cdisc

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Practices Sharing of Submitting NDA to NMPA for Vaccine MRCT Project

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ClinChoice昆翎

Meet the Speaker

Guanyu Su

Title: Senior Manager

Organization: ClinChoice Inc.

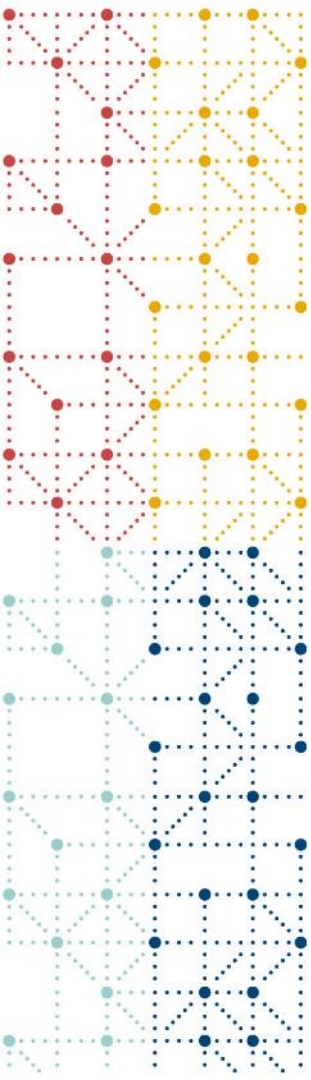
Guanyu Su is Senior Manager from statistical programming department in ClinChoice, graduated from China University of Petroleum – Beijing with bachelor's degree in Mathematics and Applied Mathematics. He has abundant experience in Oncology, Vaccine, etc. Till now, he has above 8 years experiences in clinical trial industry.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Agenda

1. Background
2. Key Process to Prepare for NMPA Submission
3. Introduction of the CFDI Inspection
4. Summary and Thought



Background

Background of the project

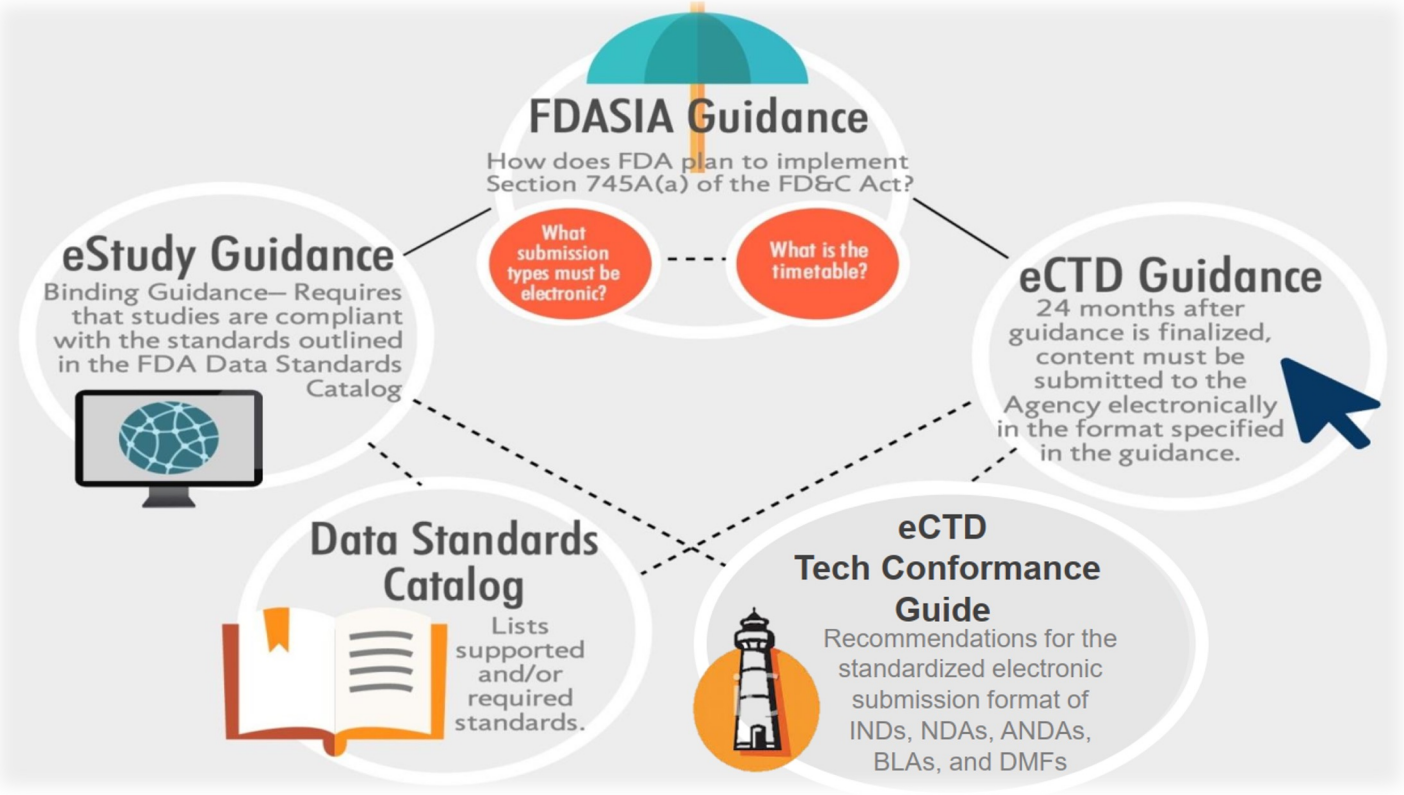
Challenges of the Project

FDA and NMPA Dual Submission

NMPA EUA Submission

Vaccine Study

FDA Guides


FDASIA Guidance
How does FDA plan to implement Section 745A(a) of the FD&C Act?
What submission types must be electronic?
What is the timetable?
eStudy Guidance
Binding Guidance– Requires that studies are compliant with the standards outlined in the FDA Data Standards Catalog
eCTD Guidance
24 months after guidance is finalized, content must be submitted to the Agency electronically in the format specified in the guidance.
Data Standards Catalog
Lists supported and/or required standards.
eCTD Tech Conformance Guide
Recommendations for the standardized electronic submission format of INDs, NDAs, ANDAs, BLAs, and DMFs

FDA Guides

Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

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Guidance for Industry

Technical Specifications Document

This guidance is for immediate implementation.

Table of Contents

FDA，《Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review, Version 2.1》，2019-12

FDA Data Standards Catalog v9.1 (04/19/2023)

FDA Data Standards Catalog v9.1 (04/19/2023) - Submission Data Standards

For full description of column headings, see Instr.& Column Descriptions tab

Use	Data Standard	Exchange Format	Standards Development Organization (SDO)	Version(s)	Designated Implementation Guide Version(s)	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY) [10] [11]	Date Requirement Ends (MM/DD/YYYY)	Statutory, Regulatory, or Guidance Authority Sources	Statutory, Regulatory, or Guidance Authority Sources
Clinical study datasets	ADaM	XPT	CDISC	ADaM v 2.1	1	CDER, CBER	Ongoing	03/15/2019 [1] 03/15/2020 [2] [12]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2] [12]	Standardized Study Data	
Clinical study datasets	ADaM	XPT	CDISC	ADaM v 2.1	1.1	CDER, CBER	03/15/2018		03/15/2019 [1] 03/15/2020 [2]		Standardized Study Data	
Clinical study datasets	ADaM	XPT	CDISC	ADaM v 2.1	1.2, 1.3	CDER, CBER	07/18/2022		03/15/2024		Standardized Study Data	
Clinical study datasets	SDTM	XPT	CDISC	SDTM v1.1	3.1.1	CDER, CBER	Ongoing	1/28/2015 [12]				Study Data Technical ...nce Guide
Clinical study datasets	SDTM	XPT	CDISC	SDTM v1.2	3.1.2	CDER, CBER	2009/10/30	03/15/2019 [1] 03/15/2020 [2] [12]				
Clinical study datasets	SDTM	XPT	CDISC	SDTM v1.2	Version 3.1.2 Amendment 1	CDER, CBER	08/07/	...15/2019 [...2020 [12]				
Clinical study datasets	SDTM	XPT	CDISC	SDTM v 1.3	3.1.3	CDER, CBER	12/01/2012	3/15/2021 [12]				
Clinical study datasets	SDTM	XPT	CDISC	SDTM v 1.4	3.2	CDER, CBER	08/17/2015		03/15/20... 03/15/2019 [2]			
Clinical study datasets	SDTM	XPT	CDISC	SDTM v 1.7	3.3	CDER, CBER	03/15/2021		03/15/2023		Standardized Study Data	
Nonclinical study datasets	SDTM	XPT	CDISC	SDTM v1.8	SENDIG-AR v1.0	CDER	03/15/2020		3/15/2022 [1] 3/15/2023 [2]		Standardized Study Data	
Study data definition	Define	XML	CDISC	1	N/A	CDER, CBER	Ongoing	3/15/2018 [12]	12/17/2016 [1] 12/17/2017 [2]	3/15/2018 [12]	Standardized Study Data	
Study data definition	Define	XML	CDISC	2	N/A	CDER, CBER	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		Standardized Study Data	
Study data definition	Define	XML	CDISC	2.1	N/A	CDER, CBER	03/15/2021		03/15/2023		Standardized Study Data	

- **Exchange Format Standards**
- **Study Data Standard**
- **Controlled Terminology Standard**

Exchange Format – Electronic Submissions

- ✓ Extensible Mark-up Language (XML)
  - Facilitates the sharing of structured data across different information systems.
- ✓ Portable Document Format (PDF)
  - Versions
  - Security
  - Fonts
  - Optimize For Fast Web View
  - Document Navigation (TOC(Table of Content), hypertext links, bookmarks)
  - Initial View Settings
- ✓ File Transport Format
  - SAS Transport Format (XPORT, xpt v5)
  - Dataset Size (maximum size, split if > 5 GB)
  - Dataset Column Length (maximum length of the variables)
  - Variable and Dataset Descriptor Length (Maximum length: Variable Name:8, Label:40)
  - Special Characters: Variables and Datasets (ASCII text code only)
  - Variable and Dataset Names
  - Variable and Dataset Labels

Study Data Standardization Plan (SDSP)

2. Planning and Providing Standardized Study Data

2.1 Study Data Standardization Plan

For clinical and nonclinical studies, sponsors should include a plan (e.g., during the early stages of product development conducted under the IND) describing the submission of standardized study data to FDA. The Study Data Standardization Plan (SDSP) assists FDA in identifying potential data standardization issues early in the development program. Sponsors may also initiate discussions at the pre-IND stage. For INDs, NDAs, and BLAs, the SDSP should be located in eCTD sections 1.13.9 General Investigational Plan or 1.20 General investigational plan for initial IND. Although a specific template is not specified, an example SDSP is available.[11]

The SDSP should be updated in subsequent communications with FDA as the development program expands and additional studies are planned. Updates to the SDSP should not be communicated each time a study is started. The cover letter accompanying a study data submission should describe the extent to which the latest version of the SDSP was executed. An SDSP should be provided with pre-NDA and pre-BLA meetings.

In addition, for clinical studies that will be submitted to CBER, the SDSP appendix should be provided to the review office no later than the End-of-Phase 2 (EOP2) meeting. The CBER SDSP appendix should include tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis.

Study Identifier	Brief Title	Study Design	Study Status	Study Start Date	Exchange Standards	Terminology Standards
Phase 2 Interventional Studies – Advanced Non-hematological Malignancies						
ABC-AM-002	MyNewDrug Orally Administered Drug-drug Interaction with Ketoconazole in Patients with Advanced Non-hematologic Malignancies	Randomized, Control None, Cross-Over Assignment, Double Blind, Pharmacokinetic/ Pharmacodynamic, Diagnostic	COMPLETED	2010-07-09	SDTM v1.1/ SDTM IG 3.1.1 SDTM define.xml 1.0 ADaM v2.1/ ADaM IG 1.0 ADaM define.xml 1.0 ***Up-versioned 2015-06-09*** SDTM v1.2/ SDTM IG 3.1.2 SDTM define.xml 2.0	CDISC SDTM Terminology 2007-06-05 MedDRA (Adverse Events) Initial:12.1 Final: 12.1 WHO-DD (Medications) 2009-03 ***Up-versioned 2015-06-09*** MedDRA (Adverse Events/ Medical History) Final: 18.0

FDA，《Study Data Technical Conformance Guide v5.4》，2023-06

Submission Data Package Components Requirement

aCRF

- Ensure that all fields are annotated with SDTM variables or marked as “Not Submitted”.
- Dual Bookmarking

Data

- Follow CDISC standards and provide in xpt format.
- Pinnacle 21 check the data and define
- Avoid technical rejection criteria

Controlled Terminology Standard

Common dictionaries should be used

Define-XML

Transmits metadata that describes any tabular dataset structure

Reviewer’s Guides

Suggest to use the latest version on PHUSE Website;
nsdrg, csdrg, adrg

Software Programs

- TXT format;
- Should provide the programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analysis.

NMPA Guides

- July 27, 2016. 药物临床试验数据管理与统计分析的计划和报告指导原则
- July 27, 2016. 药物临床试验数据管理工作技术指南
- June 01, 2017. 关于补交“临床试验数据库”资料的通知
- Oct 09, 2019. eCTD中临床试验数据库及相关资料的申报要求
- Jul 20, 2020. 发布《药物临床试验数据递交指导原则（试行）》的通告
- Sep 30, 2021. 关于实施药品电子通用技术文档申报的公告
- Nov 4, 2022. 公开征求《关于药品注册申请实施电子申报的公告（征求意见稿）》等文件意见

- ✓ 原始数据、分析数据建议采用XPT第5版本（简称XPT V5）或以上版本作为数据递交格式
- ✓ 鼓励申办方参照CDISC标准递交临床试验数据
- ✓ 必须递交数据说明文件，可以为XML或者PDF格式
- ✓ 鼓励递交数据审阅说明，应为PDF格式
- ✓ 注释病例报告表aCRF应为PDF格式，程序代码采用TXT格式

NMPA Data Submission Requirements

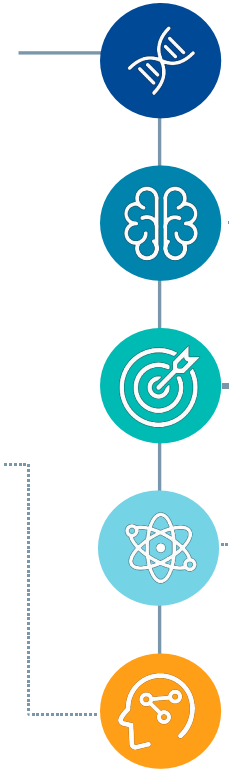
- 《药物临床试验数据递交指导原则》- 2020.07.20

原始数据库 (必须提交)

- 包含从CRF和外部文件中收集的原始数据，可能包含少量的衍生数据
- 原始数据集应按照主题进行组织命名，通常是两个英文字符，建议参考附录
- 指定的变量：STUDYID, SUBJID, USUBJID, VISIT, VISITNUM
- SDTM可以作为原始数据库

分析数据库 (必须提交)

- 用于产生和支持CSR中的统计分析结果
- 一般包含原始数据及按照规则衍生的数据
- 命名需要遵循adxxxx
- ADSL (受试者水平分析数据集)是必需的
- ADaM可以作为分析数据库



数据说明文件 (必须提交)

- 文件格式可以为XML或者PDF；通过XML提交时，需要附上可扩展样式表语言XSL(Extensible Stylesheet Language)文件
- 用于描述递交数据的文件（data metadata）
- 可以参考Define-XML模版或者简化后的中文版

数据审阅说明 (鼓励提交)

- 采用PDF格式
- 对于数据说明文件的补充，可以参考内部ADRG/cSDRG简化后的中文版

注释病例报告表 (必需提交)

- 采用PDF格式
- 在空白CRF的基础上，标准原始数据集中的变量或变量值与采集条目的映射关系
- 所有的采集条目都需要进行标注。没有采集或者使用的条目，需要特别标注为“不递交”（NOT SUBMITTED）

NMPA Data Submission Requirements

- 《药物临床试验数据递交指导原则》- 2020.07.20

内容	一般要求	外文数据库翻译最低要求
注释病例报告表aCRF	对采集的受试者数据（电子化的或者纸质的）信息单元（即字段信息）与递交原始数据集中对应的变量或变量值之间映射关系的具体描述。	为了收集数据所设计的问题描述；涉及疗效指标问题的取值或编码应为中文。
原始/分析数据库	如果申办方参照CDISC标准递交数据，则可将SDTM/ADaM视为原始/分析数据库。	数据集标签和变量标签，在临床总结报告等文件中出现的不良事件名称、合并用药名称、病史名称。
数据说明文件	至少应包含递交数据库中各数据集名称、标签、基本结构描述及每一数据集中各变量的名称、标签、类型、来源或衍生过程。	数据库中各数据集的描述 /标签和说明；数据集中各变量的描述 /标签和衍生过程；涉及疗效指标的取值或编码列表。
数据审阅说明	包括但不限于：研究数据使用说明、临床总结报告与数据之间的关系、研究文档中部分关键信息、所递交程序代码的使用说明、数据集所用编码及其它特殊情形说明等。	应为中文。
程序代码	分析数据集中衍生变量的衍生过程、疗效指标分析结果的生成过程。	

Difference for submission between FDA and NMPA

	FDA	NMPA
File Size for XPT	5GB	4GB
XPT Version	V5	V5 or above
Dataset Standard	CDISC standard	CDISC standard is recommended
Define	XML	XML or PDF

Key process to prepare for NMPA submission

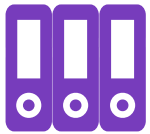
Files need to be Translated/Prepared

The submission was based on the IA results. The whole datasets and TLGs package had been completed in English. To support the NDA to NMPA, the Chinese package which met NMPA Data Submission Requirements need to be prepared.

SDTM

ADaM

aCRF



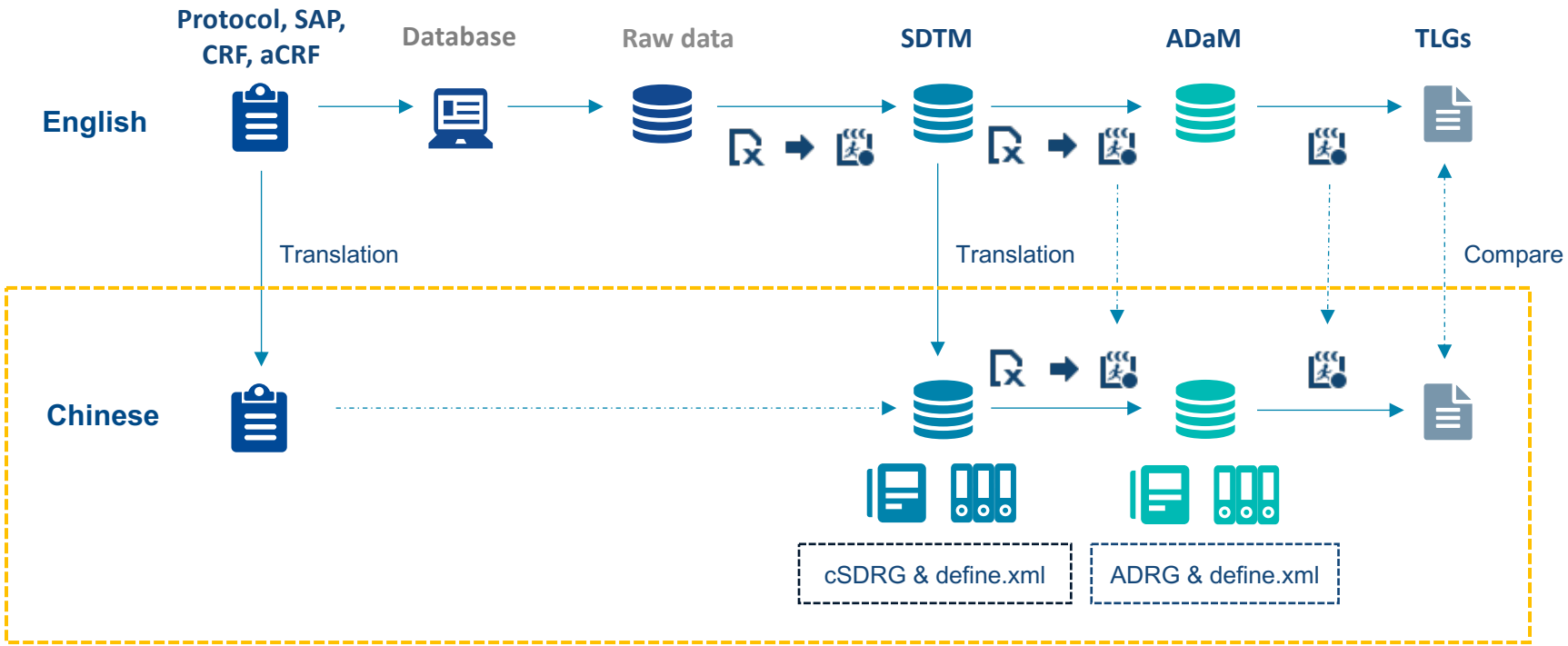
Define-XML

TLG

cSDRG

ADRG

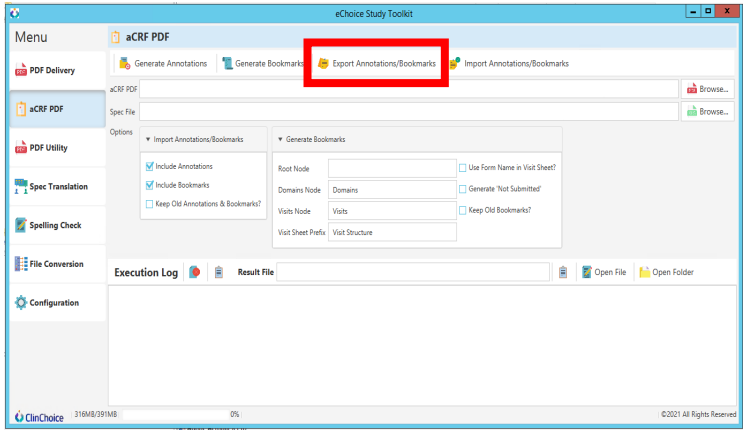
Key process to prepare for NMPA submission



aCRF translation

Export annotations/bookmarks

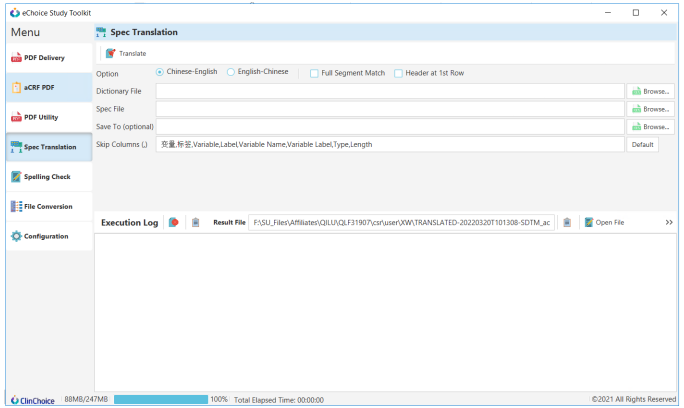
01



02

Translate aCRF annotations/bookmarks

- Central Dictionary
- Update page number if possible
- Manually review



03

Import annotations/bookmarks

- Manually review

SDTM datasets translation

Extract items need to be translated

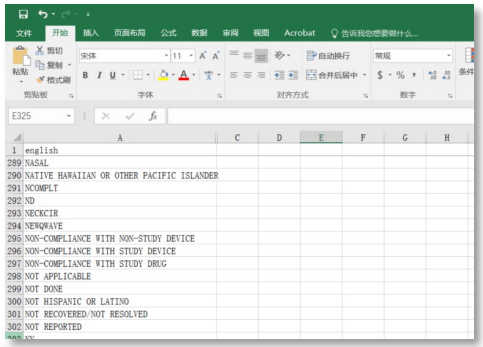
01

- Dataset label
- Variable label
- Code List
- Free text

Note: Garbled characters

Split variables

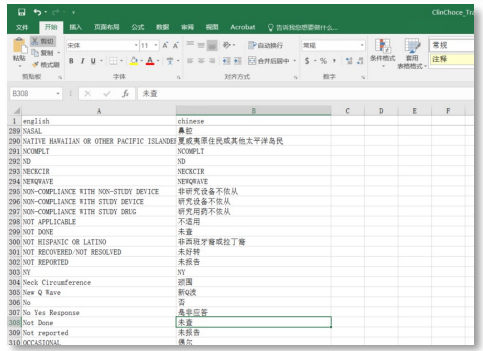
Remove duplicates



Prepare Dictionary

02

- SDTM IG3.2 Metadata
- ADaM IG1.1 Metadata
- ADaM-IG 1.1 OCCDS 1.0 metadata
- Controlled_Terminology_Chinese_Translation
- MA Team



Import items back to datasets

03

- Encoding
- Double programming
- Compliance check (P21&CCSCC)
- Compare with origin datasets
  - Truncation
  - Obs number/order
  - Variable number/type
  - Items that have not been translated should be consistent

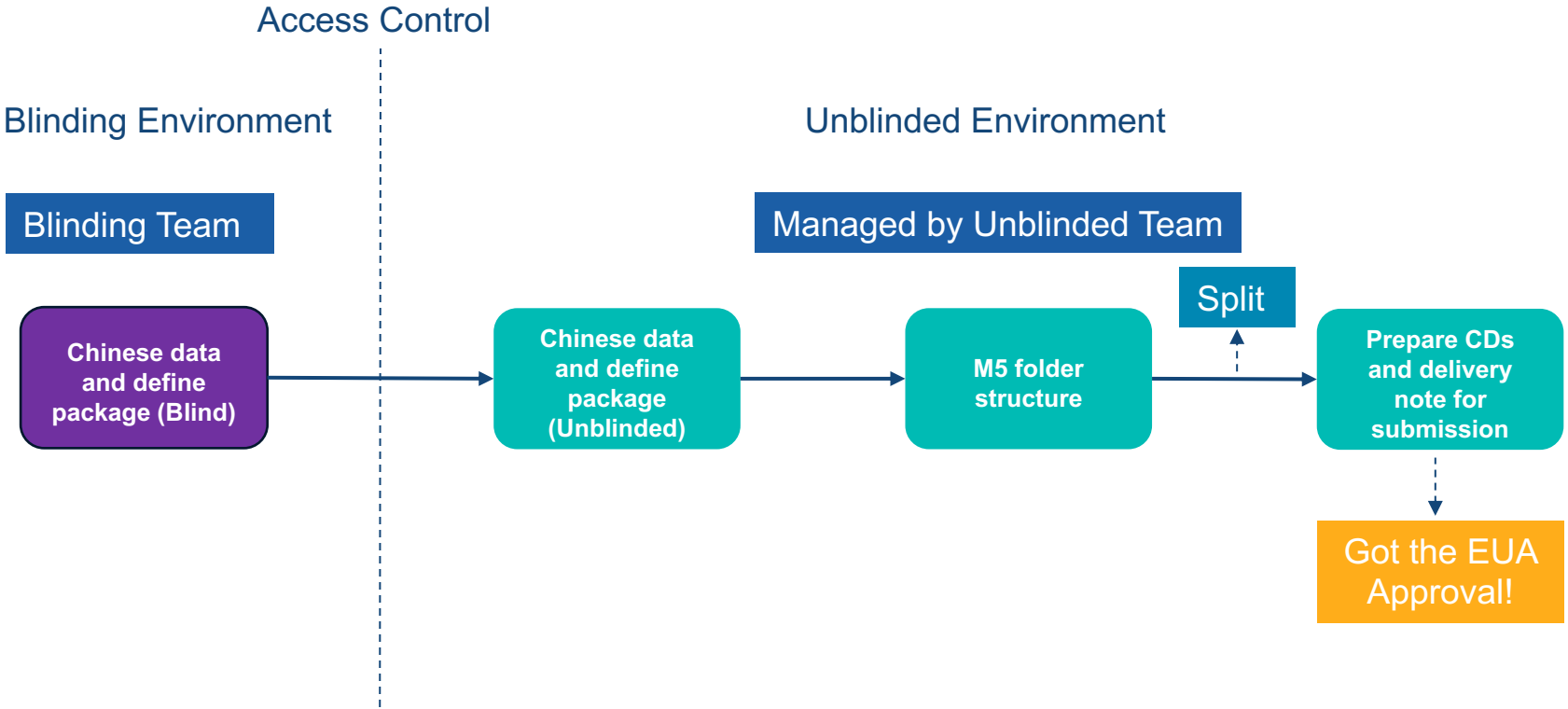
TLF translation

Dev programs (EN) → Dev programs (CN) → TLF outputs (CN) → TLF outputs (EN)

- TOC
- Header
- Tables column 1
- Listings body content
- Graphs axis label & legend
- Page break

Validation

Maintenance of Blinding



M5 Structure

Folder Name	Folder Level	Description/Contents
[module]	1	Refers to the eCTD module in which study data is being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level.
datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.
legacy	5	Contains legacy formatted analysis datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place legacy analysis datasets in this subfolder.
split	7	Place split legacy analysis datasets in this subfolder.
programs	6	Place software programs for legacy analysis datasets, tables and figures in this subfolder.
misc	4	Place miscellaneous datasets that don't qualify as analysis, profile, or tabulation datasets in this subfolder. This subfolder was formerly named "listings".
profiles	4	Place patient profiles in this subfolder.
tabulations	4	Contains subfolders for tabulation datasets. Do not place files at this level.
legacy	5	Place legacy (non-standardized) tabulation datasets in this folder.
split	6	Place any split legacy tabulations datasets in this subfolder.
sdtm	5	Place SDTM tabulation datasets in this subfolder. Should only be used in m5 for clinical data.
split	6	Place any split SDTM files in this subfolder.
send	5	Place SEND tabulation datasets in this subfolder. Should only be used in m4 for animal data.

Some Key Points

1. Consistency
Dictionary Control

2.Variable Split
Translate the merged text, split the translated text base on actual length

3.Encoding
UTF8

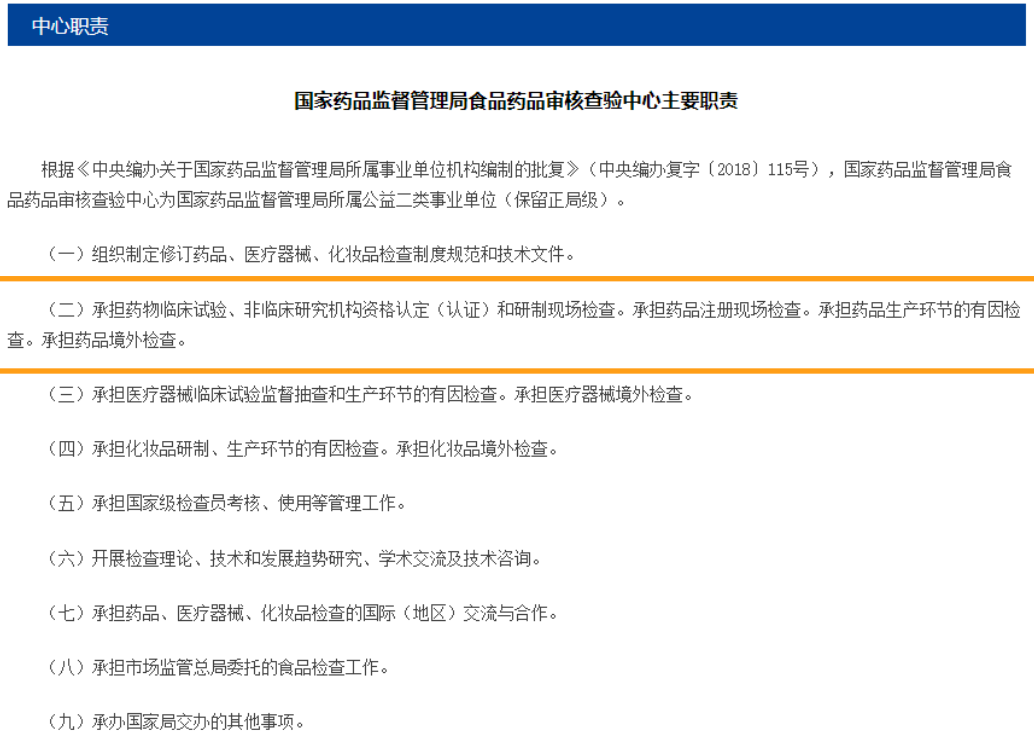
4.Page number in translated files
Bookmark and Annotation in aCRF

5.Derivation、Complex Algorithms、Review Guide
Translation department, Programmer review

6.Validation
Double programming
Pinnacle 21
CCSCC tool

Introduction of the CFDI inspection

Introduction of the CFDI inspection



中心职责

国家药品监督管理局食品药品审核查验中心主要职责

根据《中央编办关于国家药品监督管理局所属事业单位机构编制的批复》（中央编办复字〔2018〕115号），国家药品监督管理局食品药品审核查验中心为国家药品监督管理局所属公益二类事业单位（保留正局级）。

（一）组织制定修订药品、医疗器械、化妆品检查制度规范和技术文件。

（二）承担药物临床试验、非临床研究机构资格认定（认证）和研制现场检查。承担药品注册现场检查。承担药品生产环节的有因检查。承担药品境外检查。

（三）承担医疗器械临床试验监督抽查和生产环节的有因检查。承担医疗器械境外检查。

（四）承担化妆品研制、生产环节的有因检查。承担化妆品境外检查。

（五）承担国家级检查员考核、使用等管理工作。

（六）开展检查理论、技术和发展趋势研究、学术交流及技术咨询。

（七）承担药品、医疗器械、化妆品检查的国际（地区）交流与合作。

（八）承担市场监管总局委托的食品检查工作。

（九）承办国家局交办的其他事项。

Refer to: https://www.cfdi.org.cn/cfdi/index?module=A002&m1=15&m2=1501&nty=STA001&tcode=STA002

Introduction of the CFDI inspection

Part.1

Study Lead Programmer support on-site

Answer questions about the data and results, and help to filter and check data for CDE experts

+

Part.2

Statistician and Programming manager support online

Answer questions and do some analysis per experts' request

+

Part.3

PM, QC, RA, etc.

Coordination, communication, support any other document verification

=

Part.4

To pass the CFDI inspection successfully

One week to full time on it

Focus points during the CFDI inspection

Points

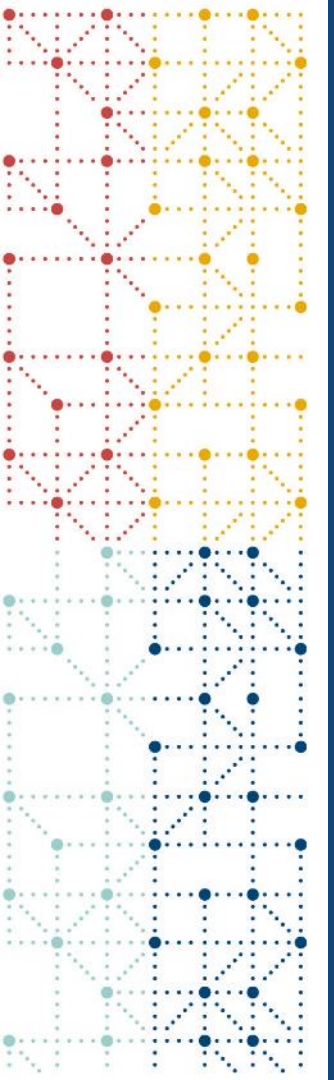
- Randomization and sample selection
- Data and analysis results
- Protocol deviation
- SOP training
- Servers, tools
- Documentations

Questions

- Randomization can be reproduced?
- Need to review data for selected sites
- What's the PD codes stand for?
- Did everyone finished SOP training before joining the study?
- Do the servers, tools safety?
- Why some documents didn't be signed, or didn't be signed by everyone involved

Solutions

- Reproduced on the randomization software
- Generated some outputs for selected sites only; Provide program to convert XPT to SAS
- Provided the instruction file
- Provided the training records
- Provided the validation files of the severs and tools by IT
- Provided note to file



Summary and Thought

Summary and Thought

During the preparation of the NMPA submission for this study, what's more important is to keep consistent between the Chinese version and English version data/documents, and to meet the NMPA submission requirements. We were searching and practicing a better way to make the process more efficient and accurate.

Summary and Thought

For programming process:

- Suggest to prepare both English and Chinese version at the same time if possible.
- Suggest to follow CDISC standard as much as possible when we prepare NMPA submission.
- It's important to keep consistent between English version and Chinese version.
- The blinding should be strictly maintained through all processes until the study is unblinded.
- Obey the local law/policy first.

For CFDI inspection:

- Any key or important process need a signed file to support.
- A signed meeting minutes for everyone is required for any key meeting.
- Any import files to support the inspection need to have a Chinese version.
- Everyone who need to support CFDI inspection is expected to be familiar with the study.

Thank You!