NONMEM PK/PD DATASET Programming
Making it Simpler

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NONMEM

- Have you ever been in a conversation with someone in pharmacokinetics and heard the term “NONMEM”?

- Is it a Complex Methodology or a PK Parameter or a Monk who sits on Mountain Top ? ☹

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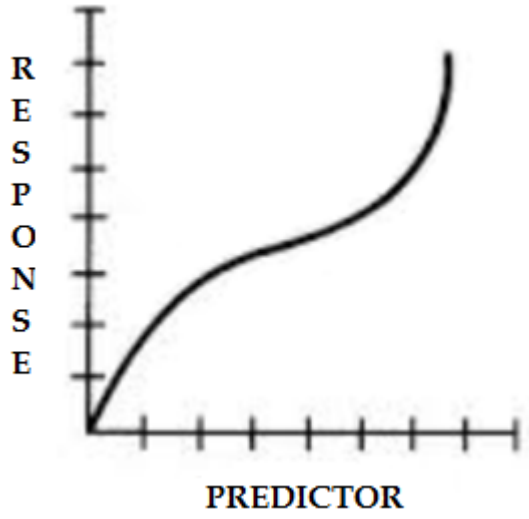
NONMEM

- NONMEM is a software package, just like Microsoft Office. It is a specialized software for the analysis of pharmacokinetic and pharmacodynamics data.
- Developed at University of California at San Francisco by two professors, Lewis Sheiner and Stuart Beal.
- Written in ANSI FORTRAN 77 Version.
- Mixed Effect Modelling = Fixed Effect + Random Effect



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Scope

- What is PK/PD?
- Why PK/PD analysis is needed?
- Different POP PK/PD models.
- Hierarchy of NONMEM Dataset.
- General conventions.
- Let's start with Programming.
- Conclusion.

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What is PK?

- The Pharmacokinetics (PK) is the study of what the body does to a drug.
- ADME Process

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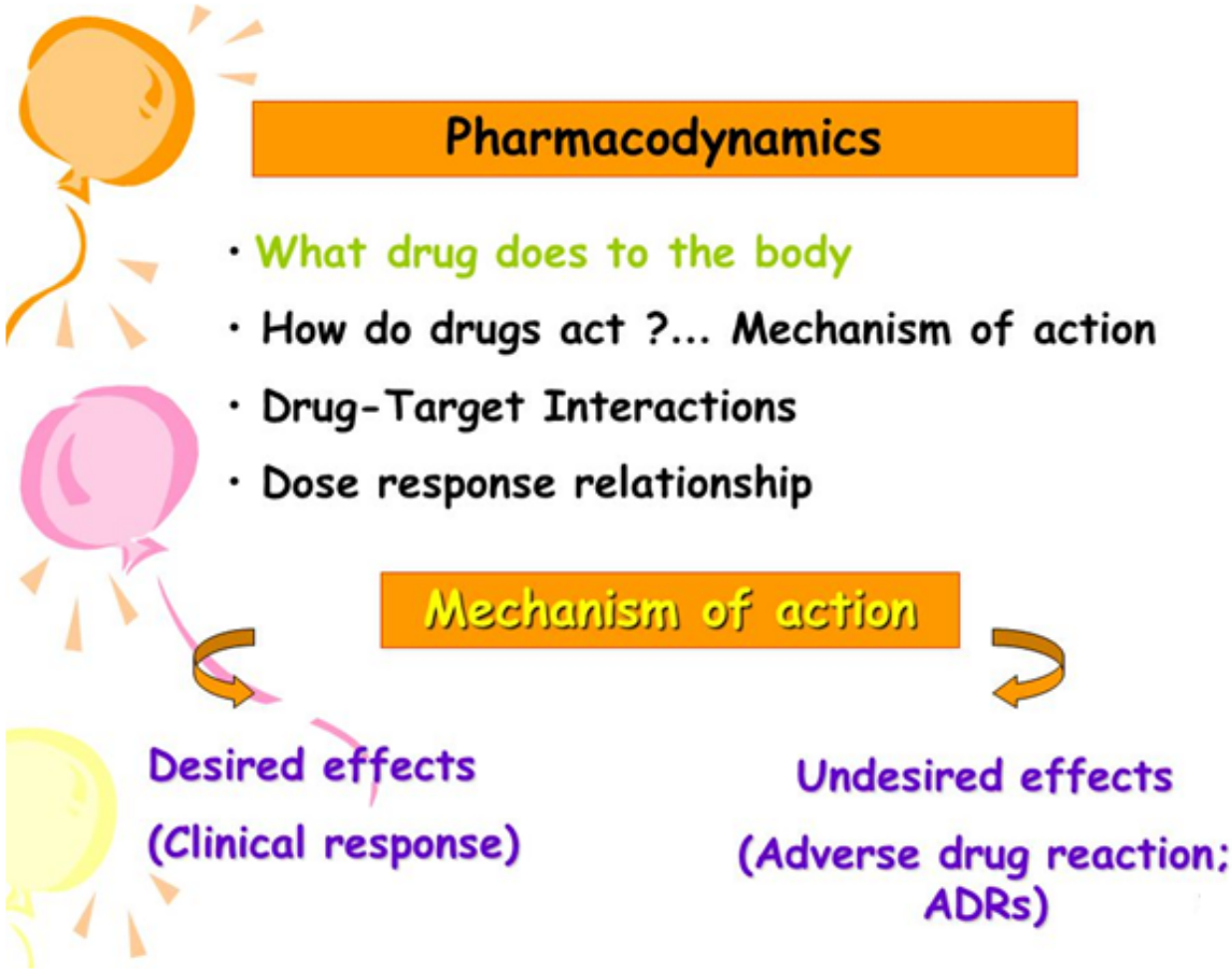
What is PD?

- It helps understand the relationship between dose & response.



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Why PK/PD analysis is needed?

- To Summarize & assess effects of covariates on PK and PD.
- Optimal Dosing Regimen with dense/sparse data.
- To estimate the random residual variability (including intra-patient measurement error).
- To estimate the magnitude of inter-patient variability.
- To assist in developing a preclinical, clinical pharmacokinetic program for an NDA submission.

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Major PK / PD Software models

- NONMEM
- S-Plus– Software that uses ***nlme*** function
- SAS (v8)– PROC NLMIXED.– A macro NLINMIX is available for pre-v8 users.
- WinNonMix – GUI Windows “Point and click” interface.
- PKBUGS uses Pharmaco Function & GUI Interface.

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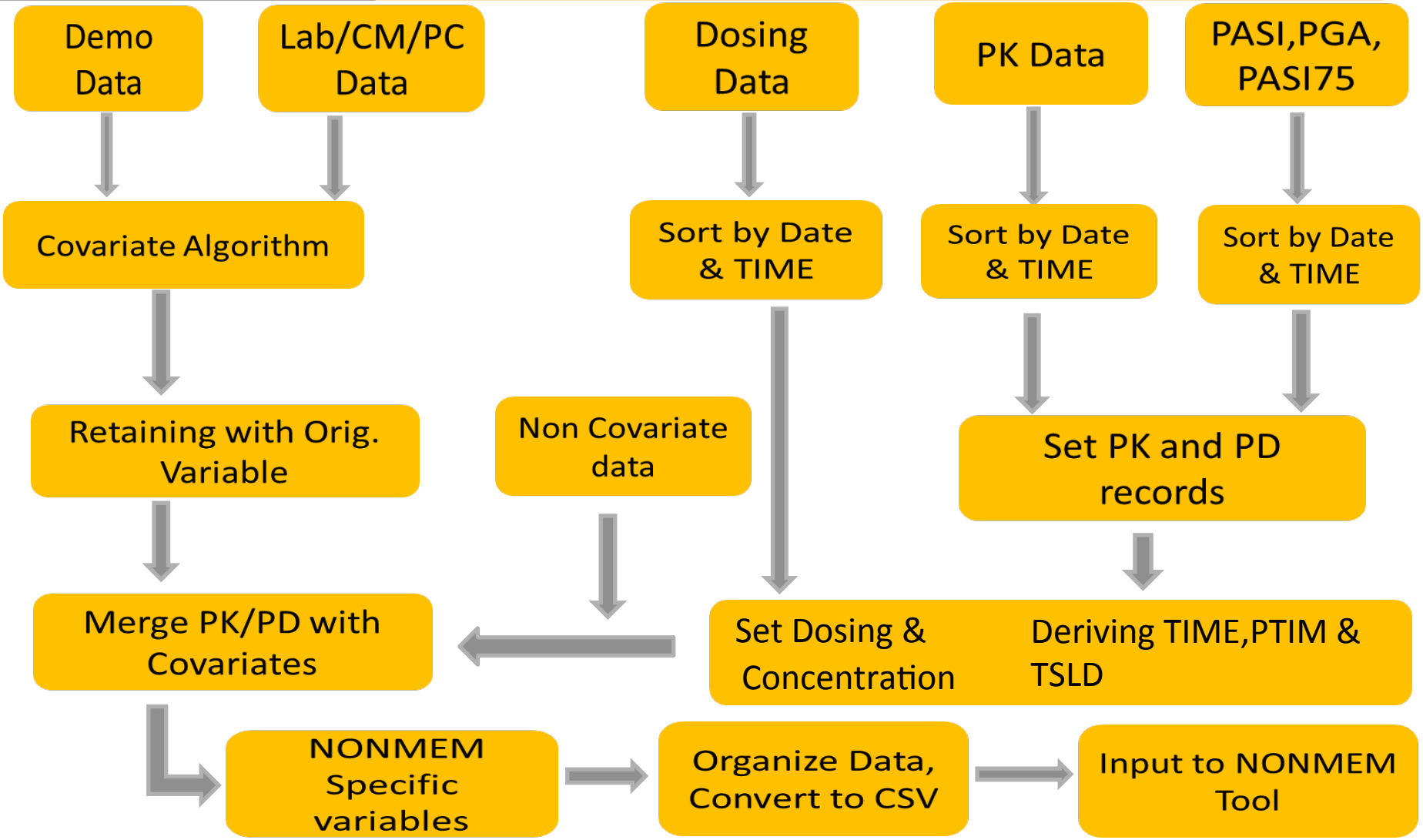
Flowchart



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General Conventions

- The first row of the data file should contain the names of data items (Columns).
- Names of data items <= 4 char(letters and numbers),only uppercase letters, of Numerical type.
- Two kinds of records(Observational, Dosing), each should not appear on same row. Dosing rec should be followed by Obs rec.
- Records organized chronologically (ID/TIME/PTIM/EVID/FLAG).

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Programming Steps

Structure → **Dosing Records**

- Accurate dosing information and history such as dose formulation, dosage.

→ **PK Conc Records**

- Plasma/blood concentrations from a validated assay (sparse or dense)

→ **PD Conc Records**

- Pharmacodynamics measurements and safety profiles (e.g., PGA,PASI etc.).

Covariates → **Variables**

- Covariate data demographics, lab values, concomitant meds, disease, fasting.

Timing Variables → **Organizing the data**

- Accurate capture of time/date associated with above items and organizing it accordingly.

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Programming, contd.

- Defining Structure
- **Dosing records:** Records those involve information about drug administered.

- You will basically exclude missing dose along with dosing times but before this you need to take care of **data issues** or data **inconsistency** before doing analysis.

- So How you do that??? ☹ ☹

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Programming, contd.

Data Issues or Inconsistency

- Missing drug? Amount? Date?
- Wrong data may affect the **Steady State Conc**
- Drug not administered as per Protocol Schedule Window.

- So These issues in the CRF/eCRF are to be clarified with CDM or DM in fixing them all before we start digging into the Ocean.

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Programming, contd.

- PK studies are Blinded so we get the real data after the Data Base Lock(DBL).

- And after DBL, The team will quickly look for quality NONMEM dataset but if these issues or inconsistency are not resolved then its tough task for programmers to meet the time with good quality.

- So its good process to identify these discrepancies rather than keeping them untouched and consuming more time.

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Programming, contd.

- Standard Specification file has to be created which includes some I/E criteria as follows.

  - If it is a crossover study then exclude the placebo records by prioritizing more on active drug, if parallel study proceed as normal.
  - Data after missing dosing information excluded.
  - At least 1 active dosing and 1 non missing conc after 1st active dose.

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Programming, contd.

- **Concentration/ Observation records**
  - These includes the results, date and time of serum blood samples collected, will be across multiple visits based on the samples collected.
  - Again Specification file should have these mentioned as follows:
    - Any samples with a missing concentrations value (“.”) or sampling time should be excluded.
    - Timing variables are to be derived based on 1st active dosing date.

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Programming, contd.

Concentration/ Observation records.

- For Population PK analysis, all the observation records for placebo subjects prior to receiving the active study agent will be excluded.
- For PD analysis, records may include serum conc, PASI Response, PGA score, PASI75 Response etc.

- In the event that placebo subjects crossover to active study agent, the elapsed time (including PTIM and TIME) for all the remaining records in these subjects should be re-calculated relative to the start of the administration of the first active dose.

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Covariates

- What are covariates?
- Why covariates are needed?
- Covariates Classified as :
  - Continuous Covariates
  - Categorical Covariates

- Covariates Algorithm that act as a catalyst for the analysis?

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Covariates

- Covariates are patient specific factors, such as weight, age, and gender, that might affect the pharmacokinetics or the pharmacodynamics of a drug.
- **Covariate** is also a secondary variable that can affect the relationship between the dependent variable and other independent variables of primary interest.

- Covariates are to be collected from different source of datasets as follows:
  - Demographic covariates (like Sex, age, Race, height, weight etc.).
  - BMI, BSA derived from weight & height covariates.
  - Lab Covariates such as ALB, ALT, AST, WBC, CRCL
  - Concomitant Therapies like corticosteroids.

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Covariates Algorithm

- Missing covariate data is a frequently encountered problem in analyses of clinical data, and to not venture the predictability of the developed mode, it is of great importance that the method chosen to handle the missing data is adequate for its purpose.

- Missing covariates may bias the results.

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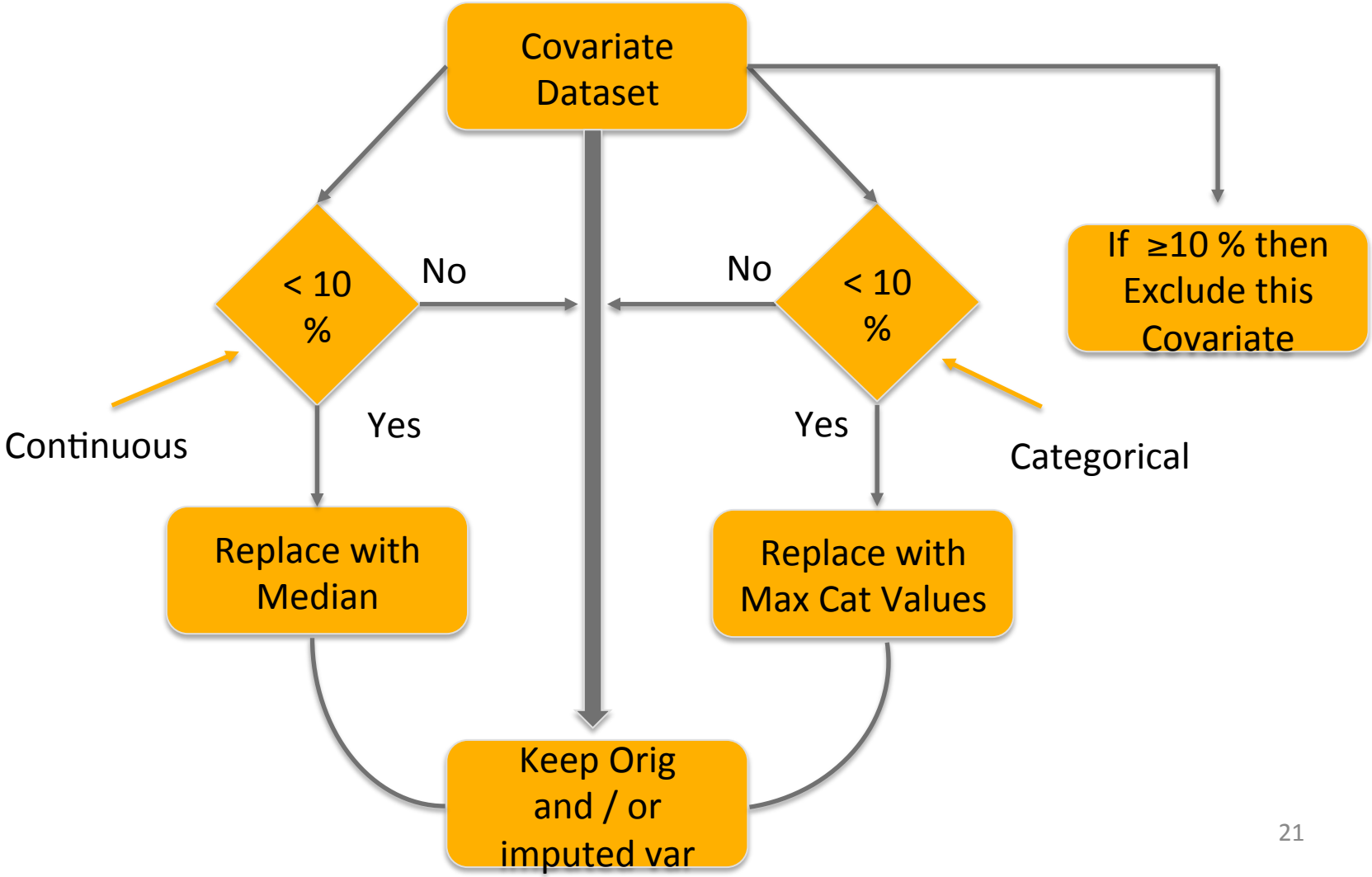
Covariates Algorithm



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Timing Variables

Some of the timing variables that are derived in NONMEM are TIME, PTIM, TSFD, TSLD etc.

- TIME: Actual elapsed time (in days) from first dose date and time.

- PTIM :Planned time (in days) relative to the first dose per the protocol schedule of assessments.

  For dosing & Obs records, PTIM is derived by making use of Visit variable.

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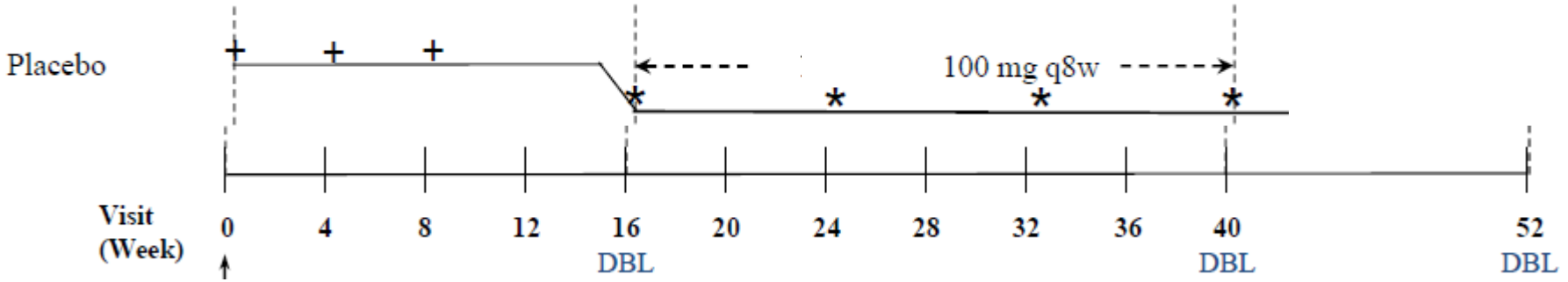
Timing Variables

- For Crossover, PTIM has to be carefully derived so that it wont affect other records.



- If placebo records are deleted then Week 16 will become the first visit. So Week 16 has to be replaced to Week 0 to get the PTIM to 0 days followed by 4,8,12 etc.

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Timing Variables

- TSFD: Elapsed time since first active dose.

- TSLD: Elapsed time since last prior **active** dose, derived after both the dosing & obs records are set together.
- This is calculated only for Obs records w.r.t prior dosing records.

STDY	ID	PTIM	TIME	TSLD	AMT	DV	CMT
DRUGA	10000001	0	0	0		0	2
DRUGA	10000001	0	0	0	50		1
DRUGA	10000001	28	26.628	26.628		2.03046	2
DRUGA	10000001	28	26.66	0	50		1
DRUGA	10000001	56	54.632	27.972		2.63537	2
DRUGA	10000001	84	82.649	55.99		0.49661	2
DRUGA	10000001	112	110.91	84.25		0.26357	2

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NONMEM Specific Variables

- ID, DV, MDV, EVID variables.
- ID: Variable that holds the information of subject and will always be the 1st column.
- DV is the dependent variable that holds concentration results.
- MDV means “missing dependent variable”. It tells NONMEM that it should NOT estimate the value of the dependent variable for that particular record.

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NONMEM Specific Variables

DV	Serum drug concentration (μg/mL) PASI PGA PASI75	DV is measurable serum concentration for CONC records. **PASI:** 0 to 72 with 0 being Remission & 72 being 100 % psoriasis. **PGA:** If 'Cleared – 0', set to 0; 'Minimal – 1' set to 1; 'Mild – 2' set to 2; 'Moderate – 3' set to 3; 'Marked – 4' set to 4; 'Severe – 5' set to 5. **PASI75**=1, if achieved (≥75%) **PASI75**=0, if not achieved (<75%)
FLAG	DV Flag	For dose records, set to 0. IF DV is concentration, set to 1. IF DV is PASI, set to 2. If DV is PGA, set to 3. If DV is PASI75, set to 4.
CMT	Compartment Number	1 = SC dosing records 2 = concentration records 3=other DVs (PASI, PGA, PASI75)
FBQL	Flag to indicate BQL for drug concentrations	<LLOQ=1 measurable=0 Dosing=. This flag only apply to drug concentration. For other DVs, FBQL=.
EVID	Event ID	1 = dose record 0 = dose-related observations.
MDV	Missing Dependent Variable	For dosing record, set MDV=1 For concentration records, set MDV=0 except <LLOQ values; for <LLOQ values, set MDV=1. For other DVs, MDV=0 if there is record

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CSV Output as an input to NONMEM

- Exporting the file to csv.
- PK CSV output.
- PD CSV output.
- Records should be chronologically arranged (ID/TIME/PTIM/ EVID/FLAG).
- How the data is read into NONMEM tool.

Some Control elements

$INPUT, $PROB, $PRED, $THETA, $OMEGA, $SIGMA, $EST, $TABLE

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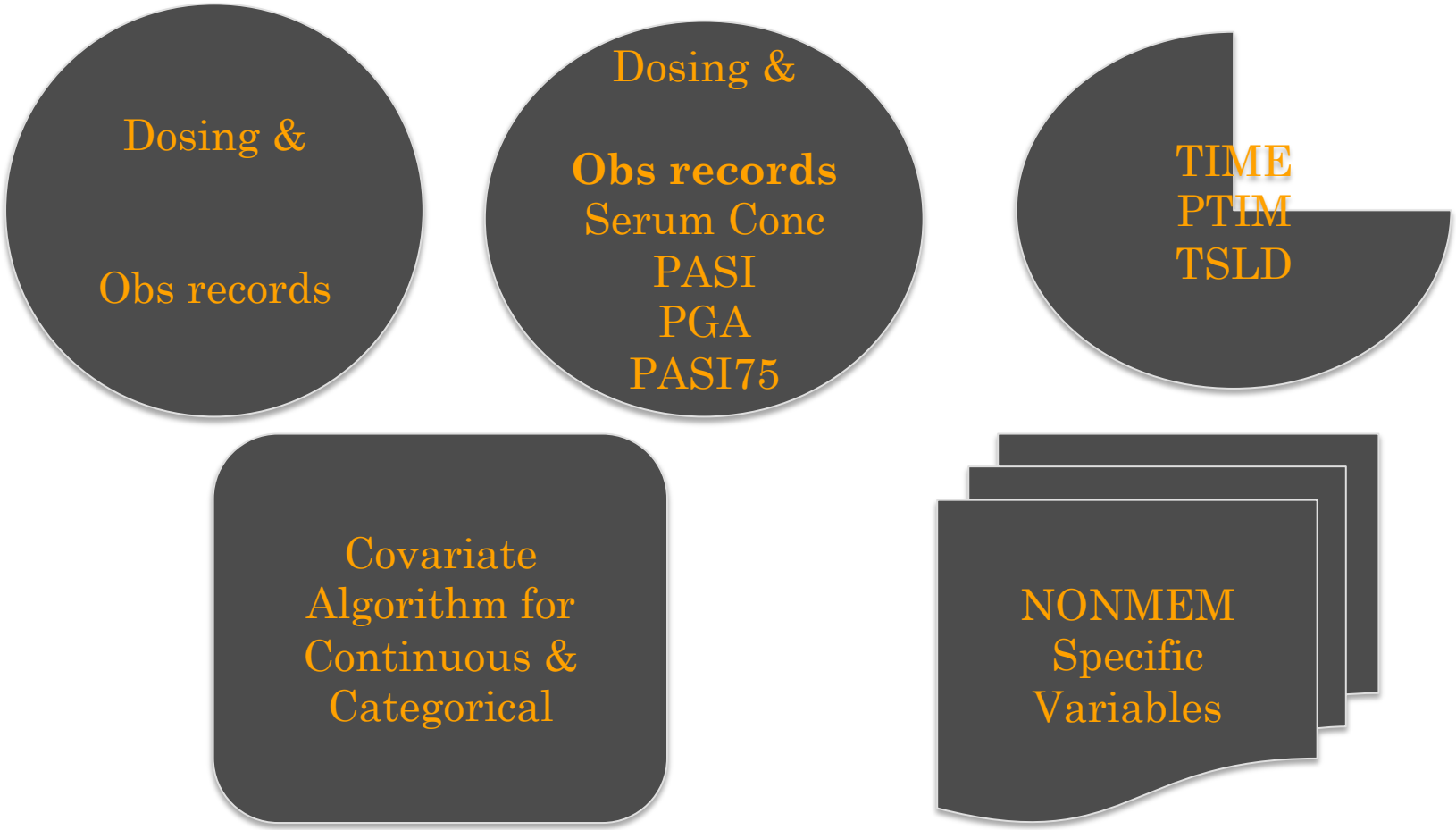
Conclusion



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References

- http://learnpkpd.com by Nathan Teuscher

- PDF file “Fisher/Shafer NONMEM Workshop Pharmacokinetic and Pharmacodynamic Analysis with NONMEM”

  by Steven Shafer.

ANY QUESTIONS??

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THANK YOU

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