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Annotated CRF Submission to NMPA for Foreign Database

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ABSTRACT

As a component of the SDTM submission package, the importance of annotated CRF has been clearly stated in the guidance documents from regulatory agencies like FDA and PMDA. On July 20th, 2020, The National Medical Products Administration (NMPA) from China released the "***Guideline on the Submission of Clinical Trial Data (Provisional)***", specifically, this document provided key guidance on how to do data submission to the agency in China. we can see the same requirement regarding aCRF from this guideline.

This paper summarizes the regulatory requirements of annotated CRF submission to NMPA, aiming to provide the best practice for aCRF submissions in the context of submitting foreign database to NMPA. Furthermore, the implementation processes used in aCRF submission to NMPA from our company's pilot studies are introduced here.

INTRODUCTION

"Submission of clinical trial data is usually a package that includes database and its supportive documents, like data definition file, data reviewer's guide, data derivation and analysis programs, and annotated case report forms (aCRFs)."[1] From NMPA's guideline, it's mentioned that an annotated CRF should be delivered with the data when submission. In terms of how to achieve a successful and high-quality aCRF submission to health agencies like FDA and PMDA, there are several requirements and guidelines identified from different authorities and organizations in our industry. This paper will primarily focus on how to do a submission-ready CRF in China: briefly summarizing all available requirements and guidelines on Annotated CRF, describing what is expected from NMPA, and further discussing how we understand and practically implement these as a global pharmaceutical company, not only to ease the review of aCRF but also to fulfill the needs of sponsors.

EXISTING REQUIREMENTS AND GUIDANCE

As known in our pharmaceutical and biotechnology industry, the following documents were served as main references regarding the setup of aCRF for submission to health agencies like FDA and PMDA[2], providing key guidance on contents, formats, and technical requirements.

- CDISC: SDTM Metadata Submission Guideline
- FDA: Study Data Technical Conformance Guide
- FDA: Portable Document Format Specifications

Besides, there are extensive sources that offer various levels of informative instructions on this topic, from which the sponsor may choose to improve and optimize the quality of aCRF. The potential sources are listed below.

- CDISC
- FDA
- PMDA
- EMA
- P21
- PhUSE

NMPA'S GUIDELINES ON ANNOTATED CRF

GENERAL REQUIREMENTS FROM NMPA

In guideline[1] released by NMPA, all requirements related to aCRF can be found from section 2.5, section 3.1, and section 4.3 respectively, which the sponsor must consider since those contents are quite basic, although the implementations may differ depending on the sponsor's understanding and discretion. The key points are summarized below.

- Annotations should reflect the mapping relationship between data units (i.e. field) and variables/variable values.
- Annotated CRF should be submitted in PDF.
- For data fields collected on the CRF but not included in submitted datasets, the aCRF should be marked as "NOT SUBMITTED", the reason(s) for not submitting these data should be clarified in the data reviewer's guide.
- For documents submitted in PDF, it's recommended that PDF version 1.4 and above should be used.
- All PDF files should use .pdf as the file extension.
- The submission materials related to clinical trial data should be mainly in Chinese. For foreign language database, the minimum requirements for translating aCRF are the description of questions designed to collect data; values or codes list of efficacy indicators.
- For foreign language database, the translating consistencies between all documents in the submission package should be considered, for example, adverse event terms in the analysis database should correspond to the ones in the clinical study report.

ADDITIONAL ECTD PDF SPECIFICATIONS FROM NMPA

As we know, the annotated CRF is a PDF file. Unlike FDA, NMPA does not officially offer any specification document for PDF, however, in Sep 2021, NMPA released a series of guidance documents of eCTD[3], to accelerate the construction of eCTD system in China and instruct the applicants to prepare submission materials using eCTD.

According to NMPA's <***eCTD Specifications>, "ICH Specification for Submission Formats for eCTD V1.2"*** provides suggestions on creating PDF files, including limitation, version, font, page setting, source of the electronic document, etc. If you read the complete format specifications, you will notice that these requirements can be quite similar to FDA's ***Portable Document PDF Specifications***[4], which will not be discussed here since our topic is NMPA submission. It is worth attention that from this document, some additional requirements specifically for Chinese submission materials using PDF can be found. Briefly, the key points are summarized below table.

Category	**Recommendations Details**
Table of Contents (for all tables, figures, publications, other references, and appendices.) and bookmarks	Should be provided (page number > 5, except for references, publications, and application tables,)
Hypertext	Can be provided to improve navigation through PDF documents if no table of contents and bookmarks available.
Fonts for Chinese	SimSun (Song Ti);

Category	Recommendations Details
Font Size for Chinese	Contents: not smaller than small four (12pt) Table: not smaller than five (10.5pt) Table of Contents: small four (12pt) Footnote: five (10.5pt)
Font Colors for Chinese	Narrative Text: blank Hyperlinks: using a rectangle or blue text

Table 1. Additional requirements specifically for Chinese submission materials using PDF

OUR UNDERSTANDING AND IMPLEMENTATION PROCESSES

OUR UNDERSTANDING AND TRANSLATION

As a global pharmaceutical company, we have constructed very complete and mature processes and systems for preparing the entire electronic submission package for FDA, NMPA, and EMA, consisting of everything related to clinical trials like data sets, reviewer's guides, define.xml, and programs. Under this background, when it comes to NMPA's submission, the first thing we need to consider might be translation, since we are consistently using the foreign database from the very early stage of data collection towards subsequent data creation and analysis. As per the previous section "general requirements from NMPA", the last two points serve as the main reference for translation, after a long discussion, we decided that:

1. Translate all text in blank case report form to Chinese, because it's not appropriate to have both English and Chinese printed in one document.
2. Translate "Not Submitted" from annotations to "不递交" (Chinese). As mentioned in the guideline, "some data fields may be collected on the CRF but not included in submitted datasets. These data fields should be marked as " 不递交" on the aCRF". We regard this as a sign of translation for the wording of "Not Submitted".
3. Translate dataset description from annotation to Chinese, keep translation conformed to Chinese version of SDTM IG released by CDISC, although this point was not mentioned in the guideline. Our purpose is to maintain the translation consistencies within the whole e-sub package. According to the guideline's requirement, the dataset labels in the submitted raw database need to be in Chinese, and this information corresponds to domain level annotation in aCRF.
4. Translate all bookmarks to Chinese. As we know, the aCRF is suggested to be bookmarked in two ways: by visit and by form according to CDISC Metadata Submission Guidelines (MSG)[5]. Since all text in blank CRF has been decided to be in Chinese, it makes sense to also have a bookmark in Chinese, as the bookmarks help to navigate the content within the document.

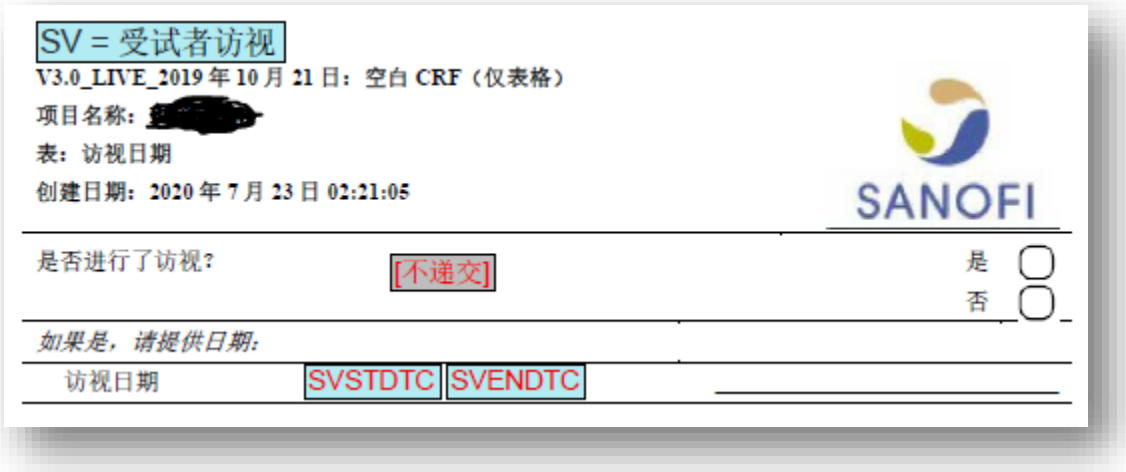

Figure 1. Example of Translated aCRF Page

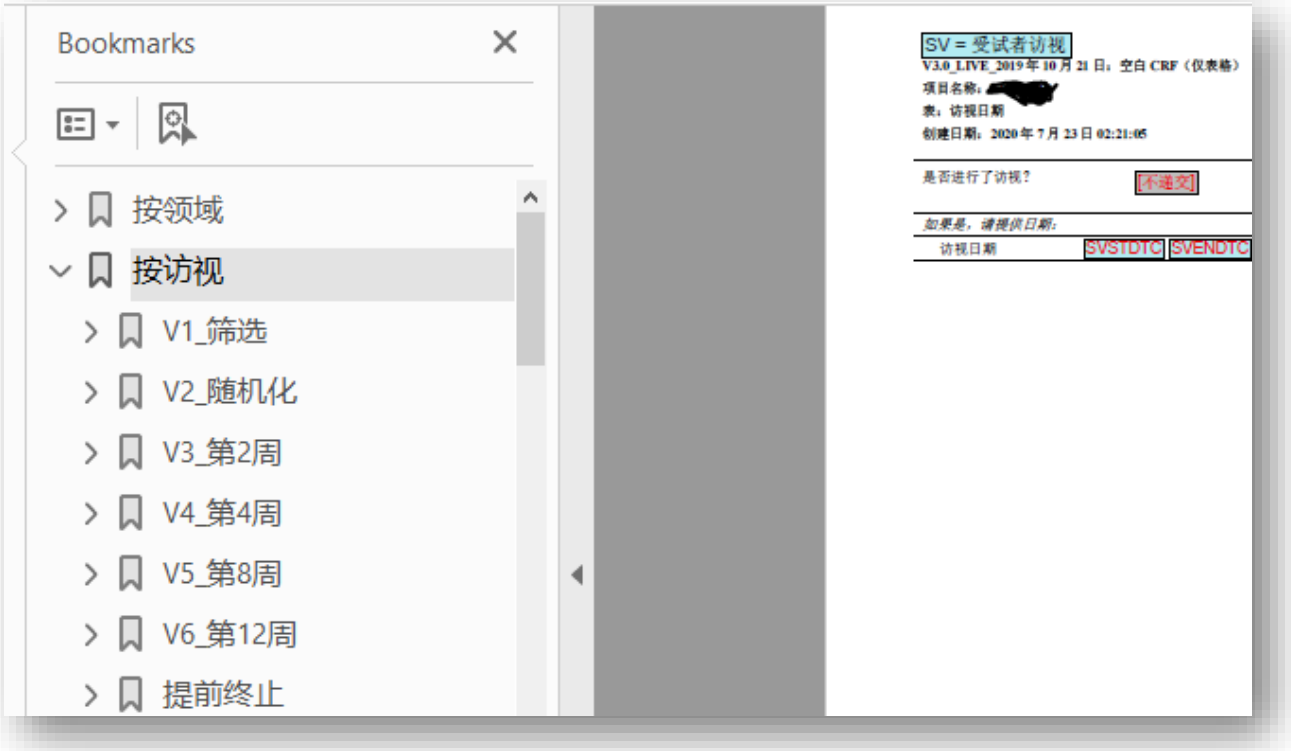

Figure 2. Example of Translated Bookmarks in aCRF

OUR IMPLEMENTATION PROCESS INVOLVED

Except for translation, the second step we need to take into consideration is how to integrate the preparation of NMPA's e-submission data into our current process, this process is used primarily for FDA and PMDA's submission. Given the situation, we divided our whole process according to two scenarios:

one is when a global submission package (FDA&PMDA) is available, the other is when a global submission package isn't available. Therefore, we have below processes for annotated CRF in our company, which, as you can see below, really rely on contributions from different roles and groups, such as data manager, statistical biostatistician, programmer, external vendors, and so on.

Figure 3. Process of aCRF Creation in Scenario 1

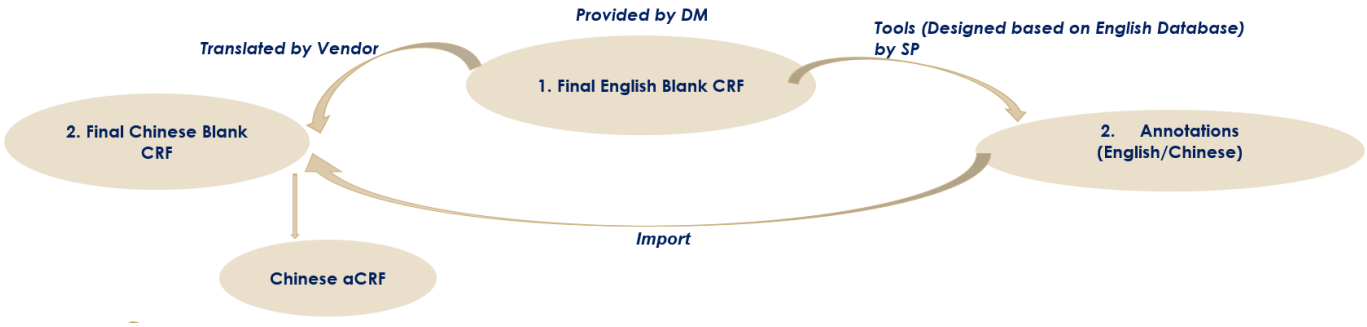

Figure 4. Process of aCRF Creation in Scenario 2

CONCLUSION

For all sponsors, achieving a successful submission of electronic clinical data is not an easy task, especially for NMPA submission, it's quite challenging for now when the related clinical trial data standards are still in need of development and improvement. It is very important to increase the familiarity and expertise in this area, not only for aCRF but also the whole e-submission package. Hopefully, this paper can provide some good practices and suggestions on this topic.

REFERENCES

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CONTACT INFORMATION

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