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Single Day Event

Overview of NMPA eDATA Submission Process

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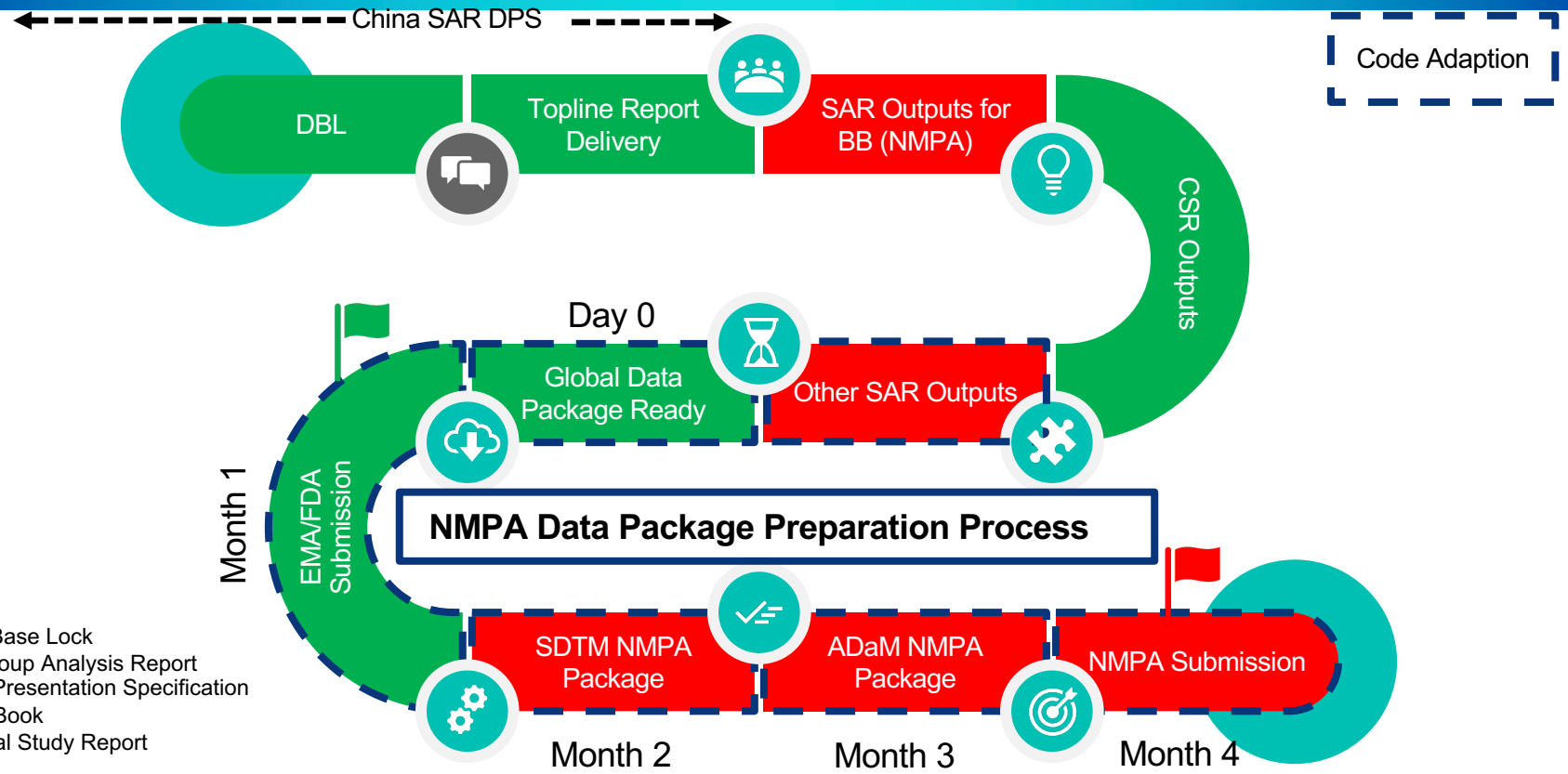
NMPA Submission Overview



DBL: Data Base Lock
SAR: Subgroup Analysis Report
DPS: Data Presentation Specification
BB: Brief Book
CSR: Clinical Study Report

NMPA Submission Requirements

NMPA Submission Documentations

- SAR
- Pre NDA/BLA BB
- CDx Bridge Study Report

China Subgroup Analysis Report

Health Authority Requirement

- **NMPA guideline of multi-regional clinical trials (trial implementation) on Jan 30, 2015**

  if using MRCT data to support China registration, besides overall data evaluation, additional China and Asian data trending analysis is needed

- **CDE clinical trial subgroup analysis guideline issued on Dec 30, 2020**

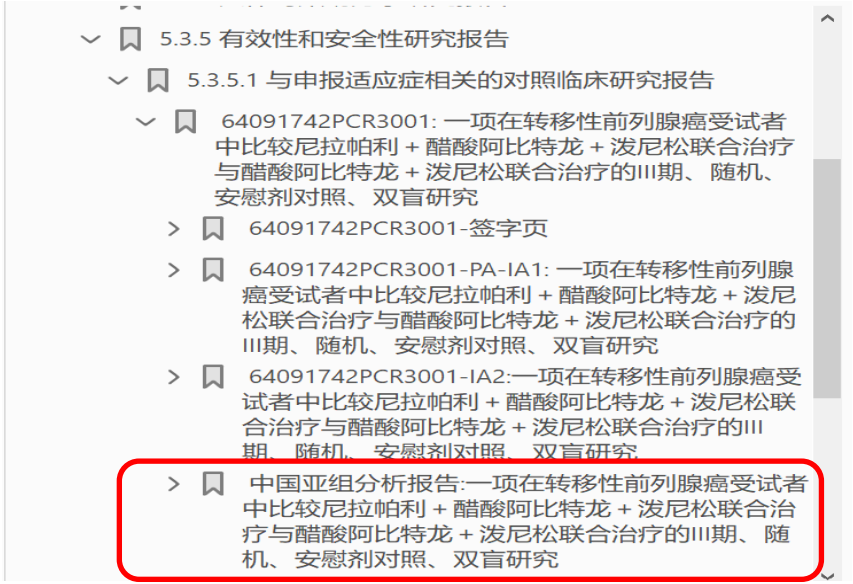
China Subgroup Analysis Report

- **The China SAR usually follows the format of a CSR but with a short front section**
  - **description of the disease**
  - **a brief overview of the study**
  - **objectives of the report and select pharmacokinetic, efficacy, and/or safety data.**

- **The SAR may contain**
  - **only data for the subgroup of interest (e.g. Asian subjects)**
  - **a comparison with the entire study population and/or other subgroups**
  - **Side-by-side tables for China, Eastern Asia, and Overall Population**

China Subgroup Analysis Report

Common Technical Document(CTD)



Pre-BLA/NDA BB & Meeting

MAGNITUDE (Cohort 1)– Subgroup Results (Chinese vs East Asian): Generally Consistent rPFS Results with Overall Population

- **Consistent rPFS results were seen among Chinese, East Asian and overall population, in favor of NIRA+AAP treatment for both BRCA subgroup and HRR+**
  - ✓ For Chinese subjects with HRR+, X rPFS events observed in PBO+AAP arm, and X rPFS events observed in NIRA+AAP arm.
  - ✓ As Chinese patients were largely BRCA subjects, rPFS results in HRR+ Chinese subjects is more reflective of the BRCA enrollment. Median rPFS and HR estimate should be interpretated with caution due to limited sample size and small number of observed rPFS events.

rPFS Analysis Group	N (No. of Events)	Niraparib + AAP	Placebo + AAP	HR (95% CI)	P-value* (log-rank test)
		median rPFS (months)			
All HRR					
--Overall	XXX (XXX)	XX.X	XX.X	0.XXX (0.XXX, 0.XXX)	0.XXXX
--East Asian	XX (XX)	XX.X	XX.X	0.XXX (0.XXX,0.XXX)	0.XXXX*
--Chinese	XX (X)	XX.X	XX.X	0.114 (0.XXX,0.XXX)	0.XXXX*
BRCA subgroup					
--Overall	XXX (XXX)	XX.X	XX.X	0.XXX (0.XXX,0.XXX)	0.XXXX
--East Asian	XX (XX)	XX.X	XX.X	0.XXX (0.XXX,0.XXX)	0.XXXX*
--Chinese	XX (X)	XX.X	XX.X	0.XXX (0.XXX,0.XXX) [a]	0.XXXX*

AAP=abiraterone acetate plus prednisone; BICR=blinded independent central review; BRCA=breast cancer (gene); rPFS=radiographic progression-free survival; NE=not estimable
[a] HR estimate should be interpreted with caution due to the small number of events observed from a subpopulation with a small sample size.
* nominal p-value
Note: Chinese includes patients from China and Taiwan. East Asian include China, Taiwan and Korea.

janssen Oncology

Content & Format for eData in BB

Data

- **Sponsor proposal of the content of the eData package:**
  - **Study list, description of datasets(trial / integrations)**
  - **SDTM & ADaM IG, define version**
  - **English & Chinese Version**

Code

- **Sponsor proposal of the content of the programming code:**
  - **Scope: datasets & outputs, efficacy & safety, study list**
  - **Format & location**

Companion Diagnostic(CDx) Bridge Study Report

- **A medical device, often an in vitro device (IVD), provides information essential for the safe and effective use of a corresponding drug or biological product.**

- **抗肿瘤药物的伴随诊断试剂对采集自肿瘤患者的样本进行检测，其结果可以为患者使用抗肿瘤药物的安全性和有效性提供重要的信息，包括：确定最有可能从药物中受益的患者，确定该药物相关严重不良反应风险较大的患者，确定已经过充分研究具备安全性和有效性的人群亚组等。**
  -2021<抗肿瘤药物的非原研伴随诊断试剂临床试验注册审查指导原则>

- **NMPA注册获批体外诊断试剂; Label标明对应的药物名称，检测结果指导用药。**

CDx Bridge Study

- ***Internal*** **agreement study of CDx and CTA using the clinical trial screened/enrolled patient samples when CTA is used for patient enrollment in clinical trial**
- **Primary objectives:**
  - **Assess agreements between CDx and CTA**
  - **Estimate CDx clinical performance (defined by treatment efficacy) in its intended patient population e.g. for selection test, the drug efficacy in CDx+ patient population.**
- **How**
  - **Retest available screened patient samples of the clinical trial (including both some CTA- samples and all enrolled CTA+ if possible) by CDx**

CTA: Clinical Trial Assay

CDx Bridge Study Report Outputs

Janssen China: CDx output

Janssen global: CDx sensitivity analysis

- **Summary Listing**
- **Concordance between CDx & CTA**
- **Efficacy in overall patient population and CDx selected patients**
- **Sensitivity analysis(Missing Data & CTA- but CDx+)**

- **Tissue CDx report for pivotal study (samples from China & Global)**

NMPA Submission Package

- **NMPA Guidance**
- **Package Preparation**
  - **Database in .xpt**
  - **Define.xml, Define.pdf**
  - **ADRG/cSDRG**
  - **Programming code – de-macro/annotation**
- **eSubmission Delivery Method**

NMPA Guidance

- Guideline on the Submission of Clinical Trial Data (trial implementation)

  --Center for Drug Evaluation (CDE), NMPA
- Issued in July 2020
- Primarily applicable to key clinical trials for the purpose of drug registration and marketing approval.
- Encourage to submit according to CDISC standards.
- Specific requirements for the content and format of the clinical trial submission package

NMPA eSubmission Package

Deliverable	NMPA Requirement	Uniqueness	Solution
Database (SDTM & ADaM)	Submission materials related to clinical trial data should be mainly in Chinese	Minimum translation requirements	Dictionary-derived translation tool & data translation
	Maximum file size: 4 GB	5 GB per FDA	Spilt macro
define.xml	Mainly in Chinese	Provide details, particularly about derived variables. Provide key program codes if necessary.	Translation tool
ADRG	In Chinese	Data conformance summary is not mandatory	Specify Encoding system(uft-8, euc-cn, etc.), xpt version, programming code update per guideline
aCRF	Minimum translation requirements	Translate description of questions, code list/value of efficacy endpoints	Translation and function validation
Programming Code	Easily understandable, highly readable, sufficient comments, avoid external program(macro) calls.	Sufficient comments, Avoid external program(macro) calls	De-macro tool & annotation tool
File Types	PDF, XML, XSL,XPT, TXT	No XLS or XLSX	xls/xlsx → xpt
eCTD	NMPA specific folder structure	'split', 'send', 'misc', and 'profiles' folders per FDA removed.	split datasets in "datasets", Convert miscellaneous files to xpt and store them in "datasets"

NMPA Package Preparation

Database in .xpt

- Chinese translation in database consistent with all other documents
- Minimum translation requirements: AE, CM, MH terms, datasets & variables labels.
- Macros developed to increase efficiency
  - Search SDTM, ADaM, and external files to get items for translation
  - Match terms with Chinese MedDRA/WHODrug dictionary, preliminary translation
  - Export un-matched items for Language Solution translation and Function Validation
  - Import translated files and create xpt files in Chinese.(xpt v8 engine implemented if appliable)

NMPA Package Preparation

ADRG & cSDRG

- All in Chinese
- Add a description of the encoding system used(e.g. UTF-8)
- Specify the xpt version(v5 or v8) of the datasets
- Data conformance summary in ADRG & Issue Summary in cSDRG are not applicable since the issues addressed by the engines are not applicable to NMPA submission.

NMPA Package Preparation

Define.xml & define.pdf

- **Minimum translation requirements: datasets description/label, variables description/label and derivation process, code list/value of efficacy endpoints.**
- **Applicable to supplemenaldefinitions.pdf if any.**
- **Macros/tools for efficiency**
  - **Export metadata for Language Solution translation**
  - **Import translated files and create define.xml & define.pdf in Chinese (macro for v1.0, P21E for v2.0)**
  - **define.pdf prepared for inspection support.**

NMPA Package Preparation

Programming Codes

- Include but not limited to, the derivation process of derived variables of analysis datasets and the generation process of analysis results for efficacy endpoints.
- Easily understandable, highly readable, sufficient comments, avoid external program(macro) calls.
- Cross-function discussion to propose code packages
- Utility tools developed to automatically reduce levels of macro call, export, translate English comments into Chinese, and import into submitted codes.

NMPA eSubmission Delivery Method

- **Physical electronic medium**
  - **CD-R**
  - **DVD + R**
  - **DVD – R**
- **NO Double-side DVD**
- **NO password**

- **Follow eCTD to prepare submission material after 29Dec2021**
- **Submit paper materials within 5 WD after eCTD acceptance. Terminate register process if not submit.**
- **Ensure consistence between electronic and paper materials.**

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