TRANSFORMING PROMISING IDEAS INTO COMMERCIAL REALITY

From Soup to Nuts

Creating the BDS Model and Tracing it Back

inVentiv Health clinical

Agenda

- Dissecting the first table
- Creating the analysis metadata
- From analysis to parameter creation
- Combining parameters into datasets
- Putting it all together

Step 1 – The Preparation

- Protocol
- Statistical Analysis Plan (SAP)
- Table shells
- The data in SDTM format

ADSL

- Required for all other datasets and tables
- Includes
  - All analysis population flags
  - Treatment arm information
  - Important dates
  - Required demographic variables
  - Covariates needed for efficacy and safety analyses

For this presentation, we expect ADSL has already been created.

Let's Get Started- At The End

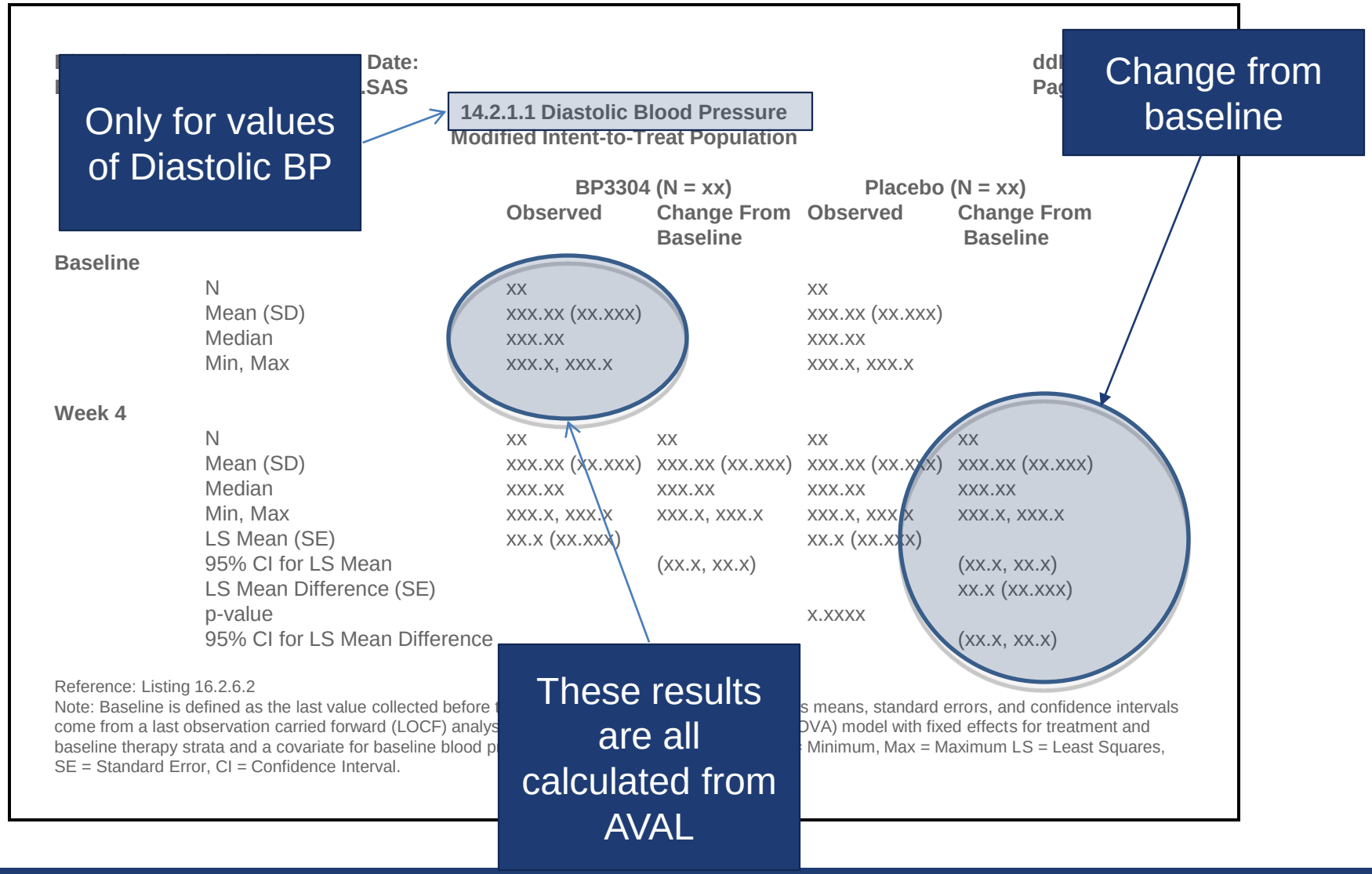
Bigg Pharmaceutical Company Date: **ddMONyyyy**
BP3304-002 Program xxxxxxxx.SAS **Page X of Y**

14.2.1.1 Diastolic Blood Pressure
Modified Intent-to-Treat Population

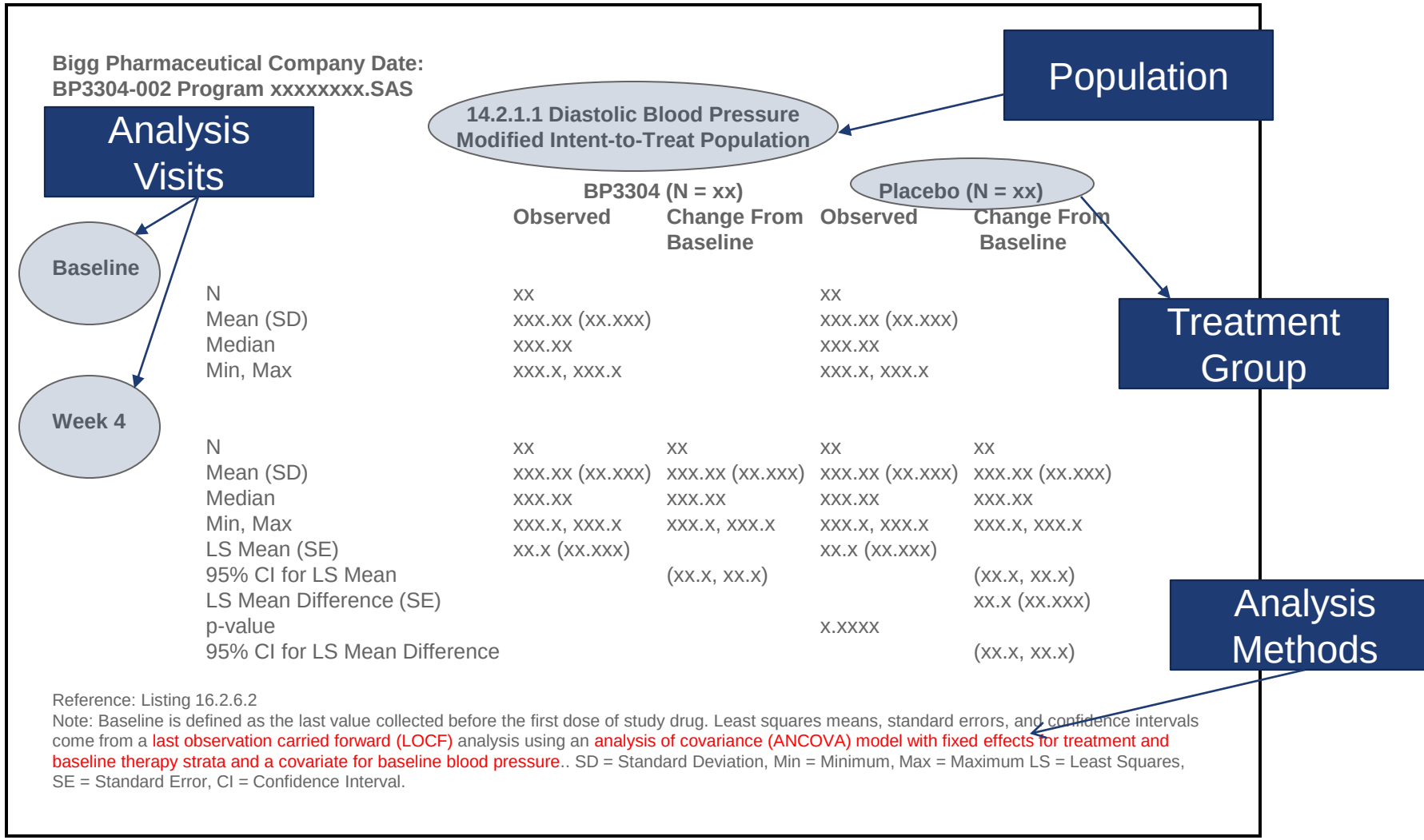
		BP3304 (N = xx)		Placebo (N = xx)	
		Observed	Change From Baseline	Observed	Change From Baseline
Baseline					
	N	xx		xx	
	Mean (SD)	xxx.xx (xx.xxx)		xxx.xx (xx.xxx)	
	Median	xxx.xx		xxx.xx	
	Min, Max	xxx.x, xxx.x		xxx.x, xxx.x	
Week 4					
	N	xx	xx	xx	xx
	Mean (SD)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)
	Median	xxx.xx	xxx.xx	xxx.xx	xxx.xx
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
	LS Mean (SE)	xx.x (xx.xxx)		xx.x (xx.xxx)	
	95% CI for LS Mean		(xx.x, xx.x)		(xx.x, xx.x)
	LS Mean Difference (SE)				xx.x (xx.xxx)
	p-value			x.xxxx	
	95% CI for LS Mean Difference				(xx.x, xx.x)

Reference: Listing 16.2.6.2
Note: Baseline is defined as the last value collected before the first dose of study drug. Least squares means, standard errors, and confidence intervals come from a last observation carried forward (LOCF) analysis using an analysis of covariance (ANCOVA) model with fixed effects for treatment and baseline therapy strata and a covariate for baseline blood pressure.. SD = Standard Deviation, Min = Minimum, Max = Maximum LS = Least Squares, SE = Standard Error, CI = Confidence Interval.

Let's Get Started….



Let's Get Started….



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Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
LS Mean (SE)	xx.x (xx.xxx)		xx.x (xx.xxx)	
95% CI for LS Mean		(xx.x, xx.x)		(xx.x, xx.x)
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List of Data Needed

- Analysis value
- Change from baseline
- Type of measurement (parameter)
- Analysis visit
- Population flag
- Treatment group
- Baseline therapy stratum
- Baseline blood pressure

List of Data Needed for Results Metadata

- **Analysis value**
- **Change from baseline**
- Type of measurement (parameter)
- Analysis visit
- Population flag
- Treatment group
- Baseline therapy stratum
- Baseline blood pressure

Analysis Results Metadata

A text-based representation of the visual table shells that we are all familiar with.

The challenge now is how do we get that done in a way that is understandable?

Analysis Results Metadata

- Page 22 of Analysis Data Model (ADaM) v2.1
- Provides traceability from table back to data in analysis datasets
- Formal way to describe origin and analysis of each data item on a table
- Sponsor determines which analyses should have metadata

Analysis Results Metadata Fields

- Display Identifier – table number
- Display Name – table title, including population
- Result Identifier- specific analysis result within display
- PARAM – parameter
- PARAMCD – parameter code

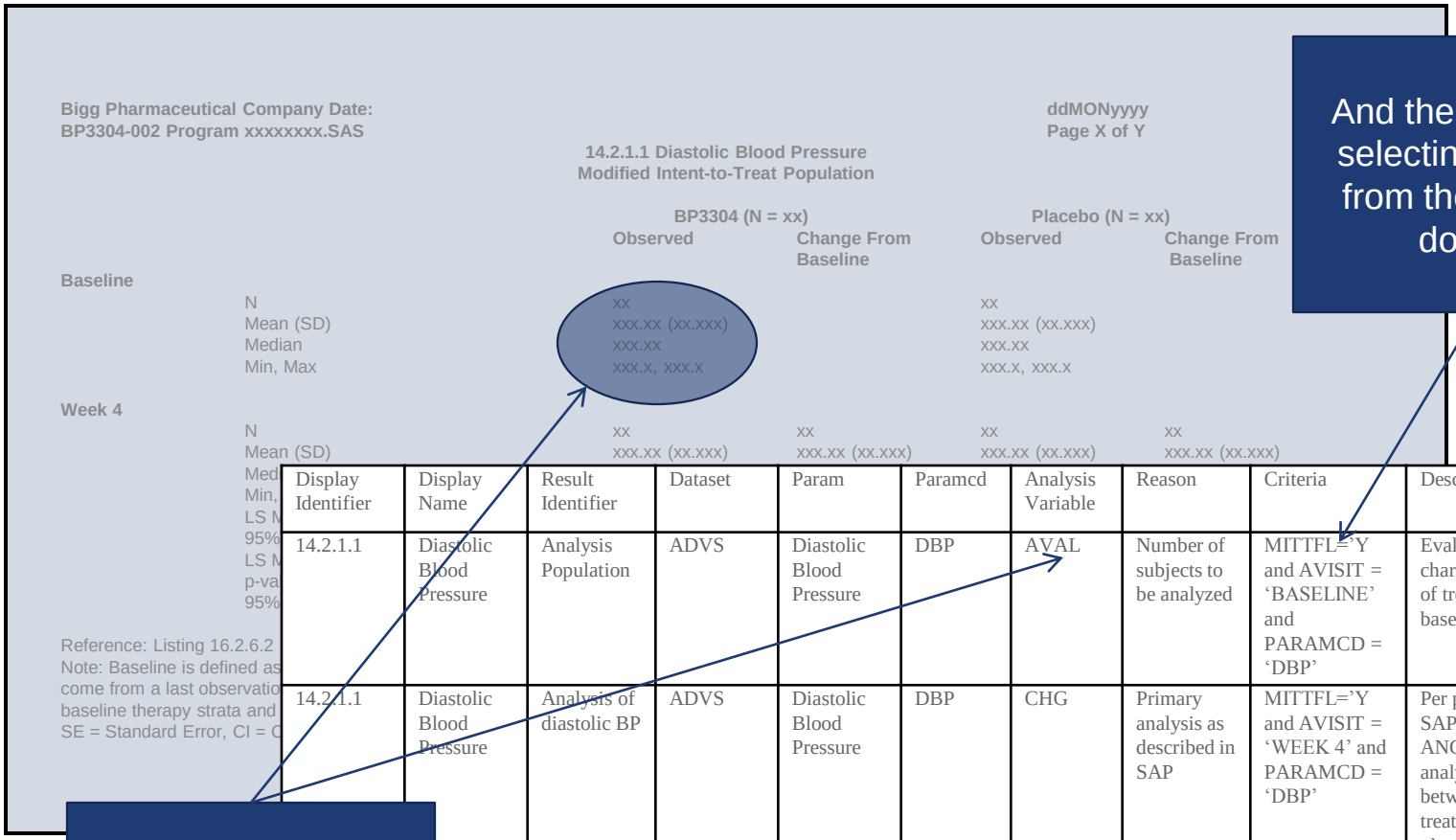
Analysis Results Metadata Fields

- Analysis Variable – variable being analyzed
- Reason – rationale for performing analysis
- Dataset – dataset(s) used for analysis

Analysis Results Metadata Fields

- Selection Criteria – selection criteria for analysis subset and/or numerator
- Documentation - text description of analysis performed
- Programming Statements – syntax used for analysis

Building Analysis Metadata…



Bigg Pharmaceutical Company Date: ddMONyyyy
BP3304-002 Program xxxxxxxx.SAS Page X of Y

14.2.1.1 Diastolic Blood Pressure
Modified Intent-to-Treat Population

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Median	xxx.xx		xxx.xx	
Min, Max	xxx.x, xxx.x		xxx.x, xxx.x	
Week 4				
N	xx	xx	xx	xx
Mean (SD)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)	xxx.xx (xx.xxx)
Med				
Min,				
LS M				
95%				
LS M				
p-va				
95%				

Reference: Listing 16.2.6.2
Note: Baseline is defined as
come from a last observatio
baseline therapy strata and
SE = Standard Error, CI = C

And the criteria for selecting the data from the analysis domain

Display Identifier	Display Name	Result Identifier	Dataset	Param	Paramcd	Analysis Variable	Reason	Criteria	Description	Program Statements
14.2.1.1	Diastolic Blood Pressure	Analysis Population	ADVS	Diastolic Blood Pressure	DBP	AVAL	Number of subjects to be analyzed	MITTFL='Y and AVISIT = 'BASELINE' and PARAMCD = 'DBP'	Evaluate basic characteristics of treated baseline subj..	PROC UNIVARIATE DATA=ADVS; CLASS TRTP; VAR AVAL;
14.2.1.1	Diastolic Blood Pressure	Analysis of diastolic BP	ADVS	Diastolic Blood Pressure	DBP	CHG	Primary analysis as described in SAP	MITTFL='Y and AVISIT = 'WEEK 4' and PARAMCD = 'DBP'	Per page 16 of SAP, perform ANCOVA analysis between treated and placebo populations.	PROC GLM Class=trtp; Model chg=trtp;

Which we map to our analysis metadata

From the Results to Parameters

- Now that we have Results Metadata, we can build Variable and Parameter Metadata
- If we were working on multiple table shells, we would want to subset the Results Metadata to those parameters needed for one analysis data set.
- The initial dataset for this will be a Basic Data Structure (BDS) based on ADaM Specifications because…

Basic Data Structure (BDS)

"A BDS contains one or more records per subject, per analysis parameter, per analysis timepoint." (Analysis Data Model v2.1, page 11)

"Long and narrow" instead of "short and wide"

Variable List

- **Subject identifier**
- **Type of measurement (parameter)**
- **Analysis visit**
- Analysis value
- Change from baseline
- Population flag
- Treatment group
- Baseline therapy stratum
- Baseline blood pressure

Analysis Variable Metadata

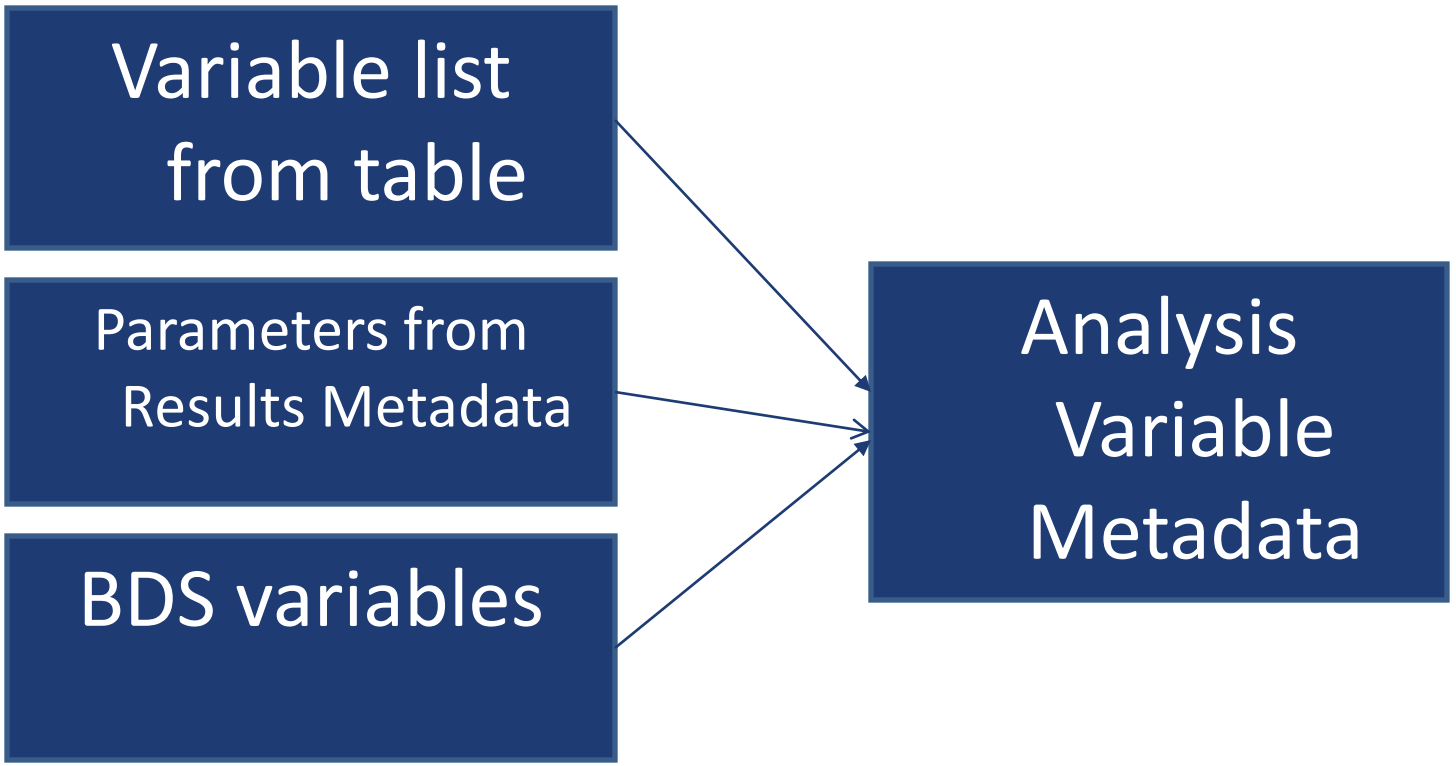
- Describes each variable in analysis dataset
  - Attributes
  - Definition / derivation
- Mandatory for all ADaM-compliant analysis datasets

Analysis Variable Metadata Fields

- Dataset name
- Variable name
- Variable label
- Variable type (text, integer, float)
- Display format
- Codelist / controlled terms
- Source / derivation

•ADaM Implementation Guide v1.0
•BDS Section begins on page 20

Putting the Pieces Together



Required BDS Variables

- STUDYID – study identifier
- USUBJID – unique subject identifier
- TRTP – planned treatment
- PARAM – parameter
- PARAMCD – parameter code
- AVAL / AVALC – value
- xxxFL – at least 1 population flag

Start Mapping Variables

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADVS	STUDYID	Study Identifier	Text		BP3304-002	VS.STUDYID
ADVS	USUBJID	Unique Subject Identifier	Text			VS.USUBJID
ADVS	PARAM	Parameter Description	Text		DIASTOLIC BLOOD PRESSURE	VS.VSTEST
ADVS	PARAMCD	Parameter Code	Text		DIABP	VS.VSTESTCD
ADVS	AVAL	Analysis Value	Integer	3.0		VS.VSSTRESN

What’s missing?

Variable List

- Subject identifier
- Type of measurement (parameter)
- **Analysis visit**
- Analysis value
- **Change from baseline**

From VS

- Population flag
- Treatment group
- Baseline therapy stratum
- Baseline blood pressure

From ADSL

Analysis Visit

Defined on page 11 of SAP:

Visit Windows: Measurements will be associated with a visit for summarization according to the **study day** associated with the **date on which the information was collected**. Target dates and the acceptable range of study days for each visit are presented in Table 2. If multiple visits occur within a visit window, the visit occurring closest to the target day will be selected for summarization. If there is a tie, the earliest visit will be chosen.

Analysis Record Flag (ANLzzFL)

- Keep all records from VS in ADVS
- Identifies specific record used for analysis (subjects with multiple records per visit)

Analysis Variable Metadata

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADVS	ADT	Date of VItals Result	Integer	DATE9.		Set to numeric version of VS.VSDTC when AVISIT comes from VS.VISIT; when AVISIT='END OF STUDY', set to the date of the last visit with a non-missing AVAL for PARAM
ADVS	ADY	Relative Day of VItals Result	Integer	4.0		ADT - TRTSDT + 1
ADVS	AVISIT	Analysis Visit	Text	$15.	Baseline, WEEK 4, WEEK 8, WEEK 12, WEEK 16, WEEK 20, WEEK 24, End of Study	Map based on visit windows in Section 3 of SAP using ADY. Set to 'Baseline' and 'End of Study' for corresponding added visit as described in parameter-level metadata
ADVS	ANL01FL	Analyzed Record Flag 1	Text	$1.	Y,N	Set to 'Y' for visit selected for summarization according to SAP Section 3, and for DTYPE='AVERAGE'.

Change from Baseline

- Derived analysis variable
- Add as record vs. add as column?
- Where does the baseline value come from?

Record vs. Column

Page 43 of ADaM Implementation Guide, v1.0:

"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."

All variables in a row should be used to describe the AVAL. Any value that itself will be analyzed should be added as a row.

Remember that the BDS is long and narrow not short and wide!

Baseline Value

SAP definition:

Baseline will be defined as the **average of three measurements taken on Day 1 before the first dose of study drug**; change will be defined as the post-baseline value minus the baseline value. If there are no measurements taken on Day 1, the value taken at the screening visit will be used as the baseline value.

Composite Baseline Value

From ADaM IG, page 46:

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.

Derivation Type (DTYPE)

- Used to identify rows that are derived within a given PARAM value
- Set to missing/blank for all non-derived records
- DTYPE='AVERAGE' for composite baseline records

Baseline Record Flag (ABLFL)

- Identifies baseline record
- For this example, composite baseline record has ABLFL='Y'

Change from Baseline (CHG)

- Defined in SAP and ADaM IG as AVAL – BASE
- BASE = baseline value
  - ABLFL='Y'

Analysis Variable Metadata

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADVS	BASE	Baseline Value	Float			For numeric tests only: AVAL where ABLFL='Y'
ADVS	CHG	Change from Baseline	Float			For numeric tests: AVAL-BASE
ADVS	DTYPE	Derivation Type	Text	$10.	AVERAGE, LOCF	Blank for records coming from SDTM. Set to 'AVERAGE' for composite baseline value and 'LOCF' for LOCF values, as described in the parameter-level metadata.
ADVS	ABLFL	Baseline Record Flag	Text	$1.	Y,N	See SAP and parameter-level metadata for numeric and categorical definitions

End of Study Analysis Value

- Per SAP, this is identified from page 16:

*The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and **end of study**.*

- Parameter is described in the Results Metadata
- What about missing values?

LOCF Analysis

From SAP:

*For change in diastolic and systolic blood pressure from baseline, a **last observation carried forward (LOCF) analysis** using an analysis of covariance (ANCOVA) model will be performed.*

LOCF Analysis – Step 1

- Create records substituting the last non-missing post-baseline value for every scheduled visit that a subject misses.
- Include scheduled visits missed by subjects who terminate the study early.
- DTYPE = ‘LOCF’
- AVAL = last non-missing post-baseline value

LOCF Analysis – Step 2

- Create a separate end of study record for each subject.
- AVISIT = ‘END OF STUDY’
- DTYPE = ‘LOCF’
- AVAL = last non-missing post-baseline value

Not a new variable- where does this metadata go?

Analysis Parameter Metadata

- Describes how variable metadata may vary by PARAM/PARAMCD.
- Also used to define additional records created for analysis.

Analysis Parameter Metadata Fields

- Identical to Analysis Variable Metadata fields, with addition of Parameter Identifier.
- *ALL* = applies to all parameters
- PARAMCD = applies to specific PARAMCD
- *DEFAULT* = applies to all parameters, except where noted

LOCF Analysis Parameter Metadata

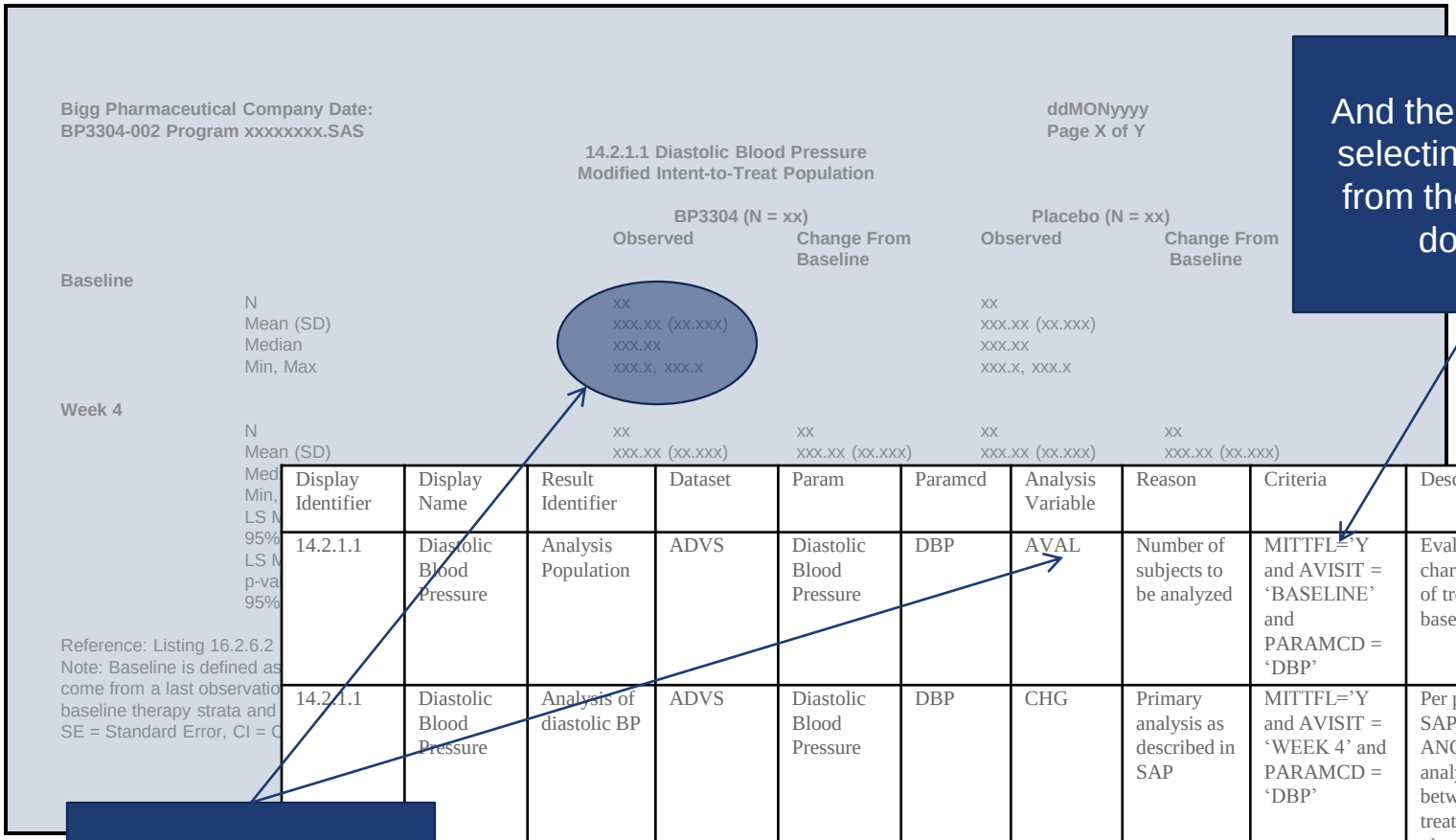
Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADVS	DIABP, SYSBP	DTYPE	Derivation Type	Char		LOCF	Last non-missing AVAL where AVISIT > 1
ADSL	DIABP, SYSBP	AVISIT	Analysis Visit	Char		END OF STUDY	Additional record created to hold last non-missing post-baseline value for each subject.

Composite Baseline Definition

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADVS	DIABP, SYSBP	DTYPE	Derivation Type	Char		AVERAGE	Additional record created to hold composite baseline value. AVAL = average of values with VSTPTNUM in (1, 2, 3). If no values on Day 1, then use last value obtained before Day 1.
ADVS	DIABP, SYSBP	AVISIT	Analysis Visit	Char		BASELINE	Additional record created to hold derived baseline value for each subject, parameter.

Putting it all together…..

Building Analysis Metadata…



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Which we map to our analysis metadata

…to build parameters…

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Where we add code on how to generate this data from the SDTM domains

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ADVS	STUDYID	Study Identifier	Text	$8.		VS.STUDYID
ADVS	USUBJID	Unique Subject ID	Text	$15.		VS.USUBJID
ADVS	SITEID	Study Site ID	Text	$10.		VS.SITEID
ADVS	TRTP	Planned Treatment	Text	$15	100 MG BP3304, PLACEBO	ADSL.TRT01P
ADVS	TRTPN	Planned Treatment (N)	Integer	1.0	1, 2	ADSL.TRT01PN
ADVS	MITTFL	Modified ITT Flag	Text	$1	Y, N	ADSL.MITTFL
ADVS	AVISIT	Analysis Visit	Text	$10	Baseline Week 4 Week 8 [more]	Map based on visit windows in Section 3 of SAP using ADY.
ADVS	PARAM	Parameter Description	Text	$20	DIASTAOLIC BLOOD PRESSURE..	VS.VSTEST
ADVS	PARAMCD	Parameter ID code	Text	$8	DBPc..	VS.VSTESTCD
ADVS	AVAL	Result	Int	8.4		VS.VSSTRESN
ADVS	BASE	Baseline Value	Int	8.4		AVAL where ABLFL='Y'
ADVS	CHG	Change from Baseline	Int	8.4		AVAL - BASE
ADVS	DTYPE	Derivation Type	Text	$10	LOCF, AVERAGE	Identifies if the AVAL is derived from prior visits.

The Analysis Metadata then get mapped to the parameters in ADVS

Questions?

Contact Us

Nancy Brucken
inVentiv Health Clinical
Nancy.Brucken@inventivhealth.com

Paul Slagle
inVentiv Health Clinical
Paul.Slagle@inventivhealth.com