基于标准化数据统计分析

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工作经验：13年以上CRO和药企工作经验，负责多个治疗领域和适应症的产品的I - IV期临床试验统计编程，熟悉监管机构临床数据递交规范，熟悉CDISC标准，SAS编程熟练

爱好：瑜伽，旅行，咖啡，音乐，阅读

个人声明

以下仅为个人观点，不代表公司立场。

ADaM基本原则

- 数据集及相关元数据必须促进清晰无歧义的交流
- 数据集及相关元数据必须提供可追溯性 (Metadata, Data point)
- 数据集必须适用于常用软件工具
- 数据集必须和元数据相关联
- 数据集必须“分析就绪”

- 实施考虑
  - 必须包含ADSL
  - 数据集命名遵循ADxxxxxx规范
  - 尽量使用ADaM标准变量,遵循命名规范
  - SDTM变量：同名、同义、 同值
  - 一致性

ADaM版本

ADaMIG Version	Compatible Model	Conformance Rules	Implementation Guide & Examples Documents
ADaMIG v1.3 29 Nov 2021	ADaM v2.1	ADaM Conformance Rules v5.0	ADaMIG for Medical Devices v1.0 ADaMIG for Non-compartmental Analysis (NCA) Input Data v1.0 ADaM Structure for Occurrence Data (OCCDS) Implementation Guide v1.1 Basic Data Structure for ADaM popPK Implementation Guide v1.0 ADaM Metadata Submission Guidelines v1.0 ADaM Examples of Traceability v1.0
ADaMIG v1.2 3 Oct 2019	ADaM v2.1	ADaM Conformance Rules v5.0	ADaM Structure for Occurrence Data (OCCDS) Implementation Guide v1.0 ADaM Basic Data Structure (BDS) for Time-to-Event (TTE) Analyses v1.0 ADaM Examples in Commonly Used Statistical Analysis Methods Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0
ADaMIG v1.1 12 Feb 2016	ADaM v2.1	ADaM Conformance Rules v5.0	ADaM Structure for Occurrence Data (OCCDS) Implementation Guide v1.0 ADaM Basic Data Structure (BDS) for Time-to-Event (TTE) Analyses v1.0 ADaM Examples in Commonly Used Statistical Analysis Methods Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0
ADaMIG v1.0 17 December 2009	ADaM v2.1	ADaM Conformance Rules v5.0	ADaM Data Structure for Adverse Event Analysis v1.0 ADaM Basic Data Structure (BDS) for Time-to-Event (TTE) Analyses v1.0 ADaM Examples in Commonly Used Statistical Analysis Methods Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0

ADaMIG更新

- ADaM IG V1.2
  - BDS variable PARAMTYP was deprecated in ADaMIG v1.1
  - New variables:
    - ATOXGRN and BTOXGRN were added representing the numeric versions of ATOXGR and BTOXGR.
    - Ten new variables were added for bi-directional lab toxicity: ATOXGRL, ATOXGRLN, ATOXGRH, ATOXGRHN, BTOXGRL, BTOXGRLN, BTOXGRH, BTOSGRHN, ATOXDSCL, & ATOXDSCH
  - Examples added for the new Bi-directional Lab Toxicity variables

- ADaMIG v1.3:
  - OCCDS v1.1:
    - New variables: TREMxxFL, TRTEMwFL, ONTRxxFL, ONTRTwFL, ADECODy
    - Cumulative Dose Group 1 from DOSCMGR1 to DOSCUMG1
    - Added analysis of protocol deviations example
  - ADaMIG-NCA v1.0, ADaMIG-MD v1.0

ADaM数据结构

- ADSL (Subject-level Analysis Dataset)
  - 受试者水平分析数据集
- BDS (ADaM Basic Data Structure)
  - 基本数据结构
  - TTE (Time-to-Event Analysis Dataset)
    - 时间事件分析数据集
- OCCDS (ADaM Occurrence Data Structure)
  - 发生类数据结构

ADSL变量

- 标识符变量
  - STUDYID, USUBJID, SUBJID, SITEID, SITEGRy, SITEGRyN
- 受试者人口学变量
  - AGE, AGEU, AGEGRy, AGEGRyN, SEX, RACE, RACEGRy, RACEGRyN
- 人群标志变量
  - FASFL, SAFFL, ITTFL, PPROTFL, COMPLFL, RANDFL, ENRLFL
- 治疗组变量
  - ARM, ACTARM, TRTxxP, TRTxxPN, TRTxxA, TRTxxAN, TRTSEQP, TRTSEQPN, TRTSEQA, TRTSEQAN, TRxxPGy, TRxxPGyN, TRxxAGy, TRxxAGyN
- 治疗时间变量
  - TRTSDT, TRTSDTM, TRTEDT, TRTEDTM, TRxxSDT, TRxxSDTM, TRxxEDT, TRxxEDTM

ADSL变量（续）

- 受试者级别的阶段，子阶段，和分期时间变量
  - APxxSDT, APxxSDTM, APxxEDT, APxxEDTM
- 受试者级别试验经历变量
  - EOSSTT, EOSDT, DCSREAS, EOTSTT, DCTREAS, EOTxxSTT, DCTxxRS, EOPxxSTT, DCPxxRS, RFICDT, ENRLDT, RANDDT, LSTALVDT, TRxxDURD, TRTDURD, DTHDT, DTHCAUS
- 分层变量
  - STRATAR, STRATARN, STRATwR, STRATwRN, STRATAV, STRATAVN, STRATwV, STRATwVN

ADSL示例

ADSL where ITTFL = 'Y'

Table 14.2.1
Demographics
ITT Population

	Placebo N=xx	CDE_01 n(%)	Total n(%)
Age			
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.x	xx.x	xx.x
Min	xx	xx	xx
Max	xx	xx	xx
Age Group, n (%)			
<65	xx (xx.x)	xx (xx.x)	xx (xx.x)
65-80	xx (xx.x)	xx (xx.x)	xx (xx.x)
>80	xx (xx.x)	xx (xx.x)	xx (xx.x)

AGE

TRT01P

AGEGR1N

ADSL讨论

- Q1: All baseline/disease characteristics variables in ADSL?
- Q2: ADSL to be created at first or at last?

ADVS where PARAMCD in ('HEIGHT' 'WEIGHT') and ABLFL = 'Y'

	[Header]
Height (cm)	
n	xx
Mean	xx.x
SD	xx.x
Median	xx.x
Q1, Q3	xx.x, xx.x
Min, Max	xx, xx
Weight (kg)	
n	xx
Mean	xx.xx
SD	xx.xx
Median	xx.xx
Q1, Q3	xx.xx, xx.xx
Min, Max	xx.x, xx.x

ADSL讨论（续）

1	2	3
Pre-ADSL[1]	ADxxxxxx	ADSL[2]

1. Contains core variables and additional ones that are needed for other ADaM datasets
2. Contains variables that are better derived at other ADaM datasets

BDS变量

- 研究记录水平的治疗变量
  - TRTP, TRTPN, TRTA, TRTAN, TRTPGy, TRTPGyN, TRTAGy, TRTAGyN, DOSEP, DOSCUMP, DOSEA, DOSCUMA, DOSEU
- 时间变量
  - ADT, ADTM, ADY, AVISIT, AVISITN, ATPT, ATPTN, ATPTREF, APERIOD, APERIODC
- 分析参数变量
  - PARAM, PARAMCD, PARAMTYP, PARCATy, PARCATyN, AVAL, AVALC, AVALCATy, AVALCAyN, BASE, BASEC, BASECATy, BASECAyN, BASETYPE, CHG, CHGCATy, CHGCATyN, PCHG, PCHGCATy, PCHGCAyN, SHIFTy, SHIFTyN
- 分析参数准则变量
  - CRITy, CRITyFL, MCRITy, MCRITyN

BDS变量（续）

- 分析描述符变量
  - DTYPE, AWTARGET, AWTDIFF, AWLO, AWHI
- 达到事件时间变量
  - STARTDT, STARTDTM, CNSR, EVNTDESC, CNSDTDSC
- 毒性和范围变量
  - ATOXGR, ATOXGRN, BTOXGR, BTOXGRN, ANRIND, BNRIND, ANRLO, ANRHI, ATOXGRL, ATOXGRLN, ATOXGRH, ATOXGRHN, BTOXGRL, BTOXGRLN, BTOXGRH, BTOXGRHN
- 标识变量
  - ABLFL, ANLzzFL, ONTRTFL, LVOTFL
- 数据点的可追溯性变量
  - SRCDOM, SRCVAR, SRCSEQ

BDS示例

ADVS where ITTFL = 'Y' and PARAMCD = 'PULSE' and ANL01FL = 'Y' and ABLFL ^= 'Y'

CHG/BASE

TRTPN

AVISITN

Table 14.x.x

Mixed-effects Model Repeated Measures Analysis of Change from Baseline of **Pulse**

ITT Population

	Placebo	CDE_01	Difference (CDE_01 vs Placebo)
Week 2			
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Min; Max	xx; xx	xx; xx	xx; xx
LS Mean (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
95% CI	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x
P value			x.xxx
...			
Week 8			
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x
Min, Max	xx	xx	xx
LS Mean (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
95% CI	xx.x; xx.x	xx.x; xx.x	xx.x; xx.x
P value			x.xxx

BDS - ANCOVA

Summary E.1
Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24
(ITT Population, LOCF Data, ANCOVA Model)

		% Change From Baseline		Treatment Difference (Drug ABC – Placebo)		
	n	LS Mean[a]	95% CI[a]	LS Mean[a]	95% CI[a]	p-value[a]
Drug ABC (N = xxx)	xxx	x.x	(x.x, x.x)			
Placebo (N = xxx)	xxx	x.x	(x.x, x.x)	x.x	(x.x, x.x)	x.xxxx

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N = ITT population, n = number of subjects with non-missing percent change from baseline at month 24
CI = Confidence interval
LS = Least squares
[a]Based on ANCOVA model adjusting for planned treatment, baseline BMD value, machine type, and baseline BMD value by machine type interaction.

BDS - ANCOVA（续）

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.1
DISPLAY NAME	Lumbar Spine Bone Mineral Density Percent Change From Baseline at Month 24 (ITT Population, LOCF Data, ANCOVA Model)
RESULT IDENTIFIER	Treatment difference results (LSMean, confidence interval, p-value)
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	PCHG
REASON	Primary efficacy analysis as pre-specified in protocol
DATASET	ADBMD
SELECTION CRITERIA	ITTFL="Y" and PARAM="DXA BMD at Lumbar Spine (g/cm^2)" and AVISIT="MONTH 24" and ANL01FL="Y"
DOCUMENTATION	See SAP Section XX for details.
PROGRAMMING STATEMENTS	PROC MIXED DATA= ADBMD; CLASS TRTP BMMCHTYP; MODEL PCHG = BASE BMMCHTYP BASE*BMMCHTYP TRTP; LSMEANS TRTP / OM PDIFF = CONTROL ("Placebo") CL; RUN;

BDS - ANCOVA（续）

PARAMCD	AVISIT	AVISITN	TRTP	ITTFL	AVAL	BASE	CHG	PCHG	ABLFL	DTYPE	AWTDIFF	ANL01FL
BMDLS	BASELINE	2	Drug ABC	Y	0.992	0.992			Y		0	Y
BMDLS	MONTH 6	3	Drug ABC	Y	1.025	0.992	0.033	3.33			20	Y
BMDLS	MONTH 12	4	Drug ABC	Y	1.033	0.992	0.041	4.13			1	Y
BMDLS	MONTH 18	5	Drug ABC	Y	1.025	0.992	0.033	3.33			26	Y
BMDLS	MONTH 24	6	Drug ABC	Y	1.060	0.992	0.068	6.85			30	
BMDLS	MONTH 24	6	Drug ABC	Y	1.072	0.992	0.080	8.06			10	Y
BMDLS	MONTH 30	7	Drug ABC	Y	1.072	0.992	0.080	8.06		LOCF	173	Y
BMDLS	MONTH 36	8	Drug ABC	Y	1.021	0.992	0.029	2.92			2	Y
BMDLS	MONTH 36	8	Drug ABC	Y	1.086	0.992	0.094	9.48			2	

BDS - Category Analysis

Summary E.2
Subjects with >3% Change from Baseline in Lumbar Spine Bone Mineral Density at Month 36
(ITT Population, OC Data)

	Drug ABC (N=xxx)	Placebo (N=xxx)
Subjects completing Month 36	xxx	xxx
Subjects with >3% change from baseline	xxx (xx.x%)	xxx (xx.x%)
P-value [1]		x.xxxx

N=ITT population
OC Data are data as observed (i.e., no imputation for missing values)
Subjects with missing BMD data at Month 36 are excluded from the analysis.
[1] p-value computed using Fisher's Exact Test.

BDS - Category Analysis（续）

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.2
DISPLAY NAME	Subjects with >3% Change from Baseline in Lumbar Spine Bone Mineral Density at Month 36 (ITT Population, OC Data)
RESULT IDENTIFIER	<intentionally left blank>
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	CRIT1FL
REASON	Pre-specified in SAP
DATASET	ADBMD
SELECTION CRITERIA	ITTFL="Y" and PARAMCD="BMDLS" and AVISIT="MONTH 36" and ANL01FL="Y" and DTYPE=" " and PCHG not missing
DOCUMENTATION	……
PROGRAMMING STATEMENTS	…

BDS - Category Analysis（续）

PARAMCD	AVISIT	AVISITN	AVAL	BASE	CHG	PCHG	CRIT1	CRIT1FL	ABLFL	DTYPE	AWTDIFF	ANL01FL
BMDLS	BASELINE	2	0.992	0.992					Y		0	Y
BMDLS	MONTH 6	3	1.025	0.992	0.033	3.33	>3% change from baseline	Y			20	Y
BMDLS	MONTH 12	4	1.033	0.992	0.041	4.13	>3% change from baseline	Y			1	Y
BMDLS	MONTH 18	5	1.025	0.992	0.033	3.33	>3% change from baseline	Y			26	Y
BMDLS	MONTH 24	6	1.060	0.992	0.068	6.85	>3% change from baseline	Y			30	
BMDLS	MONTH 24	6	1.072	0.992	0.080	8.06	>3% change from baseline	Y			10	Y
BMDLS	MONTH 30	7	1.072	0.992	0.080	8.06	>3% change from baseline	Y		LOCF	173	Y
BMDLS	MONTH 36	8	1.021	0.992	0.029	2.92					2	Y
BMDLS	MONTH 36	8	1.086	0.992	0.094	9.48	>3% change from baseline	Y			2	

BDS - Repeated Measures Analysis

Summary E.3
Lumbar Spine Bone Mineral Density Percent Change From Baseline to Month 24
(ITT Population, OC Data, Repeated Measures Analysis)

	% Change From Baseline		Treatment Difference (Drug ABC – Placebo)		
	LS Mean[a]	95% CI[a]	LS Mean[a]	95% CI[a]	p-value[a]
Drug ABC (N = xxx)	x.x	(x.x, x.x)			
Placebo (N = xxx)	x.x	(x.x, x.x)	x.x	(x.x, x.x)	x.xxxx

N = ITT population
OC Data = Observed Cases Data (i.e., data as observed with no imputation for missing values)
LS = Least squares
[a]Based on mixed-effects model repeated measures analysis, adjusting for planned treatment, time and treatment by time interaction, baseline BMD value, and baseline BMD value by time interaction.

BDS - Repeated Measures Analysis（续）

Metadata Field	Metadata
DISPLAY IDENTIFIER	Summary E.3
DISPLAY NAME	Lumbar Spine Bone Mineral Density Percent Change From Baseline to Month 24 (ITT Population, OC Data, Repeated Measures Analysis)
RESULT IDENTIFIER	Treatment Difference (LSMean, confidence interval, p-value)
PARAM	DXA BMD at Lumbar Spine (g/cm^2)
PARAMCD	BMDLS
ANALYSIS VARIABLE	PCHG
REASON	ad hoc analysis
DATASET	ADBMD
SELECTION CRITERIA	AVISITN>2 and AVISITN<=6 and ITTFL="Y" and DTYPE = " " and PARAMCD="BMDLS" and ANL01FL="Y"
DOCUMENTATION	….
PROGRAMMING STATEMENTS	PROC MIXED DATA=ADBMD; CLASS USUBJID AVISITN TRTPN; MODEL PCHG = TRTPN AVISITN TRTPN*AVISITN BASE BASE*AVISITN / OUTP=PRED DDFM=KR; REPEATED AVISITN / SUBJECT=USUBJID TYPE=UN; LSMEANS TRTPN / DIFF CL; RUN;

BDS - Repeated Measures Analysis（续）

PARAMCD	AVISIT	AVISITN	TRTP	ITTFL	AVAL	BASE	CHG	PCHG	ABLFL	DTYPE	AWTDIFF	ANL01FL
BMDLS	BASELINE	2	Drug ABC	Y	0.992	0.992			Y		0	Y
BMDLS	MONTH 6	3	Drug ABC	Y	1.025	0.992	0.033	3.33			20	Y
BMDLS	MONTH 12	4	Drug ABC	Y	1.033	0.992	0.041	4.13			1	Y
BMDLS	MONTH 18	5	Drug ABC	Y	1.025	0.992	0.033	3.33			26	Y
BMDLS	MONTH 24	6	Drug ABC	Y	1.060	0.992	0.068	6.85			30	
BMDLS	MONTH 24	6	Drug ABC	Y	1.072	0.992	0.080	8.06			10	Y
BMDLS	MONTH 30	7	Drug ABC	Y	1.072	0.992	0.080	8.06		LOCF	173	Y
BMDLS	MONTH 36	8	Drug ABC	Y	1.021	0.992	0.029	2.92			2	Y
BMDLS	MONTH 36	8	Drug ABC	Y	1.086	0.992	0.094	9.48			2	

增加列 vs 增加行

- Rule 1. A parameter-invariant function of AVAL and BASE on the same row that does not involve a transform of BASE should be added as a new column. 同行无转换 –> 增加新列
- Rule 2. A transformation of AVAL that does not meet the conditions of Rule 1 should be added as a new parameter, and AVAL should contain the transformed value. 数据转换 –> 增加新参数
- Rule 3. A function of one or more rows within the same parameter for the purpose of creating an analysis timepoint should be added as a new row for the same parameter. 同参-新分析时间点 –> 新行
- Rule 4. A function of multiple rows within a parameter should be added as a new parameter.同参多行 –> 新参数
- Rule 5. A function of more than one parameter should be added as a new parameter. 多参 –> 新参数
- Rule 6. When there is more than one definition of baseline, each additional definition of baseline requires the creation of its own set of rows. 多基线 –> 新行（BASETYP区分）

OCCDS变量

- 字典编码和分类变量
  - MedDRA: --TERM, --DECOD, --BODSYS, --LLT, --HLT, --HLGT, --SOC
  - WHO Drug: CMTRT, CMDEOCD, CMCLAS, ATCy
  - 其他分类变量：--CAT, --SCAT, ACATy
- 时间变量
  - ASTDT, ASTDTM, ASTDTF, AENDT, AENDTM, AENDTF, ASTDY, AENDY, ADURN, ADURU, APERIOD, APERIODC
- 标识变量：
  - --OCCUR, --PRESP, ANLzzFL
  - AE: TRTEMFL, TREMxxFL
  - CM: ONTRTFL, ONTRxxFL
  - AE & CM: PREFL, FUPFL

OCCDS变量（续）

- 事件标记变量
  - AOCCFL, AOCCPFL, AOCCIFL, AOCCPIFL, AOCCzzFL
  - MedDRA事件标记变量：AOCCSFL, AOCCSIFL
- 治疗/剂量变量
  - DOSEON, DOSCUMA, DOSEU
- 描述变量
  - --SEV vs ASEV/ASEVN, --REL vs AREL/ARELN, --TOXGR vs ATOXGR/ATOXGRN
  - SEVGRy, SEVGRyN, RELGRy, RELGRyN, TOXGGRy, TOXGGRyN
- MedDRA标准化查询变量
  - SMQzzNAM, SMQzzSC, CQzzNAM

OCCDS示例

ADAE where SAFFL = 'Y' and TRTEMFL = 'Y'
ADSL where SAFFL = 'Y'

Table 14.2.7.1

Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term

Analysis Population: Safety

AEBODSYS
AEDECOD

TRTA

SYSTEM ORGAN CLASS Preferred Term	Treatment A (N = xxx) n (%)	Treatment B (N = xxx) n (%)	
Number of subjects reporting at least one adverse event	x (x.x)	x (x.x)	**AOCCFL=Y**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
At least one event	x (x.x)	x (x.x)	**AOCCSFL=Y**
Anaemia	x (x.x)	x (x.x)	**AOCCPFL=Y**
…	x (x.x)	x (x.x)	

OCCDS - Overlapping or Consecutive AE

Subjects with any resolved event - n (%)	xx (xx.x)
Number of resolved events	xx
Number of days experiencing resolved events (days)	
n[a]	xx.x
Mean	xx.x
SD	xx.xx
Median	xx.xx
Q1, Q3	xx.x, xx.x
Min, Max	xx.x, xx.x
Subjects with unresolved event - n (%)	xx (xx.x)
Number of unresolved events	xx

OCCDS - Overlapping or Consecutive AE（续）

ADAE

AEDECOD	AETOXGR	ASTDT	AENDT	ADURN	ADURU	DOSEON	DOSEU
Nausea	1	2024/1/1	2024/1/5	5	DAYS	10	mg
Nausea	2	2024/1/6	2024/1/10	5	DAYS	10	mg

ADAE-Pooled

AEDECOD	TOXGGR1	ASTDT	AENDT	ADURN	ADURU	DOSEON	DOSEU
Nausea	1	2024/1/1	2024/1/10	10	DAYS	10	mg
Nausea	2	2024/1/6	2024/1/10	5	DAYS	10	mg

ADaM新动态

- ADaM model v3.0 for public review in 2025
  - Consolidation of ADaM model v2.1 and IGs (ADaMIG v1.3, OCCDS v1.1, NCA v1.0) into an overarching ADaM Model & IG
- ADaMIG for Anti-Drug Antibody (ADA) v1
- ADaM examples for Pharmacokinetics Parameters (PP) v1
  - To detail the process starting from the creation of non-compartmental analysis (NCA) file to ADPP
- ADaM Oncology Examples
- ADaM example datasets for Lab Displays v1
  - To support the draft FDA Standard Safety Tables and Figures Integrated Guide (ST&F IG)*

** https://www.regulations.gov/document/FDA-2022-N-1961-0046*

Q & A

Thank You