



SA05 – Navigating first Data Submission: Pierre Fabre's Journey and Insights into Data Submission Challenges with the NMPA

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PHUSE EU Connect 2024: Submissions & Agencies (SA)



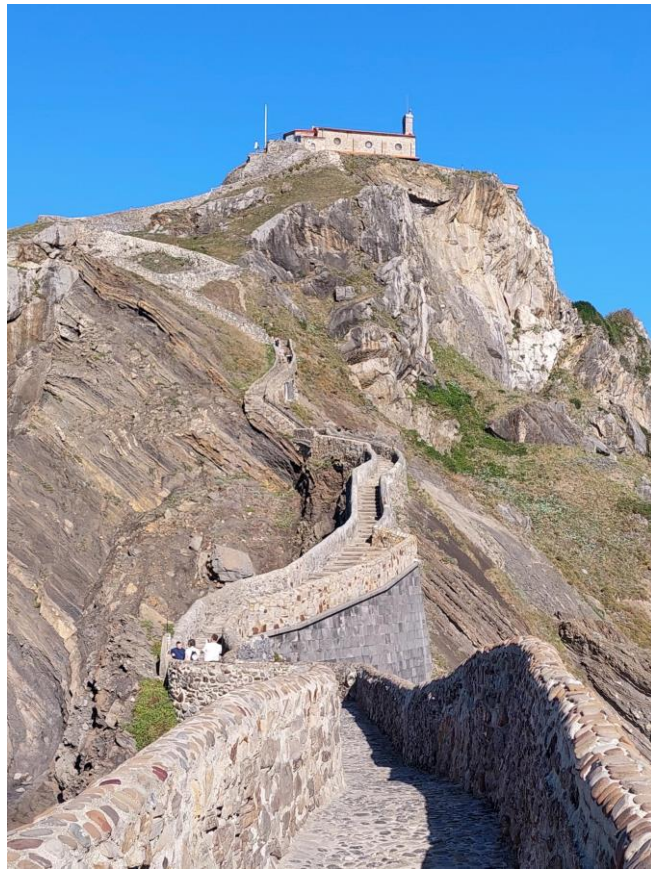
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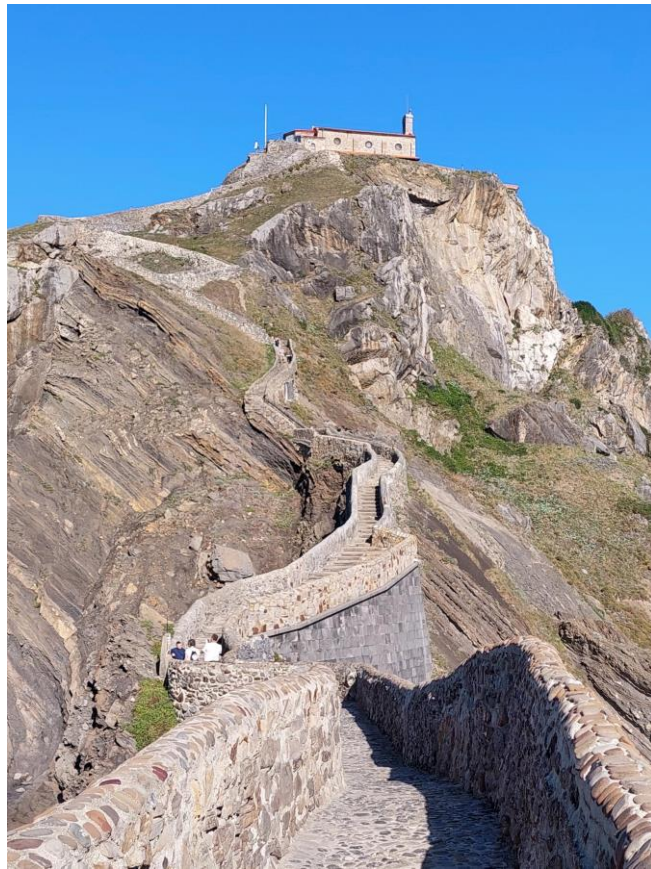
Introduction

- Pierre Fabre conducted global pivotal worldwide clinical trials for oncology product in CRC and NSCLC:
 - Supported FDA and EMA approvals
 - China mainland not included
- Pierre Fabre initiated in 2021 specific clinical trials in China mainland and Taiwan to access Chinese market:
 - First submission to NMPA in August 2024
 - Second submission planned in January 2025

How data submission to NMPA looks like for Pierre Fabre?



How data submission to NMPA looks like for Pierre Fabre?



Let's start with NMPA Guidance

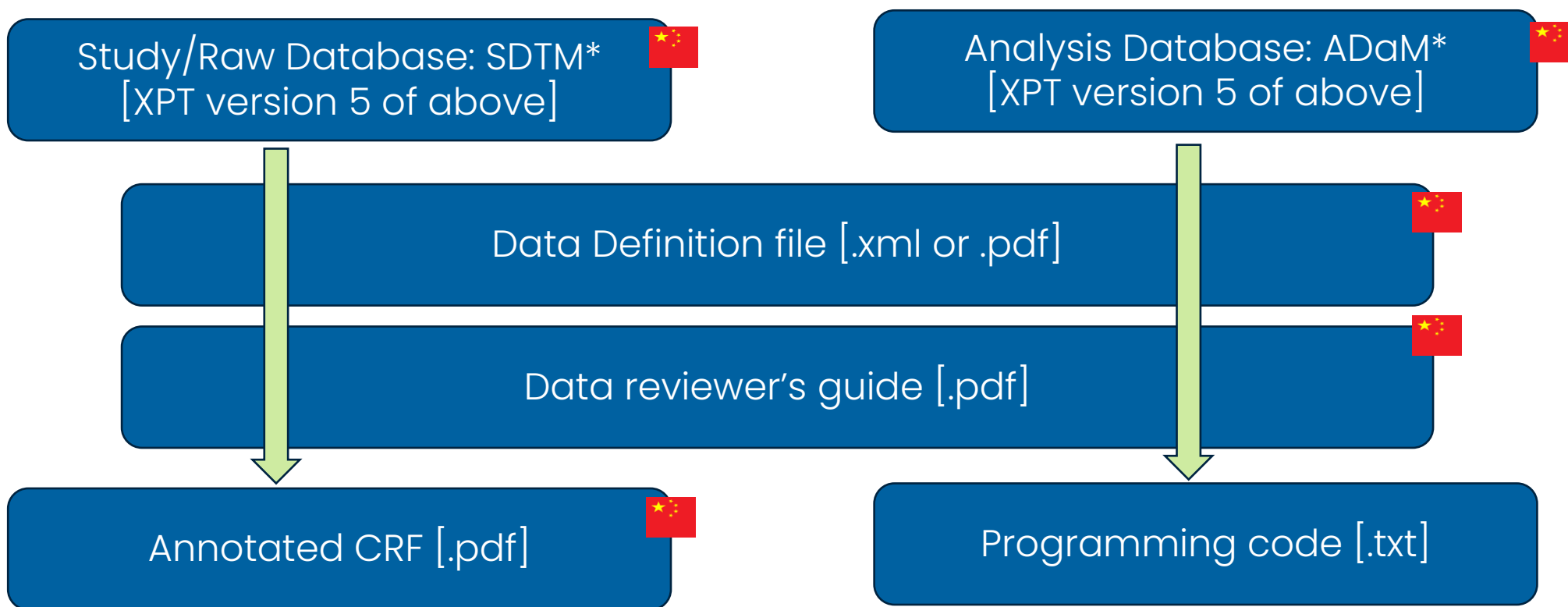
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6 **Guideline on the Submission of Clinical Trial**
7 **Data**
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9 **(for trail implementation)**
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20 **Center for Drug Evaluation, NMPA**
21 **Jul, 2020**
22
23
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- Available in Chinese on the NMPA website
- Translated version obtained from professional network
- Additional documentation found on the web: P21 webinar, PharmaSUG or PHUSE archives

药物临床试验数据递交指导原则 (nmpa.gov.cn)

Six key elements of clinical data package



** If a sponsor submits clinical trial data according to CDISC standards; not mandatory*

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CDE consultation

- One of Pre-NDA meeting objectives was to ensure the data package and translation strategy is adequate

	English Version	Chinese Version
Global worldwide trial	Yes	Yes
Local safety lead-in trial (different dosage)	Yes	No
Local pivotal trial in China	Yes	Yes
Integrated Safety Pool	Yes	No

- Response from CDE: *"Please submit the Chinese version of the relevant contents"*
- Recommendation from Affiliate and Global CRO regulatory teams based on guidance:
 - No change in data package submission
 - Integrated Safety Pool translated but not submitted: upon request during the NDA review (timelines)

Study and Analysis databases – Translation

- For study database, at least the following content should be in Chinese:
 - dataset label and variable label
 - adverse events terms
 - generic name of concomitant medications
 - Medical history in CSR and other documents
- Process:
 - Excel file created with all unique terms translated, reviewed by Sponsor Affiliate
 - Translated terms uploaded and replacing English terms

AETERM_EN	AETERM_CN
ABDOMINAL BLOATING	腹部膨胀
ABDOMINAL CRAMP	腹部痉挛性绞痛
ABDOMINAL CRAMPS	腹部痉挛性绞痛
ABDOMINAL DISCOMFORT	腹部不适
ABDOMINAL DISTENSION	腹胀
ABDOMINAL PAIN	腹痛
ABDOMINAL PAIN (LOWER)	腹痛 (下)

Study and Analysis databases - Example

Dataset label and variables label are translated



SITEID	AGE	AGEU	AGEGR1	AGEGR1N	SEX	RACE
15601	47	YEARS	<65	1	M	ASIAN
15601	68	YEARS	65 - 74	2	M	ASIAN
15601	55	YEARS	<65	1	M	ASIAN
15601	67	YEARS	65 - 74	2	F	ASIAN
15601	71	YEARS	65 - 74	2	F	ASIAN



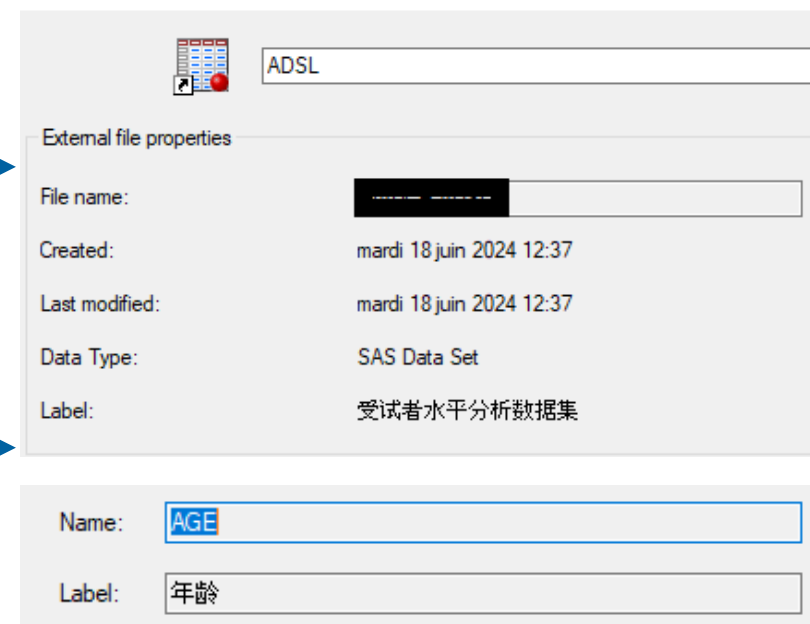
SITEID	AGE	AGEU	AGEGR1	AGEGR1N	SEX	RACE
15601	47	YEARS	<65	1	M	ASIAN
15601	68	YEARS	65 - 74	2	M	ASIAN
15601	55	YEARS	<65	1	M	ASIAN
15601	67	YEARS	65 - 74	2	F	ASIAN
15601	71	YEARS	65 - 74	2	F	ASIAN

*View with variable
name*



研究中心标识符	年龄	年龄单位	年龄组 1	年龄组 1(N)	性别	种族
15601	47	YEARS	<65	1	M	ASIAN
15601	68	YEARS	65 - 74	2	M	ASIAN
15601	55	YEARS	<65	1	M	ASIAN
15601	67	YEARS	65 - 74	2	F	ASIAN
15601	71	YEARS	65 - 74	2	F	ASIAN

View with variable label



ADSL

External file properties

File name: [REDACTED]

Created: mardi 18 juin 2024 12:37

Last modified: mardi 18 juin 2024 12:37

Data Type: SAS Data Set

Label: 受试者水平分析数据集

Name: AGE

Label: 年龄

Study and Analysis databases – Example

Adverse Event terms and coding variables translated



AETERM	⚠ AEDECOD	⚠ AEBODSYS	123 AEBDSYCD	⚠ AELLT	123 AELLTCD
ALANINE AMINOTRANSFERASE INCREASED	Alanine aminotransferase increased	Investigations	10022891	Alanine aminotransferase increased	10001551
ARTHRODYNIA	Arthralgia	Musculoskeletal and connective tissue disorders	10028395	Arthralgia	10003239
RASH ACNEIFORM	Dermatitis acneiform	Skin and subcutaneous tissue disorders	10040785	Rash acneiform	10037847
DIARRHEA	Diarrhoea	Gastrointestinal disorders	10017947	Diarrhea	10012727
DIARRHEA	Diarrhoea	Gastrointestinal disorders	10017947	Diarrhea	10012727
HEPATALGIA	Hepatic pain	Hepatobiliary disorders	10019805	Hepatic pain	10019705



AETERM	⚠ AEDECOD	⚠ AEBODSYS	123 AEBDSYCD	⚠ AELLT	123 AELLTCD
丙氨酸氨基转移酶升高	丙氨酸氨基转移酶升高	各类检查	10022891	丙氨酸氨基转移酶升高	10001551
关节痛	关节痛	各种肌肉骨骼及结缔组织疾病	10028395	关节痛	10003239
痤疮样皮疹	痤疮样皮炎	皮肤及皮下组织类疾病	10040785	痤疮样皮疹	10037847
腹泻	腹泻	胃肠道系统疾病	10017947	腹泻	10012727
腹泻	腹泻	胃肠道系统疾病	10017947	腹泻	10012727
肝痛	肝痛	肝胆系统疾病	10019805	肝痛	10019705

Study and Analysis databases – Challenges

Chinese translations in database should be consistent with all other documents in submission package

Two vendors used for translation:

- Affiliate vendor for study documents (e.g. CSR)
- Global CRO Chinese programming team for databases

→ CRO consistency step needed at the time of translation



Dataset labels and variable labels should be in Chinese and should not exceed 40 bytes in length.

After translation threshold sometimes exceeded in Chinese, label was reworded.

Study and Analysis databases – Challenges

Reencoding of study datasets using UTF-8 was needed prior to starting translation activities to allow Chinese characters which require more than one byte.

Some Chinese characters require more than one byte

PROC COMPARE was done to ensure there was no change in English version of datasets after encoding change

Due to transcoding from wlatin1 to utf8, the length of some variables increased to more than 200 characters, which is not allowed for XPT file version 5

Decision to use XPT V8 as per guidance: SAS Transport File Format version 5 (...) or above is recommended

Example: Protocol deviation terms in DV/ADDV

Data Definition file

- Data Definition file provided in the Guidance is referring to define.xml
- Both SDTM and ADaM define should be submitted
- At least the following content should be translated in Chinese:
 - description/label and specification of each dataset in the database
 - description/label and derivation process of variables in dataset
 - values or codelists of **efficacy indicators**
- Process:
 - SDTM and ADaM specification excel files were translated in Chinese to recreate Define.xml document
 - Note: aCRF or SAP pagination could change during translation, page number reference in Define.xml should be adjusted

Data Definition file – Example

Define-XML文档的创建日期/时间: 2024-06-18T23:18:52-04:00

Define-XML版本: 2.0.0

样式表版本: 2018-11-21

标准 ADaM-IG 1.1

研究名称 [REDACTED]

研究概要 [REDACTED]

协议名称 [REDACTED]

元数据名称 Study [REDACTED] Data Definitions

数据集

数据集	描述	类	结构	目的	按键	文献资料	位置
ADSL	受试者水平分析数据集	SUBJECT LEVEL ANALYSIS DATASET	每名受试者一条记录	Analysis	STUDYID, USUBJID	详情请参阅 ADRG 第 16 页。	adsl.xpt 
ADEG	心电图分析数据集	BASIC DATA STRUCTURE	每名受试者每个参数每个分析访视每个分析时间点一条记录	Analysis	STUDYID, USUBJID, PARAMCD, AVISITN, ATPTN	详情请参阅 ADRG 第 16 页。	adeg.xpt 
ADEX	暴露分析数据集	BASIC DATA STRUCTURE	每名受试者每个治疗每个参数一条记录	Analysis	STUDYID, USUBJID, ECTRT, PARAMN		adex.xpt 
ADIE	入选/排除分析数据集	BASIC DATA STRUCTURE	每名受试者每个类别每个参数每个分析访视一条记录	Analysis	STUDYID, USUBJID, SUBJID, PARAMCD, AVISITN		adie.xpt 
ADLB	实验室检查分析数据集	BASIC DATA STRUCTURE	每名受试者每个类别每个参数每个分析访视一条记录	Analysis	STUDYID, USUBJID, PARCAT1, PARAMN, AVISITN	详情请参阅 ADRG 第 17 页。	adlb.xpt 

Description

Structure

Documentation

Data Definition file – Examples

Derivation of confirmed Best Overall Response

AVALC VLM		分析值(C)	text	59		Derived 在 VLM 中描述每个参数的来源/推导 见VLM
	PARAMCD = "BRESPC" (经确 认最佳缓解)	经确认最 佳缓解	text	59	经确认最佳缓解的分析值(C) [6 术语]	Derived 1) 设置为 BRCNFL = "Y" 时的 ADTRL.AVALC (AVAL 数值)。如果患者在 ADTRL 中没有 BRCNFL = "Y" 的记录, 或者 BRCNFL = "Y" 的记录为 AVAL = -1, 则考虑 2) 如果患者有 i) AVAL = 4 或 5 的记录, 并且 ii) ADY >=43, 并且 iii) PRCANFL = "Y", 并且 iv) 之前没有 AVAL = -1 的记录, 则设置 AVALC = '疾病稳定' (AVAL = 3)。否则 如果患者在 ADTRL 中没有符合上述标准 (1) (2) 的记录, 但患者在 ADTRL 中, 则设置 AVALC = "不可评估" (AVAL = -99)。如果患者在 ADTRL 中没有记录, 然后设置为 "不可评估" (AVAL = -99)。

Label

Codelist

Description

Codelist for OS censoring

总生存期的事件或删失描述(月)

允许值 (代码)
死亡
失访
不再进行生存随访 (因撤回知情同意和失访之外的原因终止研究的存活受试者)
仍在参加研究, 未发生死亡
撤回知情同意

Codelist for confirmed Best Overall Response

经确认最佳缓解的分析值(C)

允许值 (代码)
完全缓解
非CR/非PD
不可评估
部分缓解
疾病进展
疾病稳定

CONFIDEI

Data reviewer's guide translated in Chinese, with version encoding

分析数据审阅说明

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Annotated CRF

- For aCRFs, at least the following content should be in Chinese:
 - description of questions designed to collect data
 - values or codelists of efficacy indicators
- Process:
 - aCRF translation was done starting with Blank CRF translation in Word
 - SDTM mapping added in Chinese in PDF version.

Annotated CRF – Example

DM="Demographics"

SUPPDM="Supplemental Qualifiers for DM"

5.0_PROD_CCB4_LJ_11Dec2023: All Unique Forms

Project Name: [REDACTED]

Form: Demographics

Generated On: 11 Dec 2023 12:01:23

Age at entry in the study (Years) AGE

Age Unit AGEU YEARS ☐

Sex SEX

Race RACE

If Other, Specify SUPPDM.QVAL where QNAM="RACEOTH"

DM="人口学"

SUPPDM="人口学补充修饰语数据集"

5.0_PROD_CCB4_LJ_11Dec2023: 所有唯一表格

项目名称: [REDACTED]

表格: 人口统计学

生成时间: 2023年12月11日 12:01:23

入组研究时的年龄 (岁) AGE

年龄单位 AGEU 岁 ☐

性别 SEX

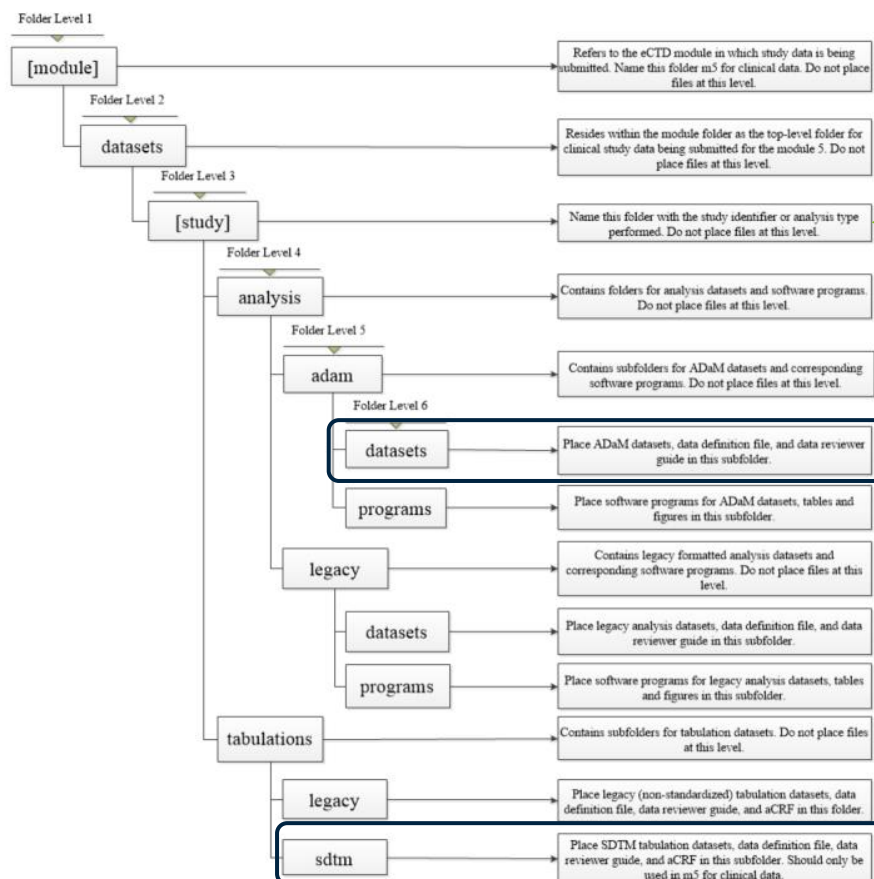
人种 RACE

如为其他, 请说明 当 QNAM="RACEOTH" 时, 设为 SUPPDM.QVAL 的值

Programming code

- Sponsors should submit programming codes in TXT format:
 - Derivation process of derived variables of analysis datasets: ADaM datasets only (not SDTM)
 - Generation process of analysis results for the efficacy endpoints
- Programming codes submitted should be readable, understandable, executable, and do not include external program calls, which in particular avoid using external macro programs:
 - Macro variables embedded at the top of each program
 - SAS programs are not translated
- Pierre Fabre decision: Submit Primary and key secondary efficacy endpoint programs

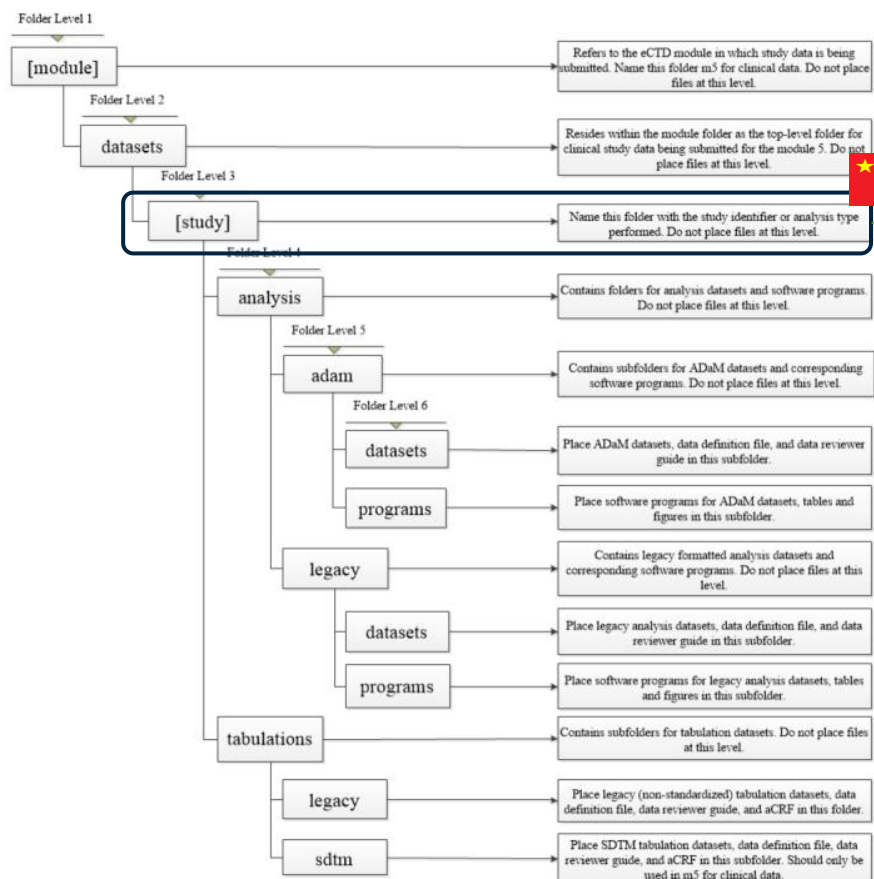
How to integrate the Chinese documentation in module 5?



Option 1: Create a new « Study » folder for Chinese translated databases

Option 2:
Create subfolders for Chinese translated databases

How to integrate the Chinese documentation in module 5?



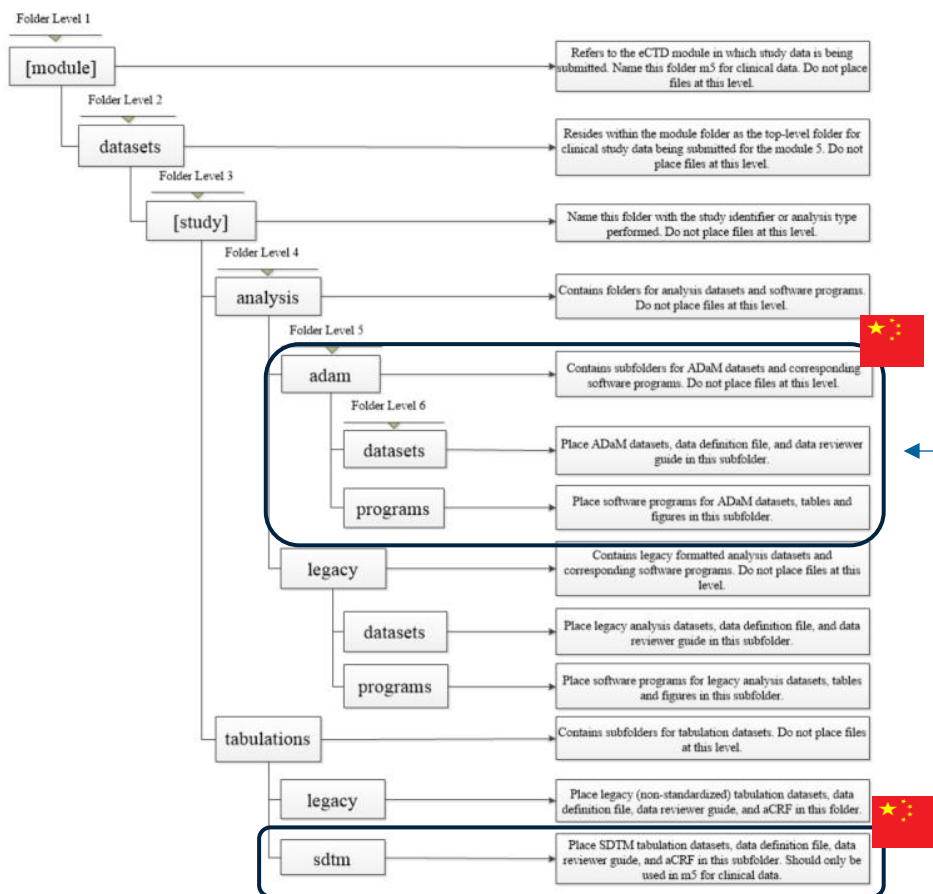
PF decision to create a dedicated STUDY folder for each translated study

- ▼ m5
 - ▼ datasets
 - ▼ globaltrial-chinese
 - ▼ analysis
 - ▼ adam
 - datasets
 - programs
 - ▼ tabulations
 - sdtm
 - ▼ globaltrial-english
 - ▼ analysis
 - ▼ adam
 - datasets
 - programs
 - ▼ tabulations
 - sdtm
 - > iss-en
 - > localtrial-chinese
 - > localtrial-english

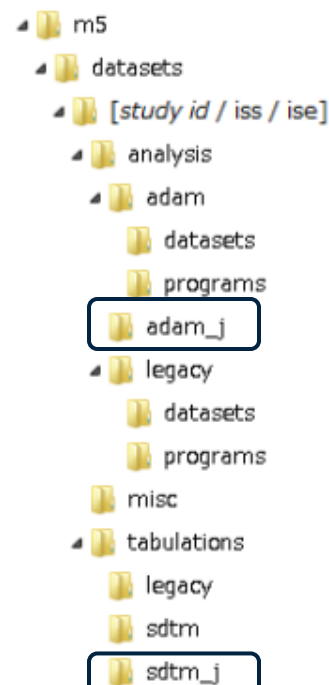
Global Study NDA data package translated

Global Study NDA data package

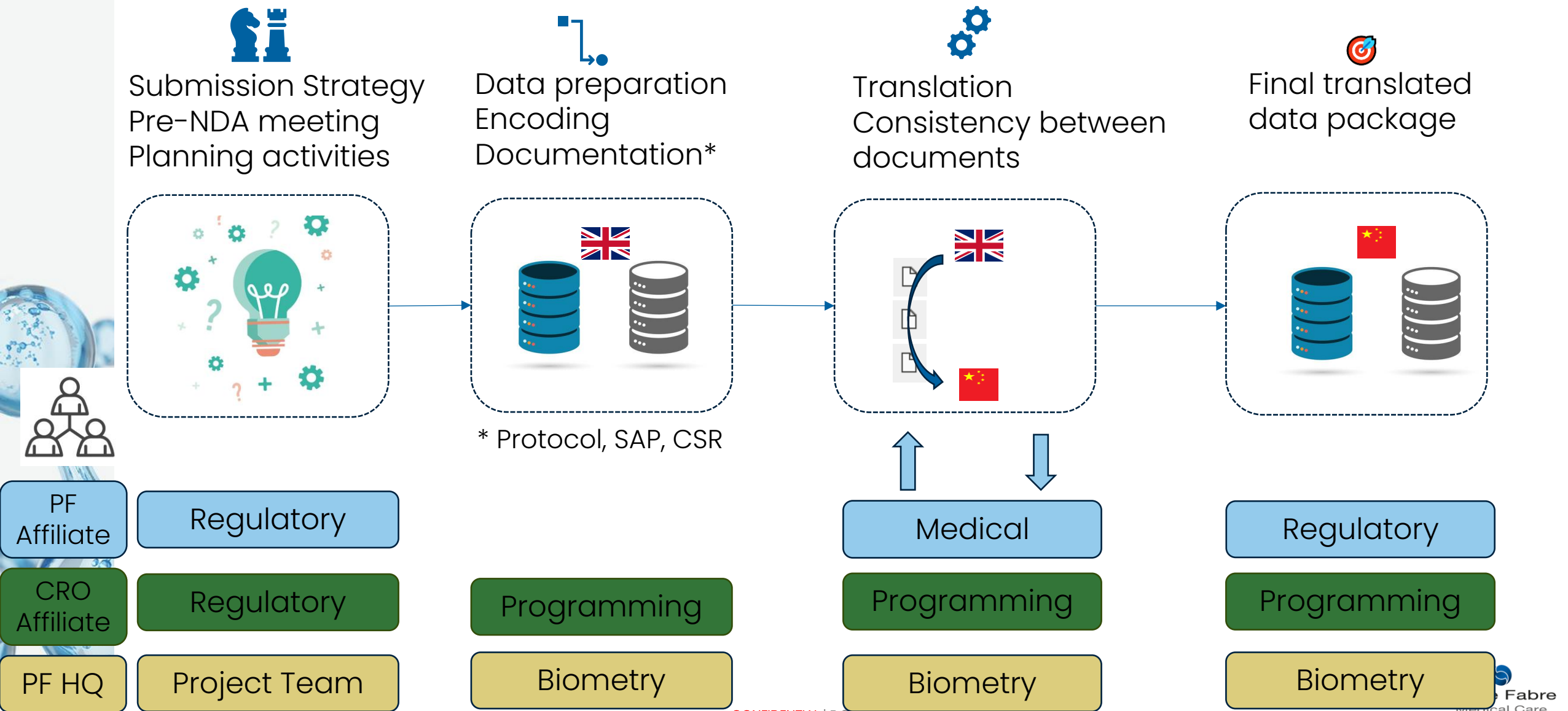
How to integrate the Chinese documentation in module 5?



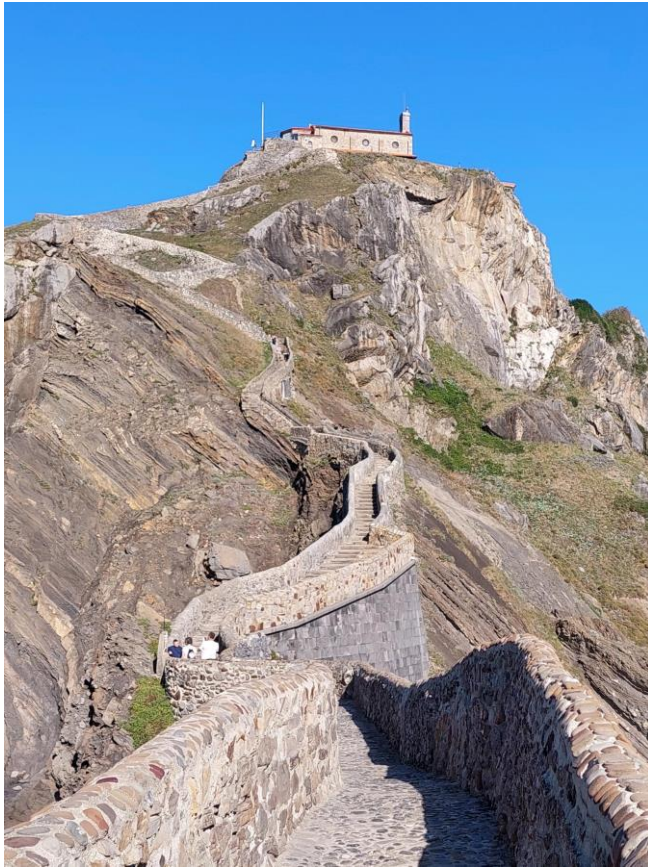
Option 2:
Create subfolders for Chinese documentation
PMDA recommendation April 2024: [LINK](#)



Teamwork was key element of success



You remember how data submission to NMPA initially looked like for Pierre Fabre, right?



Well, that's how it really was!



Thank you for your attention

Q&A

SA05

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into Data Submission Challenges
with the NMPA

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Links

- [Preparing CDISC Submissions for China's NMPA \[Updated\] | Pinnacle 21](#)
- [New Requirements of Clinical Trial Data Submission for China Filing: An Implementation \(lexjansen.com\)](#)
- [Challenges and solutions for e-data submission to NMPA under new regulation \(lexjansen.com\)](#)
- [Submitting Software Programs to the Regulatory Agencies – Clinical Trial Software & Data Analysis | Cytel | Contact Us](#)