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Getting e-Closer to Multi-Regional Clinical Trials

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ABSTRACT

With the increasing globalization of drug development, it has become more important and popular that data from multi-regional clinical trials (MRCTs) can be accepted by regulatory authorities across regions and countries. The multi-regional data often serves as the primary source of evidence to support marketing approval of drugs. This paper details some experience of different MRCTs filing needs across regions and countries, and different database lock (DBL) designs for MRCTs. Additionally, we will share some technical tips that make our programming more efficiently in order to better serve MRCTs.

INTRODUCTION

MRCTs have been widely used in recent years to conduct a clinical trial in more than one region under a single protocol. From the perspective of pharmaceutical companies, MRCTs serve as a strategy to get parallel approvals in different regions. For the patients, MRCTs provide an opportunity of gaining accelerated access to the benefits of the latest developed drugs.

The hands-on experience described in this paper is coming from different agency submissions, especially the China National Medical Products Administration (NMPA). This paper describes the definition of an MRCT, introduces the submission requirements in US, EU, Japan and China, shows some completed MRCTs as examples, and shares some programming experiences.

It is assumed that the reader has a basic understanding of submission requirements of at least one agency.

1 WHAT'S AN MRCT?

According to the definition from International conference on harmonization (ICH) E17[1], an MRCT is a clinical trial conducted in more than one region under a single protocol. A region may refer to a geographical region, country or regulatory region.

MRCTs can facilitate simultaneous global development of a new drug and reduce some unnecessary duplication of studies conducted separately in different regions. Although MRCTs are more complex in the planning and processing, and possibly increase study start-up time, they can expedite world-wide clinical development and facilitate registration in all regions, and benefit patients in these regions with new drugs quickly.

2 AGENCY REQUIREMENTS FOR FILINGS

Recent drug development is conducted in a global and integrated way and similar clinical data packages should be used for submission to different agencies. Sponsors need to understand the requirements of each agency and consider efficient processes for a new drug application (NDA). The overall principle for NDA in most countries is, first, the overall evaluation of the global clinical trial data, and then further trend analysis of the clinical trial data generated in subgroups.

In most instance, one NDA will be submitted in US first. Application in Japan, EU, China and other countries will follow US submission closely. Generally, the submission package for U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are quite similar, while there are some additional requirements from Pharmaceuticals and Medical Devices Agency (PMDA) and NMPA. In Japan and China, the subgroup analysis and side-by-side tables for different population comparison are required for submission. The general requirements for different agencies that require programmers' inputs are shown in the below table.

Table 1: General Requirements for Different Agencies

	FDA	EMA[a]	PMDA	NMPA[b]
Annotated CRF (pdf)	√	√	√	√
SDTM/ADaM datasets (xpt)	√	√	√	√
Pinnacle 21 checks	√	√	√	
cSDRG/ADRG (pdf)	√	√	√	
Define (PDF/XML)	√	√	√	√[c]

Programs	√	√	√	
CSR	√	√	√	√
Subgroup CSR				√[d]
Regular specific tables			JCTD[e]	CSS[f]

√: requested
[a]: for EMA, most documents are not routinely requested.
[b]: NMPA has issued draft version of application requirements for clinical trial database and related materials in electronic Common Technical Document (eCTD) for public comments[3].
[C]: It is called data description file.
[d]: Only for China extension study.
[e]: Japan subgroup analysis tables and side-by-side tables for Japan population and non-Japan population comparison included in the CTD module.
[f]: China Specific Summary (CSS) is most likely required for NMPA submission if subgroup CSR is not available. The CSS includes some side-by-side tables and subgroup tables, provides a clinical overview of pharmacology, efficacy, and safety data to show the consistency between global study results and subgroup results.

3 THE PLANNING AND DESIGN OF MRCTS

3.1 CASE A: ONE DBL FOR DIFFERENT AGENCY SUBMISSIONS

There was a phase III randomized, open-label study to evaluate efficacy and safety of drug A in combination with treatment 1 versus treatment 2 monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (mRCC).
Based on the first DBL data of interim analysis (IA), the package was submitted in US, EU and Japan simultaneously. Same data submitted in different regions, this was the most efficient and ideal way to use an MRCT data for different filings.
In this case, a well-planned filing strategy, process and prompt action taken were quite critical factors to reach the target.

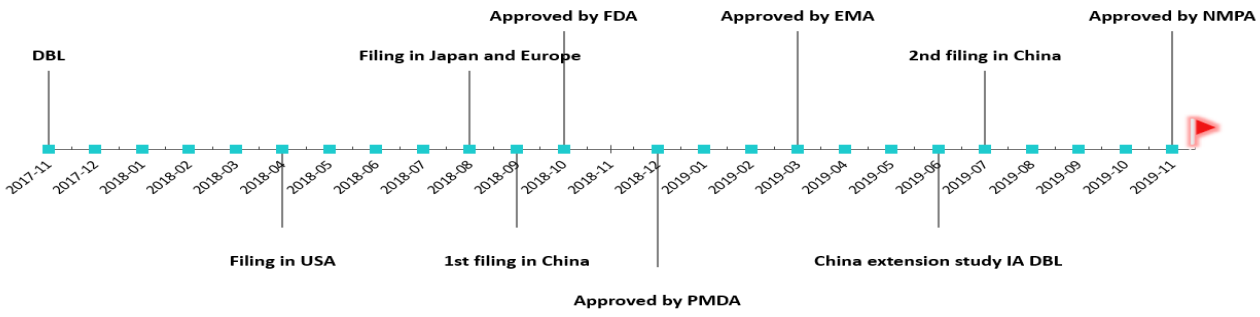
3.2 CASE B: GLOBAL TRIAL WITHOUT SPECIFIC POPULATION

There was a randomized, double-blind, phase III study of chemotherapy with or without drug A in first Line metastatic non-squamous non-small cell lung cancer (NSCLC) subjects.
In the study design, there was no Chinese population included. Considering that the pooled Asian regional subgroup analysis results were consistent with the global results and there was an unmet medical need, the pooled Asian regional subgroup submission package was used to support the filing in China, received conditional approval by the regulatory authority.
Compared to the case A, alterative analysis population and filing strategy were chosen, and thus it provided a suggestion for programmers to make the analysis programs more flexible in order to quickly deliver the analysis and reporting requirements.

3.3 CASE C: DIFFERENT DBLS FOR DIFFERENT AGENCY SUBMISSIONS

There was a randomized, double-blind, phase III study chemotherapy with or without drug A in first line metastatic squamous non-small cell lung cancer subjects.
This trial included a global study and a China extension study. The extension study was designed to determine the treatment effect of drug A regarding to overall survival as well as the consistency of safety and efficacy in subjects enrolled in China. No multiplicity adjustment was applied to the extension study.
The filing package based on the same global study data was submitted to FDA first, following by PMDA and EMA simultaneously. The NMPA submission was done in one month after the PMDA and EMA submission finished. Figure 1 shows the submission milestone.

Figure 1 Submission Milestone



Two filing packages were submitted to NMPA. The first one included the global study submission package and CSS. The second one consisted of the China subgroup CSR and data package. The CSS included subgroup tables in east Asia population, as well as the following 3 safety side-by-side tables with 5 different groups (table 2).

1. Adverse Event Summary
2. Adverse Event Summary for AEOSI Including All Risk Categories
3. Subjects with Adverse Events by Decreasing Incidence with Incidence ⩾ 10% in One or More Treatment Groups

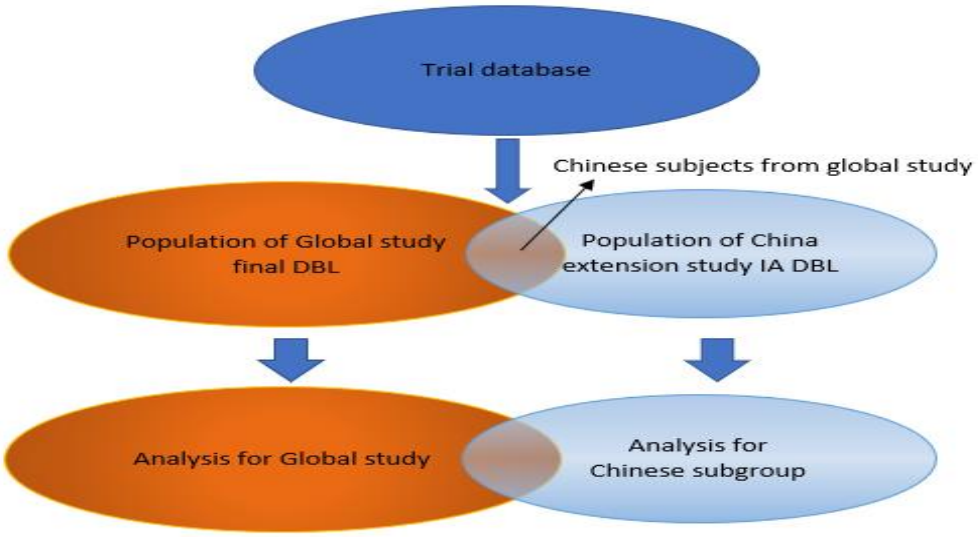
Table 2: 5 Different Groups in Side by Side Tables

Drug A Combo Group	Control Group	East Asia Population Drug A Combo Group	East Asia Population Control Group	Reference Safety Dataset for Drug A Monotherapy

China extension study IA was reached at the same time as the global study final analysis. The Chinese subjects enrolled in the global study and extension study comprised the primary efficacy population of China. However, the Chinese subjects randomized in the extension study were not included in the primary efficacy analysis global population.

The study team evaluated the most optimal approach to complete the analysis work quickly and with high quality. While taking many factors into consideration, the team successfully delivered the filing package and met the critical timeline. Two separate DBLs proceeded in parallel. Figure 2 shows the process chart for different DBLs.

Figure 2 the Process Chart for Different DBLs



4 PROGRAMMING TIPS

For MRCTs, there are different regional populations included in the study. Even for the specific agency submission, most likely the DBL is designed for the whole population. The global population analysis is initialized, some subgroup population (such as China, Japan) analysis will be based on the global population analysis results. In this situation, the most important tip for programmers is to utilize the program code for different populations as much as possible. There are 4 aspects from a programmer's perspective that will be most likely modified for different submission needs. It is best to plan the whole process in advance. To make the program more flexible, the most convenient solution is to define different global macros at the study startup step. Programming code examples are listed in Table 3.

Table 3 Programming Code Examples

Function	Programming Code Examples

i. The population selection with corresponding subtitle	`%let pop_trt=%str(TRTFL='Y'); *** global group population**;`
	`%let subtitle_trt=%str((TRT Population)); *** global group subtitle**;`
	`%let pop_trt=%str(TRTFL='Y' and country='CHN'); ** subgroup population**;`
	`%let subtitle_trt=%str((China TRT Population)); *** subgroup subtitle**;`

ii. The subgroup output file name	`%let sub_output_nam = ; **the global group output file name will be study0pop**;` `%let sub_output_nam = %str(0chn); **the subgroup output file name will be study0pop0chn**;`

iii. Subfolder selection for different region	`%let sub_pop_path = %str(\china); **for case 1, folder path**;`
	`%let sub_pop_path = %str(\east_asia); **for case 1, folder path**;`
	`libname outdata "<Path1>\outdata\&sub_pop_path."; **the libname of output datasets based on different region**;`

iv. The stratification factors selection	`/*Stratified analysis*/`
	`%let strata=var1; *stratification factors *;`
	`%let stra_footnote =%str(Based on analysis method stratified by variable 1); *stratification factors in the footnote *;`
	
	`/*Unstratified analysis*/`
	`%let strata=;`
	`%let stra_footnote =%str(Based on analysis method unstratified); *unstratified information in the footnote *;`
	
	`/*stratified or unstratified analysis selection based on the analysis needs*/`
	`%macro strata;`
	`proc sql print;`
	`create table adsl as`
	`select usubjid`
	`%if "&strata" ne "" %then %do;`
	`,&strata. as stratum`
	`%end;`
	`%else %do;`
	`, 1 as stratum`
	`%end;`
	`from lptda.adsl;`
	`quit;`
	`%mend;`

i. The population selection is set for different region submissions. It includes the analysis population selection criteria and corresponding subtitles in the outputs.

ii. For output files including log, listing, table, and figure, we use suffix to distinguish them for the same files with different analysis populations. For example, we gave the output file name as `study0pop&sub_output_nam`. It varies according to the different subgroups. This is quite useful when different population outputs are created under the same folder.

iii. Due to different subgroup analysis needs, different study paths are created for a specific region to save the specific programming outputs. One global level or region level at each study analysis milestone should be used. Different subfolders for different output types should be created. Sometimes, more than one subfolder should be set for different regional analyses, for example, there might be a China population or an East-Asia population analysis for NMPA submission. Following table (table 4) is an example showing the study folder structure.

Table 4: Study Folder Structure

Folder Name	Folder level	Content Description
Study path	1	Study path for global level or region level at one milestone
outtable	2	Study table folder for global level or region level
region1	3	Subgroup 1 table folder **only** for region level, e.g. China, East-Asia
region2	3	Subgroup 2 table folder **only** for region level, e.g. China, East-Asia
outdata	2	Subgroup output datasets folder for global level or region level
region1	3	Subgroup 1 output datasets folder **only** for region level, e.g. China, East-Asia
region2	3	Subgroup 2 output datasets folder **only** for region level, e.g. China, East-Asia
…		

Under such situation, it is very important to setup the path macro at the startup stage. This will help us modify the code as less as possible and we can easily switch different populations.

iv. Ideally, the analysis will be the same between global population and subgroup population. But considering of small subgroup population, it is quite often that subgroup efficacy analysis will not be based on the stratification factors.Thus the stratum factor setup should be planned in the startup step for future modification.

CONCLUSION

MRCTs play an important role in the global drug development. Similar submission package would be prepared for different agency submission. To improve the efficiency of MRCTs, it is a good practice to plan and design the programming process at the beginning phase for different filing strategies. In the future, it would be more standardized for eCDT requirements from different authorities.

REFERENCES

[1] ICH harmonised guideline general principles for planning and design of multi-regional clinical trials E17 Final version Adopted on 16 November 2017

[2] e-Data Submission Overview in US/EU/Japan/China, Phuse Shanghai, 03 Nov 2017

[3] Application Requirements for Clinical Trial Database and Related Materials in eCTD draft in September 2019.

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