working group to provide subject matter expertise in developing the pain data standards. The objective of the STANDARDS group is to provide a standard or process template for clinical trials in Analgesia, which will allow for a unified transformation of data from a variety of different sources to:

1) Enable pooled analyses of data from analgesic trials that have already been submitted to FDA
2) Provide a recommended database format for the preparation and submission of future analgesic trials.

The STANDARDS group engaged CDISC support early in this process to lead the preparation of a CDISC-compliant database structure for analgesic clinical trials. In January 2011, additional participants were enlisted from academia, medical research, professional societies, CDISC, industry and FDA.

A key initial task was to define Pain/Analgesic primary and secondary efficacy endpoints that could be used as a framework to design clinical trials. The STANDARDS group agreed to begin with an initial set of specific Pain conditions areas of interest within Acute and Chronic Pain:

Chronic pain conditions:
1. Osteoarthritis (OA)
2. Low back pain (LBP)
3. Fibromyalgia (FM)
4. Painful diabetic peripheral neuropathy (DPN)
5. Postherpetic neuralgia (PHN)
6. HIV neuropathy (HIV)
7. Post-traumatic neuralgia and mixed neuropathic pain conditions
8. Cancer pain
9. Central neuropathic pain.

Acute pain conditions:
1. Third molar extraction
2. Bunionectomy or other orthopedic surgery (e.g., arthroplasty)
3. Abdominal surgery (e.g., hysterectomy, hernia repair)
4. Dysmenorrhea
5. Acute pain treatment in chronic pain patients.

The standard elements and terminology contained in this version of the SDTMUG-PAIN represent the initial set of data that were prioritized by the ACTTION sponsored STANDARDS Working Group.

The STANDARDS Working Group then defined the criteria for the inclusion of specific pain conditions in the CDISC process. The criteria stated that a minimum of two different companies provide standard CRFs for given pain condition. The working group next coordinated the collection of documentation (i.e. Study Synopsis and CRFs) to provide to CDISC from specific clinical studies in Pain. A total of approximately 167 studies were reviewed out of which 92 were identified as relevant to contribute to the pain data standards development process. The STANDARDS Working Group ensured the confidentiality of documents shared by pharmaceutical companies based on the CDISC Intellectual Property policy. CDISC also coordinated the resolution of the Pain Measurement copyright issues.

The STANDARDS Working Group co-chairs provided high-level guidance regarding the many pain instruments utilized in clinical studies. The WG members actively reviewed and provided input on the pain measurements identified via teleconferences conducted monthly through the identification of the commonly used pain assessments. This concluded when the STANDARDS Working Group provided a list of 35 pain

assessments for CDISC SDTM implementation. Many of these instruments required permission from the authors to implement in the data standards due to their copyright criteria. Letters from the STANDARDS Working Group co-chairs were sent to the authors explaining the project and requesting approval. This process continued through mid-December, 2011, and resulted in an initial list of 19 pain instruments, some of which were already available in the public domain, which were selected for inclusion in the Version 1.0 release of the pain data standards.

1.3 SCOPE

Because permission to use specific instruments could not be secured in some cases, the entire initial list of assessments is not currently mapped to the CDISC SDTM domains -- some assessments are awaiting approval from authors and may be added in the future once permission is obtained. The scope of the SDTMUG-Pain will likely evolve over time to include further assessments and additional concepts to reflect scientific advances.

Therefore, the current version of the SDTMUG-PAIN should not be regarded as the complete and final set of data standards required for every pain research study, but as a starting point for an inventory of standards that will improve and grow through iterative review and revision over time.

1.4 RELATIONSHIP TO PRIOR CDISC DOCUMENTS

As stated previously, this document is a supplement to the Study Data Tabulation Model (SDTM) and the Study Data Tabulation Model Implementation Guide for Human Clinical Trials (SDTMIG).

Links and usage notes in the SDTMIG point users to CDISC controlled terminology, which is registered with the National Cancer Institutes in the Enterprise Vocabulary System (NCI-EVS). Note that some examples in this guide show draft or sample terminology that was not approved as a standard when the guide was created.

All current CDISC terminology, implementation guides, and other data standards are free and available to the public in the Standards Area of the CDISC web site (http://www.cdisc.org/standards).

1.5 SUBMITTING COMMENTS

We encourage users to work together using the CDISC forum designed for user discussions at: http://cdiscportal.digitalinfuzion.com/Pages/Home.aspx.

2 STANDARD DOMAINS

2.1 SPECIAL PURPOSE DOMAINS

Refer to the SDTMIG for special purpose domains applicable to pain studies. There are no additional domains, assumptions or examples unique to pain.

2.2 INTERVENTIONS

Refer to the SDTMIG for interventions domains applicable to pain studies. There are no additional domains, assumptions or examples unique to pain.

2.3 EVENTS

Refer to the SDTMIG for events domains applicable to pain studies. The Medical History domain is the only events domain specified in the Pain data standards to identify the Primary Diagnosis.

2.3.1 Medical History (Pain)

2.3.1.1 Assumptions for Medical History Domain Model (Pain)

All assumptions for the MH domain from the SDTMIG apply for this supplemental implementation guide. Refer to SDTMIG for any non-Pain specific assumptions referenced in the domain table. Additionally, the following assumptions apply to Pain.

1. Details for MHCAT controlled terminology and handling:
    a. For MHCAT=PRIMARY DIAGNOSIS, the type of pain indication being studied, for instance “Fibromyalgia” or “Diabetic Neuropathy,” must be populated in MHTERM. If the term is coded, coding to the MedDRA preferred term may be supplied in the MHDECOD column. See Example 1 below, which shows how to map the primary diagnosis.
2. MHSTDTC is expected when MHCAT=PRIMARY DIAGNOSIS.
3. When collected, onset of symptoms for “Pain” is mapped to Findings About (FA) based on the draft proposal for handling multiple dates under consideration for a future version of the SDTMIG. See the FA Example section for an example on how to map the onset of symptoms.
4. Terminology – Existing CDISC Controlled Terminology is used for the MH domain for Pain.

2.3.1.2 Example for Medical History Domain Model (Pain)

Rows 1, 3: Displays the PRIMARY DIAGNOSIS being Fibromyalgia for 3 subjects along with the date of diagnosis in MHSTDTC. The onset of symptoms date for Fibromyalgia is stored in the FINDINGS ABOUT domain in the FA section later in the document.

ROW	USUBJID	MHSEQ	MHTERM	MHCAT	MHSTDTC
1	2324-P0001	1	Fibromyalgia	PRIMARY DIAGNOSIS	2001-05
2	2324-P0002	1	Fibromyalgia	PRIMARY DIAGNOSIS	2002-10
3	2324-P0003	1	Fibromyalgia	PRIMARY DIAGNOSIS	2011-07

2.4 FINDINGS

Refer to the SDTMIG for general findings domains such as Laboratory data, Vital Signs and other findings domains that are also applicable to pain studies. The SDTMUG-PAIN specifically focuses on use of the Questionnaire (QS) domain to represent the clinical data specific to pain studies. Assumptions and examples unique to pain questionnaires are described in this section.

2.4.1 Questionnaire — QS (Pain)

See the SDTMIG for the general description, assumptions and examples for the QS domain table.

2.4.1.1 Assumptions for Questionnaire Domain Model

All SDTMIG assumptions for the QS domain apply for this supplemental implementation guide including those referenced in the CDISC notes. In addition, the following assumptions also apply to pain:

1. The assessment scales listed below are aligned to the SDTM QS domain for Pain/Analgesic studies as part of the Pain Data Standards.
2. For CRFs in the public domain and those where author permission is secured, the assessment scales have been annotated with SDTM variable names. The SDTMUG-PAIN does not include any CRF examples in cases when author permission could not be secured or the general pain questionnaires for Pain Intensity, Pain Relief and General Clinical Global Impressions. The individual questionnaire supplemental documents along with the annotated CRFs can be referenced on the CDISC web site at http://www.cdisc.org/content2909. The annotated CRF can be cross referenced with the QS domain data example and Section 4: Mapping Strategy to better understand the alignment of the questionnaire to the SDTM QS domain and the associated controlled terminology.
3. Terminology
    1. CDISC controlled terminology has been approved for the QSCAT, QSTESTCD and QSTEST fields for all questionnaires in this data standard except for the following general pain concepts, which is being submitted:
        a. Pain Intensity
        b. Pain Relief
        c. General Clinical Global Impressions

    The existing CDISC Questionnaire Terminology and requests to add additional questionnaire controlled terminology can be found on the CDISC web site at http://www.cdisc.org/terminology.

2.4.1.2 Examples for Questionnaire Domain Model

Each questionnaire implemented within the pain data standards is unique, most with an actual questionnaire CRF example provided for reference by the author or a sponsor. The details of each questionnaire, along with the public domain or author approved annotated CRF and the mapping strategy on aligning the questionnaire to the SDTM QS domain are included in the separate individual questionnaire supplemental documents. These documents can be accessed on the CDISC web site at (http://www.cdisc.org/content2909) and collectively provide the necessary information to enable users to align each questionnaire to the CDISC SDTM QS domain.

2.4.1.3 Assessments implemented in the Questionnaire Domain Model

Pain Measures	Assessment	CDISC Permission Status
Function	Brief Pain Inventory (BPI)	Permission Given
	Brief Pain Inventory Short Form (BPI)	Permission Given
	Euroqol: EQ5D (EQ-5D-3L)	**Permission Not Given**
	Karnofsky Performance Status Scale	Public Domain
	SF-36 Health Survey	**Permission Not Given**
Emotional Function	Columbia Suicide Severity Rating Scale: Baseline (CSSRS-BSL)	Permission Given
	Hamilton Depression Scale : 17- Item Scale	Public Domain
Pain	McGill Pain Questionnaire (Short-Form) MPQ 2	Permission Given
	Faces Pain Scale – Revised (FPS-R)	Permission Given
Opioids	Screener and Opioid Assessment for Patients with Pain (SOAPP-R)	Permission Given
	Current Opioid Misuse Measure (COMM)	Permission Given
Neurological Exam	Mini Mental State Examination (MMSE)	**Permission Not Given**
Disease Specific Pain Measures		
Back Pain	Roland-Morris Disability Questionnaire (RDQ)	Public Domain
Neuropathic Pain	Michigan Neuropathy Screening Instrument	Public Domain
Arthritis	Work Productivity and Activity Impairment Questionnaire - Specific Health Problem (WPAI)	Public Domain
General Pain Measures		
	Clinical Global impressions (CGI)	Public Domain
	Pain Intensity	Public Domain
	Pain Relief	Public Domain
	General Clinical Global Impressions	Public Domain

2.4.2 Findings About Event or Interventions (Pain)

Findings About Events or Interventions is a specialization of the Findings General Observation Class. As such, it shares all qualities and conventions of Findings observations but is specialized by the addition of the --OBJ variable. See SDTMIG for domain table.

2.4.2.1 Assumptions for Findings About Domain Model

All assumptions for the FA domain from the SDTMIG apply for this supplemental implementation guide. Refer to SDTMIG for any non-Parkinson's disease specific assumptions referenced in the domain table.

1. Terminology
   a. Controlled terminology is still under development for the Pain data standards, thus some values in the examples are not CDISC controlled terms. Users should verify terminologies used in this document against current standards before adopting for use on clinical trials.

2.4.2.2 Findings About Examples

Example 2: PAIN Medical History Information

These **PAIN Medical History Findings data** are mapped to FA-FINDINGS ABOUT domain as in the following data example. This FA example is shown here based on its relationship to the related MH domain based on the FAOBJ field value equal to the MHTERM.

This example shows how to represent the question "**Year first symptoms as confirmed by history obtained by the physician?" –** The onset of symptoms date FATESTCD=SYMPDTC is used for the onset of symptoms date of the pain PRIMARY DIAGNOSIS term when the pain was observed by a physician. The actual diagnosis date (MHSTDTC) is the date the subject's physician officially diagnosed the disease. Where collected, onset of symptoms (for Pain) needs to be mapped to the FA domain as FATEST=Onset of Symptom Date in accordance with the SDS Multiple Dates proposal being sent for public review in 3Q12. This FA example is shown here based on its relationship to the related MH domain records indicated by the value of FAOBJ. The controlled terminology for FAOBJ, FATESTCD and FATEST is represented in the table.

Rows 1-3 These records show the Onset of Symptoms date for pain FA tests for each subject from the Pain Medical History information.

fa.xpt

ROW	STUDYID	DOMAIN	USUBJID	FASEQ	FATESTCD	FSTEST	FAOBJ	FAORRES	FASTRESC
1	STUDY01	FA	2324-P0001	1	SYMPDTC	Onset of Symptom Date	FIBROMYALGIA	2000-05	2000-05
2	STUDY01	FA	2324-P0002	1	SYMPDTC	Onset of Symptom Date	FIBROMYALGIA	2001-10	2001-10
3	STUDY01	FA	2324-P0003	1	SYMPDTC	Onset of Symptom Date	FIBROMYALGIA	2010-07	2010-07

APPENDICES

Appendix A: ACTTION Standards Workgroup

Name	Company
Robert Dworkin, Co-Chair	Director, ACTTION Executive Committee, University of Rochester
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Allison Lin	FDA
Frank Pucino	FDA
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Chris Tolk	CDISC
Frank Newby	CDISC

Appendix B: Glossary and Abbreviations

The following abbreviations and terms are used in this document. Additional definitions can be found in the CDISC Glossary available at http://www.cdisc.org/cdisc-glossary

ACTTION	Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks
CDE	Common Data Element
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide for Human Clinical Trials
SDTMUG-PAIN	Pain-specific Therapeutic Area User Guide Supplement to the Study Data Tabulation Model Implementation Guide
STANDARDS	STandardized ANalgesic DAtabase for Research, Discovery, and Submissions
WG	Working Group

Appendix C: Representations and Warranties, Limitations of Liability, and Disclaimers

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