

New Requirements of Clinical Trial Data Submission for China Filing: An Implementation

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ABSTRACT

The National Medical Products Administration (NMPA) has released the Guideline on the submission of clinical trial data on October 1st, 2020, which demonstrated the specific requirements of data submission to agency in China filings. This has brought new opportunities and challenges to all sponsors.

This paper introduces the new requirements of China data submission guideline, as well as two types of execution process which were used in recent pilot filings as implementations to the guideline. Moreover, the paper summarizes the benefits and issues that we encountered during the preparation of submission packages.

INTRODUCTION

With more and more applications for registration of new drugs in China, the requirements of data submission to China agency are getting much more attention. NMPA has been constantly refining the guideline on the submission of clinical trial data through the recent decade. The latest version was announced in July 2020 (draft version) and effective from October 1st, 2020, which stated the detailed requirements of data standard in the submission, the contents in the submission package, the translation of foreign language database and that each sponsor should follow.

This paper describes the key points of the new China data submission guideline, shows some experience about Chinese translation implementation based on the English submission version, and summarizes the benefits and problems during the preparation of submission packages.

NMPA NEW CLINICAL DATA SUBMISSION GUIDELINE

EVOLUTION OF DATA SUBMISSION REQUIREMENTS

The National Medical Products Administration (NMPA) has constantly improved and standardized the requirements of clinical trial data submission, especially in recent two years. The characteristics of requirements are becoming from general to comprehensive, from no data standard specified to CDISC encouraged, and from one-way message transmission to interactions between the agency and sponsors.

The diagram below shows evolution of clinical trial data submission requirements based on related official documents from China agency.

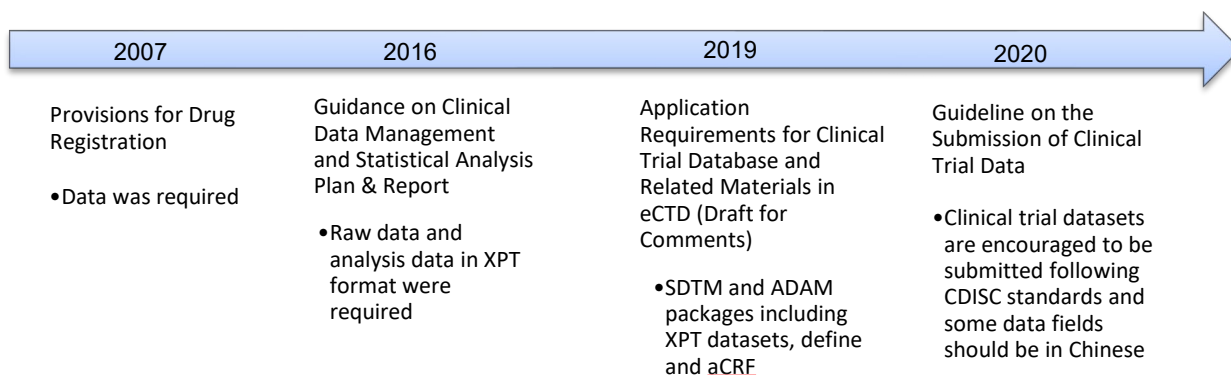


Figure 1. Evolution of Key Data Submission Requirements

ESSENTIALS OF NMPA NEW CLINICAL DATA SUBMISSION GUIDELINE

In the latest guideline, the submitted clinical trial datasets are recommended to follow CDISC standard. The submission data packages include the following items.

1. SDTM package: SDTM (Study Data Tabulation Model) datasets are source datasets to ADaM (Analysis Data Model), and they were collected from the case report forms (CRFs) or external data sources with minimum derivation.

This package should include: SDTM datasets in XPT format (usually using utf8/euc-cn encoding), data definition file (Define.xml/Define.pdf), clinical study data reviewer's guide (cSDRG.pdf), and annotated case report forms (aCRF.pdf)

2. ADaM package: ADaM datasets are the derived datasets and input to statistical results in CSR. ADaM datasets should have clear traceability from data source through the derivation support statistical analysis with minimum programming.

This package should include: ADaM datasets in XPT format (usually using utf8/euc-cn encoding), data definition file (Define.xml/Define.pdf), analysis data reviewer's guide (ADRG.pdf), statistical programs of datasets and reports in TXT format. The programs should be comprehensive, readable, with enough comments and without references to macros.

There are specific requirements to the contents in the package, major one of them is the translation of the foreign language database. The contents that should be translated to Chinese include:

1. Database: Dataset and variable labels; names of AE, CM and MH categories and terms as reported in CSR and other documents
2. Define: Description of dataset; description and derivation of variables; values or coding list for efficacy indicator
3. aCRF: Description of the questions that were designed to collect data; value or coding of questions for efficacy indicator
4. cSDRG and ADRG: Full context should be in Chinese. If the datasets need to be encoded to present the Chinese language, the encoding format (e.g. UTF-8, euc-cn, etc.) should be documented in cSDRG and ADRG.

EXECUTION PROCESSES OF TRANSLATION

In 2020, We had a few studies that should follow the new guideline to conduct the filings to NMPA. We made investigations and decided to use different types of executions to run the translation process on separate pilot studies. Both types of executions have been completed and the packages were submitted to the agency successfully.

TYPE I: TRANSLATION VENDOR + SPONSOR TRANSLATION

After we finalized the submission package in English version, a translation vendor, which had CSR translation experience, was selected to take charge of document translation, including SDTM and ADaM Pinnacle21 metadata EXCEL spec, cSDRG, aCRF, and ADRG. Sponsor took charge of datasets translation, including AE/MH/CM Term and Dataset/Variable Labels (SDTM/ADaM). Refer to Figure 2 below. After the translated deliverables were received, the sponsor made a thorough review and necessary updates:

- 1) Used SAS macros to read in the dataset/variable labels from translated metadata and applied them to the database
- 2) Used SAS macros to translate AE/MH/CM terms with the inputs of corresponding versions of MedDRA and Drug Dictionary
- 3) Created the Define.xml files from the translated metadata with Pinnacle 21 tool

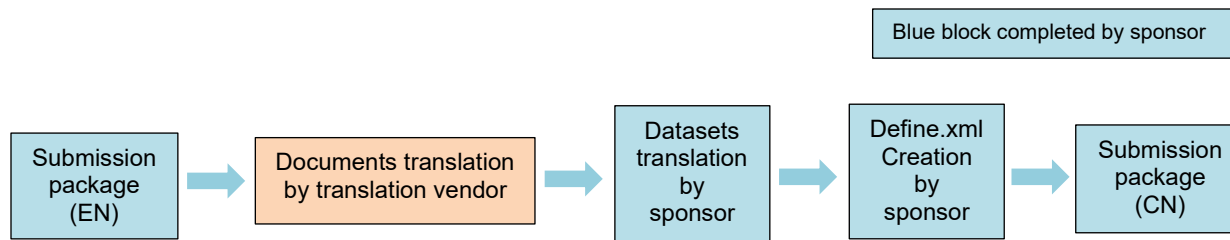


Figure 2. Type I Execution Process

TYPE II: CRO TRANSLATION

A Clinical Reach Organization (CRO) took charge of document and dataset translation, including SDTM Define.xml, cSDRG, aCRF, ADaM Define.xml, ADRG, AE/MH/CM Term, Dataset/Variable Labels (SDTM/ADaM) and other external documents used in the submission. To keep data confidential, data points in the datasets could not be provided to CRO. So, only necessary terms and labels extracted from datasets could be provided to them for translation.

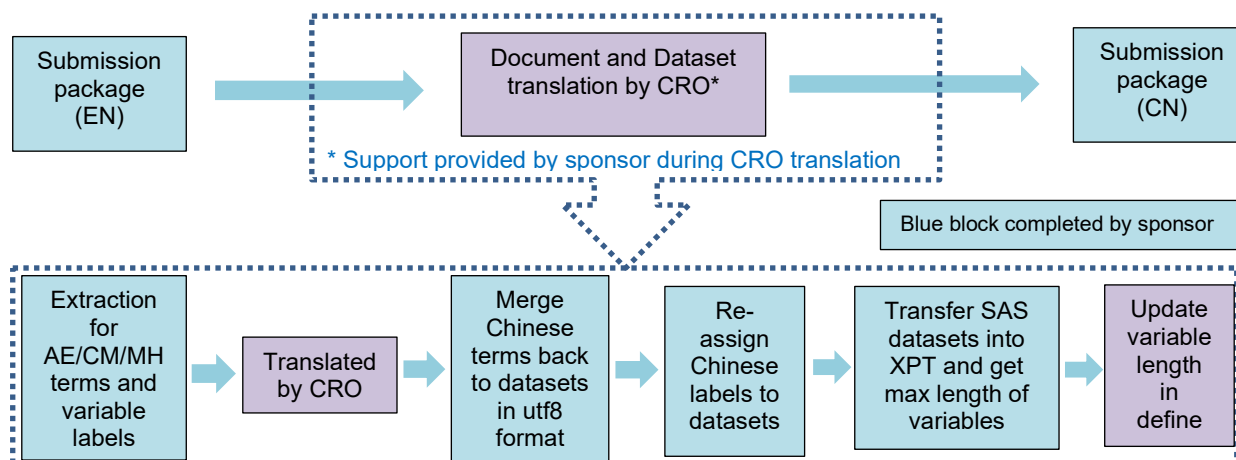


Figure 3. Type II Execution Process

RELATIVE MERITS FOR TWO TYPES OF PROCESS

Using Type I execution process, the translation work for the pilot study took about 56 calendar days from the start of vendor translation to submission, including the programming preparation phase.

Sponsor had to closely partner with the translation vendor. This partnership was important because we needed the vendor to take prompt actions on the translation of the submission packages. The translation quality was good regarding grammar. However, although the sponsor provided introductions and references to the vendor, the vendor did not have too much experience in CDISC data standard terminology and the submission document translation. There were some inconsistencies observed between the translated deliverables and standard IGs

In terms of dataset translation our programming staff had to spend considerable time on building a roadmap for the translation process, investigation in the MedDRA and Drug Dictionary logics, and development and validation of SAS programs that will translate the dataset/variable labels and medical terms. Sponsor kept the data fully in-house to maintained data confidentiality.

Using Type II execution of process, the translation work completed about 40 calendar days from contract signed to submission.

Translation tools were developed well by the CRO and they had solid process and experienced staff for the job. They could make fast action with good collaborative attitude. And CRO had a good experience about the data.

But due to the data confidentiality, sponsor preferred not to share any data points of specific trial participant to the CRO. As such it still certain amount of resources from sponsor to run intermediate tools to support the process. Sponsor needed to keep constant communications with CRO about any comments and modifications to the deliverables. This execution process involved very detailed practice so that it might take more time to learn the process for those programmers who are new to it.

When we reflect on our experience, both two types of process had advantages and disadvantages. In the future, with more advanced technology and automation we expect to conduct the entire translation process internally. We hope this approach will result in improved accuracy, efficiency and data integrity.

CONCLUSION

This paper focused on the translation on the English submission package to Chinese and provided some experience on two different types of translation execution process. The authors hope these can provide you a few implementation examples of the NMPA new clinical data submission guideline.

Furthermore, Pinnacle 21 has released a new Chinese-language validation engine for the new requirement of NMPA on October 30, 2020, available in both Enterprise and Community versions. This engine supports datasets with Chinese-encoded characters and displays rule messages and descriptions in Chinese translation. The P21 Enterprise Define.xml Designer preserves its functionality to handle Chinese character metadata, and P21 Enterprise have released Chinese xDRG templates (SDRG and ADRG) in this release. It makes the creation of define files and reviewer's guide and data validation more efficient and easier.

With more experience and well-developed tools, we believe we can simplify the translation process and make the translation delivery with enhanced quality and compliance in future.

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