CDISC Italian User Network 2020

Milan, Italy | 7 October 2020

News from the Regulatory World

Presented by Angelo Tinazzi
Senior Director, Standards, Systems and CDISC Consulting - Statistical Programming

Cytel Inc. – **angelo.tinazzi@cytel.com**

7 October 2020

>20 Years of Experience

Passion for Standards

Member of CDISC-EU Committee

CDISC Authorized Instructor for ADaM

Regulatory Update

FDA

https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

Study Data Technical Conformance Guide

- v.4.5 March 2020 → No major Update
- v.4.5.1 July 2020 → Special COVID-19 release
  - Text added referencing CDISC “Interim User Guide for COVID-19” recommendation for collection of reactogenicity data
  - Referenced in appendix both COVID-19 related guidance:
    - Interim User Guide for COVID-19
    - Guidance for Ongoing Studies Disrupted by COVID-19 Pandemic
- Data Standards Catalog v6.6 (July 29, 2020)
  - SDTM Ig 3.3 Date Support Begins: March 2021
  - ADaM Ig 1.2 Date Support Begins: Not yet communicated
  - define-xml 2.1 Date Support Begins: March 2021
- Next Version expected in the next days / weeks (Q3 Regular Update)

Regulatory Update (Cont)

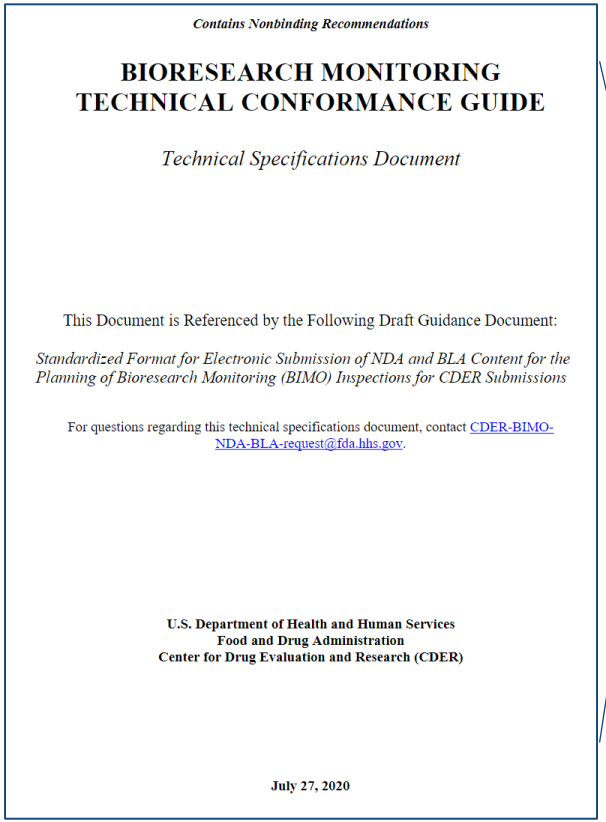
FDA (cont)

https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

BIMO Technical Conformance Guidance July 2020

FDA BIMO Technical Conformance Guidance

Only for CDER, at least for Pivotal Study(ies)



Contains Nonbinding Recommendations

BIORESEARCH MONITORING TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is Referenced by the Following Draft Guidance Document:

Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions

For questions regarding this technical specifications document, contact CDER-BIMO-NDA-BLA-request@fda.hhs.gov.

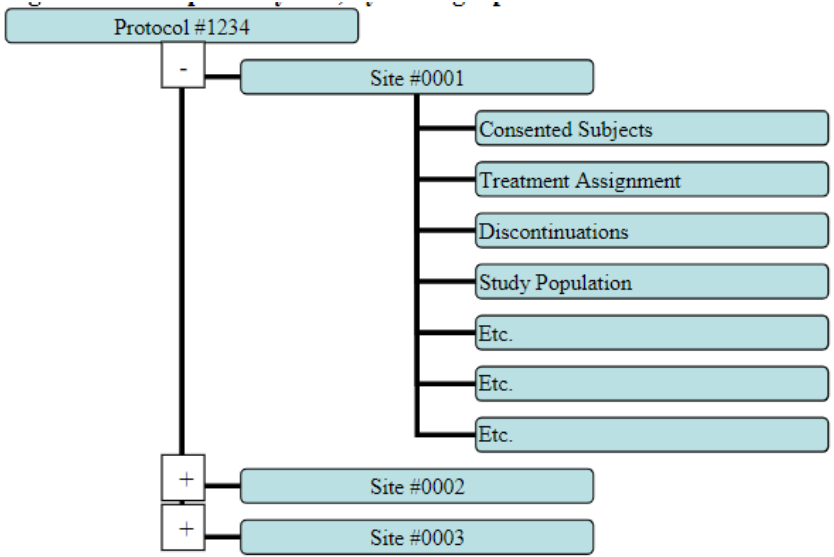
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

July 27, 2020

- **Clinical Study-Level Information**
- **Subject-Level Data Line Listings by Clinical Site**
- **Summary-Level Clinical Site Dataset**

FDA BIMO Technical Conformance Guidance (Cont)

By site investigator listings for investigator on-sites inspections



FDA BIMO Technical Conformance Guidance (Cont)

Summary-Level Clinical Site Dataset

Study Identifier	Study Title	Sponsor Name	IND Number	Study Site Identifier	Description of Planned Treatment Arm	Number of Subjects in Safety Population	Number of Subjects Screened	Number of Subject Discons from Study	Number of Subject Disc. from Study Trt	Primary Endpoint	Primary Endpoint Type	Treatment Efficacy Result	Treatment Efficacy Result Std Deviation	Site-Specific Treatment Effect	Site Trt Dev
[redacted]	Efficacy and safety of [redacted] in the treatment of [redacted]	[redacted] Limited	[redacted]	[redacted]	[redacted] U/kg	2	5	1	1	Mean Physician's Global Assessment (PGA) score at Treatment 1, Week 6	CONTINUOUS	1	0	49.940296332	*****
[redacted]	Efficacy and safety of [redacted] in the treatment [redacted]	[redacted] Limited	[redacted]		[redacted] U/kg	0	5	0	0	Mean Physician's Global Assessment (PGA) score at Treatment 1, Week 6	CONTINUOUS				
[redacted]	[redacted]	[redacted] Limited	[redacted]		[redacted] U/kg	3	5	1	1	Mean Physician's Global Assessment (PGA) score at Treatment 1, Week 6	CONTINUOUS	1	1	63.847015529	*****
[redacted]	Efficacy and safety of [redacted]	[redacted] Limited	[redacted]		[redacted] U/kg	2	5	1	1	Mean change from Baseline to Treatment 1, Week 6 in MAS score in the Treatment 1 PTMG (elbow flexors or wrist flexors)	CONTINUOUS	-3	0	39.253239851	*****
[redacted]	Efficacy and safety of [redacted] in children [redacted]	[redacted] Limited	[redacted]		[redacted] U/kg	0	5	0	0	Mean change from Baseline to Treatment 1, Week 6 in MAS score in the Treatment 1 PTMG (elbow flexors or wrist flexors)	CONTINUOUS				
[redacted]	Efficacy and safety of	[redacted]	[redacted]							Mean change from Baseline to					

"Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions"
(https://www.fda.gov/media/85056/download)
"Bioresearch Monitoring Technical Conformance Guide - Technical Specifications Document", July 2020
(https://www.fda.gov/media/85061/download)

Regulatory Update (Cont)

PMDA (Japan)

All **submission done after March 31, 2020** should make use of “standards”

Other agencies requesting datasets: Canada with CDISC format recommended but no formal guidance

Regulatory Update – China NMPA

"Guideline on the Submission of Clinical Trial Data", NMPA Center for Drug Evaluation Data", July 2020 (https://www.nmpa.gov.cn/directory/web/nmpa/images/obbSqc7vwdm0ssrU0enKb7dtd29u9a4tbzUrdTyo6jK1NDQo6mhty5wZGY=.pdf)

Only Chinese Version

Regulatory Update – China NMPA (Cont)

For more information on China NMPA reform

"China NMPA Reform and New Regulations/Guidelines/requirements"
Yi Yang, PharmaSUG 2019
https://www.lexjansen.com/pharmasug/2019/SS/PharmaSUG-2019-SS-014.pdf

Regulatory Update – China NMPA (Cont)

- **CDISC standards** for both study database (SDTM) and analysis datasets (ADaM) are recommended
- **SAS XPT version 5 or higher** is the recommended **data formats** for both study database and analysis datasets. Encoding should be specified
- No specific requirements on the **versions of the CDISC standards**
- **MedDRA is mentioned** as a possible standard for Adverse Events for Medical Dictionary. **No recommendation for standard terminology**

Regulatory Update – China NMPA (Cont)

- Recommend to use **CDISC define-xml** as a standard for data definition file if xml format is selected, otherwise **PDF is acceptable too**
- The use of **PHUSE templates for both study data reviewer guide and analysis reviewer guide** is also recommended
- Until now, the requirements seem very familiar and closed to what FDA and PMDA are already requiring, although for **Programming Code** the NMPA seems more concerned about receiving programs that could be also executed in their environment and possibly with limited use of external programs such as SAS macros

Regulatory Update – China NMPA (Cont)

Chinese Translation

Datasets

- **label** of both datasets and variables
- at least **adverse events terms**, **generic name of concomitant medications** and **medical history**

Data definition file e.g. define-xml, at least the following items:

- **description / label**
- **specifications** i.e. derivations
- values or **code list** of efficacy indicators

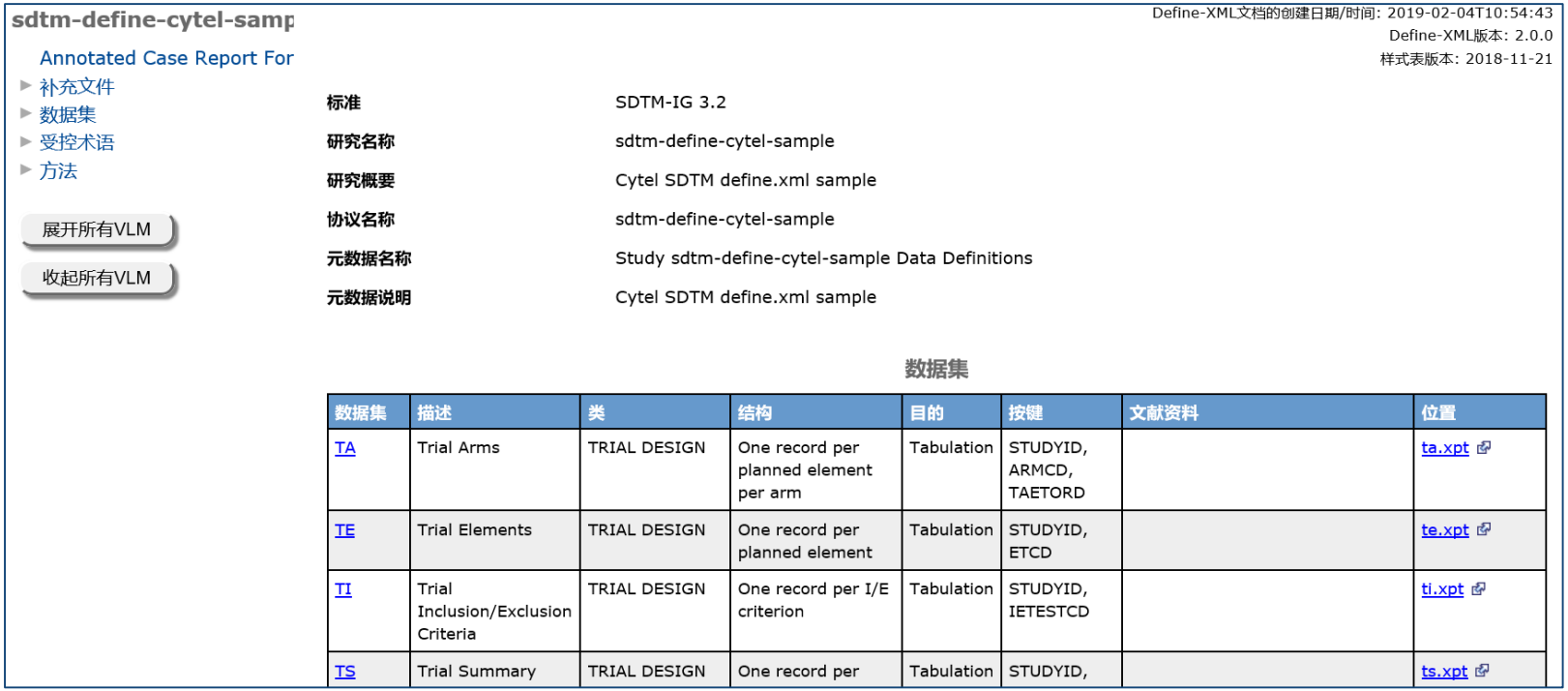
acrf.pdf at least the following items:

- description of questions designed to collect data
- values or code list of efficacy indicators

Reviewer guide

Regulatory Update – China NMPA (Cont)

Chinese define-xml stylesheet provided by Pinnacle21



sdtm-define-cytel-samp

Define-XML文档的创建日期/时间: 2019-02-04T10:54:43
Define-XML版本: 2.0.0
样式表版本: 2018-11-21

Annotated Case Report For

- 补充文件
- 数据集
- 受控术语
- 方法

展开所有VLM

收起所有VLM

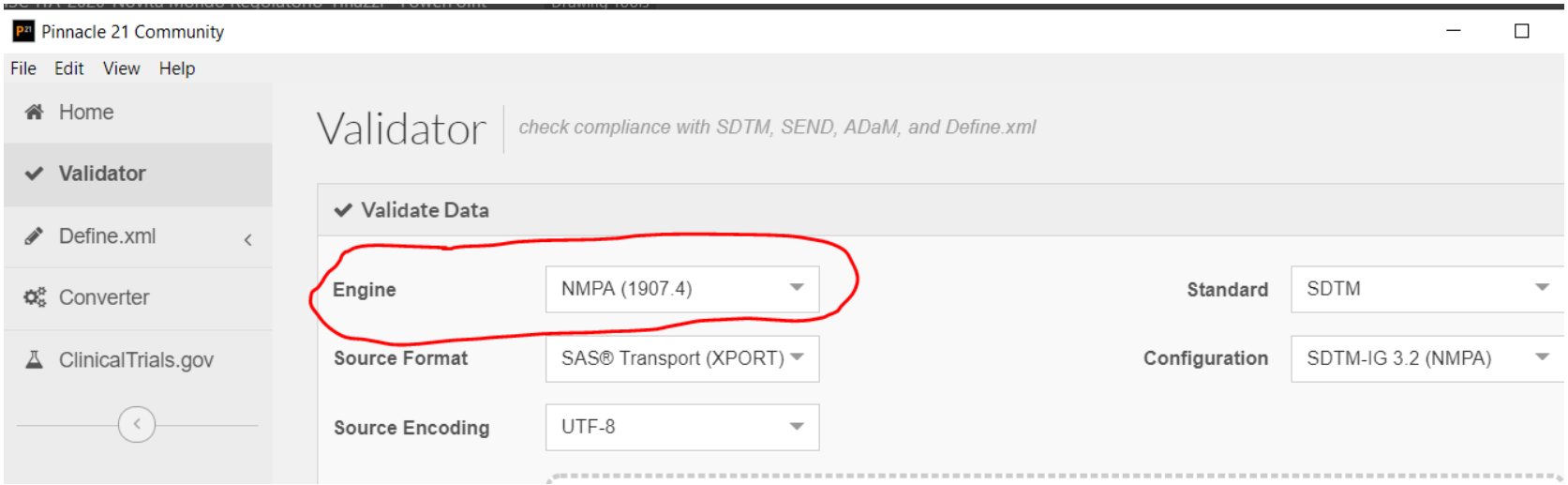
标准	SDTM-IG 3.2
研究名称	sdtm-define-cytel-sample
研究概要	Cytel SDTM define.xml sample
协议名称	sdtm-define-cytel-sample
元数据名称	Study sdtm-define-cytel-sample Data Definitions
元数据说明	Cytel SDTM define.xml sample

数据集

数据集	描述	类	结构	目的	按键	文献资料	位置
TA	Trial Arms	TRIAL DESIGN	One record per planned element per arm	Tabulation	STUDYID, ARMCD, TAETORD		ta.xpt
TE	Trial Elements	TRIAL DESIGN	One record per planned element	Tabulation	STUDYID, ETCD		te.xpt
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD		ti.xpt
TS	Trial Summary	TRIAL DESIGN	One record per	Tabulation	STUDYID,		ts.xpt

Regulatory Update – China NMPA (Cont)

Pinnacle21 NMPA SDTM Validation Engine (v3.1.0)



Regulatory Update – China NMPA (Cont)

The challenge of Chinese language and SAS XPT (v5)

- Western companies, and therefore programmers, aiming to submit data to NMPA might be not all familiar with the challenges posed by the representation of **Chinese characters in the electronic datasets and with characters encoding in general**
- Most of us are for example only familiar with the character set ***latin-1*** (ISO/EIC 8859-1), which includes **upper and lower English characters, the digits 0 through 9 and some special characters required by some national alphabet** such as German, Spanish and Danish, etc. Overall 256 points can be used, all of them represented by a specific numeric value in a **Single Byte Character Set (SBCS), with one character per byte**
- However, languages such as the Japanese or the Chinese, cannot be represented in a SBCS and a **Multiple Byte Character Set (MBCS)** is required

Regulatory Update – China NMPA (Cont)

The challenge of Chinese language and SAS XPT (v5)

- A number of papers cover very well the problematic of correct characters set representation in SAS. Essentially, the handling of **MBCS might require the flexibility in SAS to switch from one encoding system to another**, as by default in most of the SAS configurations **"wlatin1"** (or "wlatin1 Western (windows)") is the default dataset encoding.
- The **setting of the encoding system could determine the correct creation of a SAS dataset containing Chinese translated text** given the fact the encoding of a dataset is determined at the time the dataset is generated. You can check for example the encoding used by your SAS session by checking the SAS log after having submitted the proc options statements

```
28    proc options option=encoding;
29    run;

      SAS (r) Proprietary Software Release 9.4  TS1M6

 ENCODING=WLATIN1  Specifies the default character-set encoding for the SAS session.
```

- "Data Encoding: All Characters for All Countries", D. Dutton, PhUSE 2015 (https://www.lexjansen.com/phuse/2015/dh/DH03.pdf)
- "The Impact of Change from wlatin1 to UTF-8 Encoding in SAS Environment", H. Song and A. Koster , PharmaSUG 2016 (https://www.pharmasug.org/proceedings/2016/BB/PharmaSUG-2016-BB15.pdf)

Regulatory Update – China NMPA (Cont)

The challenge of Chinese language and SAS XPT (v5)

Some SDTM Labels won't fit!

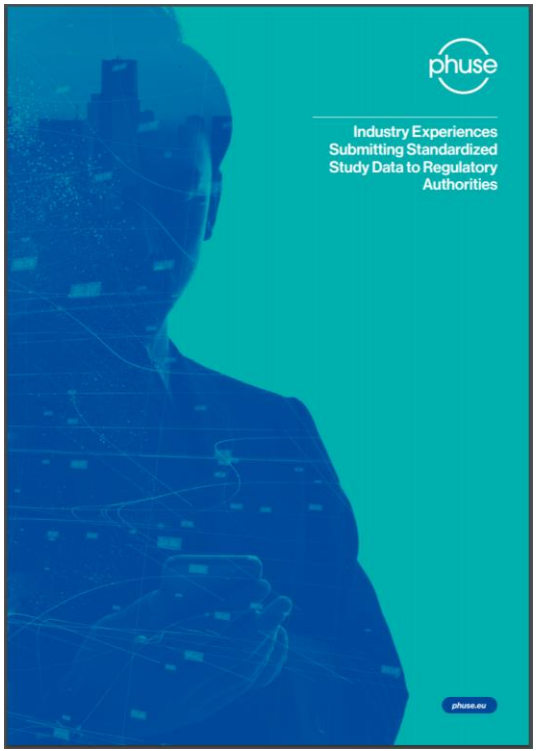
CMTRT: *Reported Name of Drug, Med, or Therapy*
Chinese: 报告药品报告药品名称,药物治疗
requires 42 bytes, available are only 40 - last character will be lost

HODECOD: *Dictionary-Derived Term for the Healthcare Encounter*
Chinese: 词典中针对医疗保健遇到的术语
requires 42 bytes, available are only 40 - last character will be lost

"Chinese and Asian characters in SAS Transport 5 datasets: Why that is the worst possible choice", J. Aerts, 2020 (unpublished CDISC-US Interchange poster)
http://xml4pharma.com/publications/Poster_Jozef_Aerts_Chinese_characters_XPT.pdf

PhUSE - Optimizing the Use of Data Standards

Industry Experiences Submitting Standardized Study Data to Regulatory Authorities

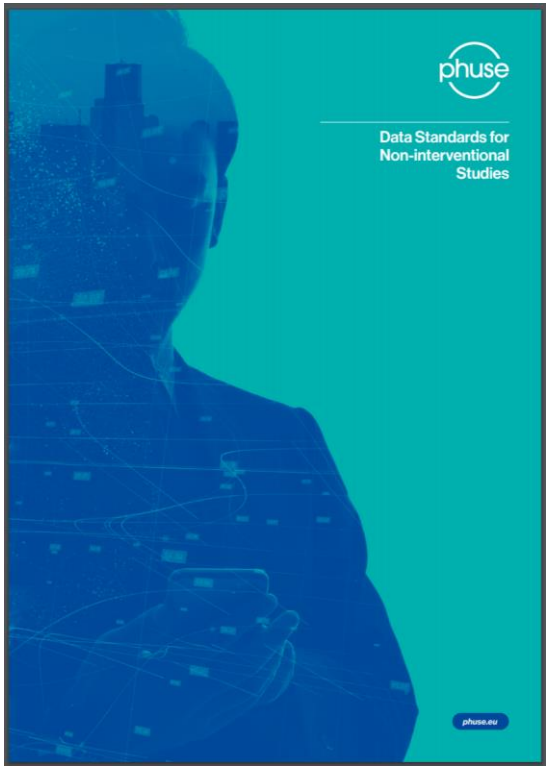


- The **FDA and PMDA** have **provided the industry with guidance documents and technical guides** for submitting **standardized study data**
- Over the course of implementation, the industry has recognized that the **requirements differ among FDA review divisions and between regulatory agencies across the globe**
- **FAQs**

http://phusewiki.org/docs/WorkingGroups/Deliverables/PHUSE%20-%20Industry%20Experiences%20Submitting%20Standardized%20Study%20Data%20to%20Regulatory%20Authorities.pdf

PhUSE - Optimizing the Use of Data Standards (Cont)

Data Standards for Non-interventional Studies



- **Non-interventional study data do not necessarily need to be submitted** to a regulatory agency, such as the FDA, there is **no strict requirement for data standards**
- However, given the **increasing interest in RWE**, this is **likely to change in the future**
- Identify the **most common data standards challenges** programmers experience while working on non-interventional studies and to suggest the means to deal with these challenges
- The practice of **mapping data to SDTM or ADaM** conventions has been identified as a **common issue**

http://phusewiki.org/docs/WorkingGroups/Deliverables/Data%20Standards%20for%20Non-interventional_%20Studies.pdf

Thank You!