

POPULATION PK DATA SET

- BASIC CONCEPTS AND
CHALLENGES FROM THE
PERSPECTIVE OF A SAS
PROGRAMMER

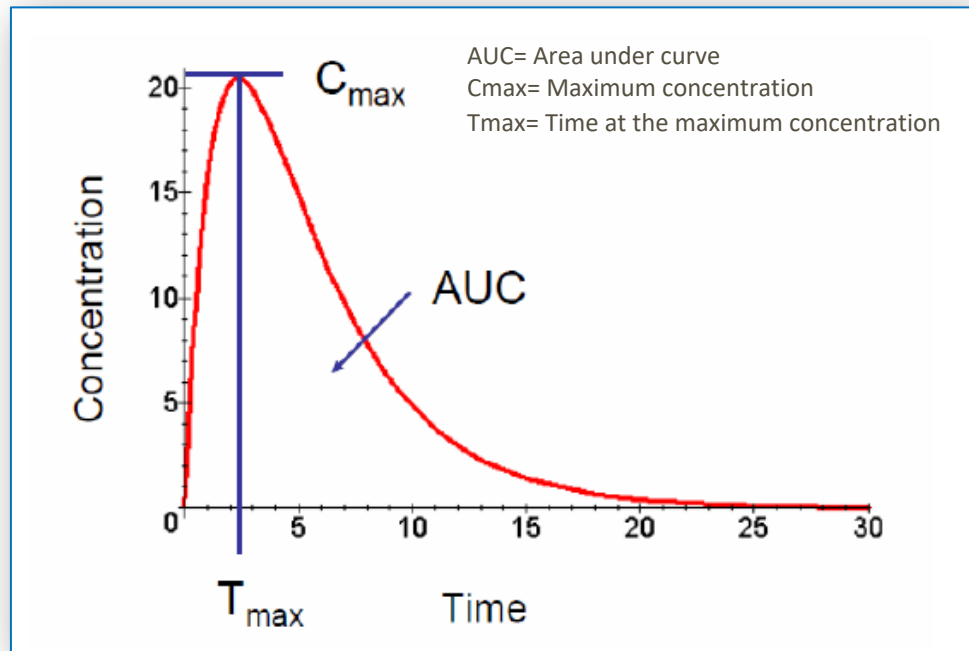
BY - NAMRATA POKHREL

WHAT IS PHARMACOKINETIC (PK) ?

- THE STUDY OF THE INTERACTIONS BETWEEN DRUG AND THE BODY. THE INTERACTIONS INCLUDE ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
- PK ANALYSIS NOT ONLY GUIDES DRUG DEVELOPMENT BUT ALSO RECOMMENDS THE TAILORED DOSING FOR INDIVIDUAL THERAPEUTIC AREA
- THE PK RESULTS ARE INFLUENCED BY SEVERAL FACTORS SUCH AS PHYSICAL ENVIRONMENT, FORMULATION, ADMINISTRATION ROUTE, SUBJECT'S HEALTH CONDITION, COVARIATES SUCH AS SUBJECT'S AGE, SEX, WEIGHT

INDIVIDUAL PK DATA SET FEATURES

- SIMPLE AND ROBUST
- USES GRAPHICAL TECHNIQUES TO DISPLAY THE RESULTS
- INDEPENDENT OF MODEL
- NOT USED FOR PREDICTIVE WORK
- ANALYSIS TIME IS SHORT
- USES DATA SETS FROM PHASE I STUDIES

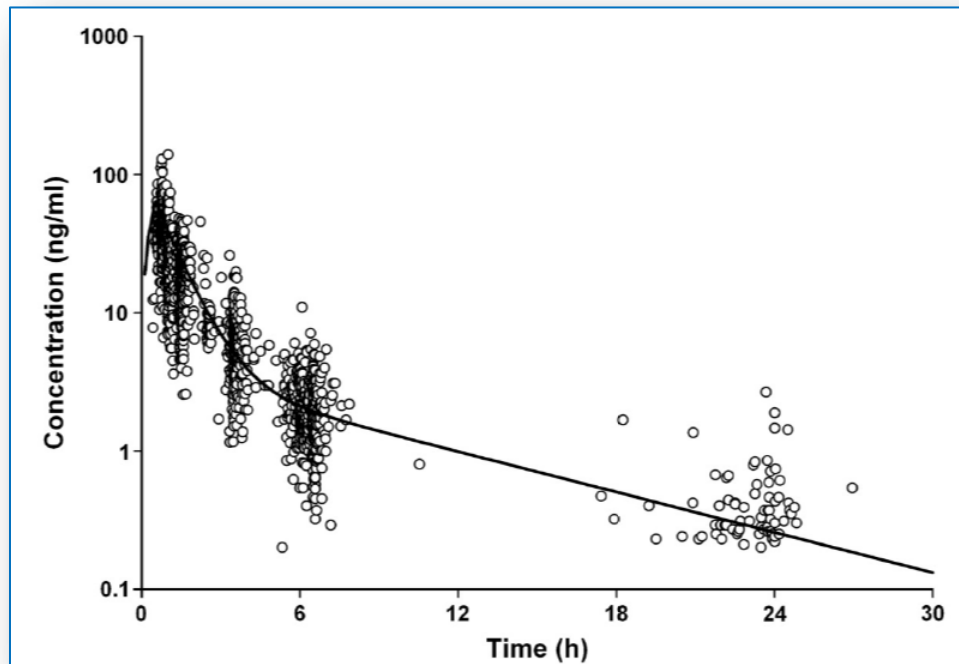


WHAT IS POPULATION PK (POP PK)?

- STUDY OF PLASMA DRUG CONCENTRATION BETWEEN SUBJECTS ACROSS MULTIPLE CLINICAL STUDIES WHEN STANDARD DOSAGE REGIMENS ARE ADMINISTERED.
- NONMEM® IS ONE OF THE TOOLS FOR POP PK MODELING AND SIMULATION ACTIVITIES NECESSARY TO ASSESS DRUG SAFETY, EFFICACY, AND DOSE-CONCENTRATION RELATIONSHIP IN TARGET POPULATION.
- POP PK REPORTS HAVE BECOME AN INTEGRAL PART OF REGULATORY SUBMISSIONS.

POP PK DATA SET FEATURES

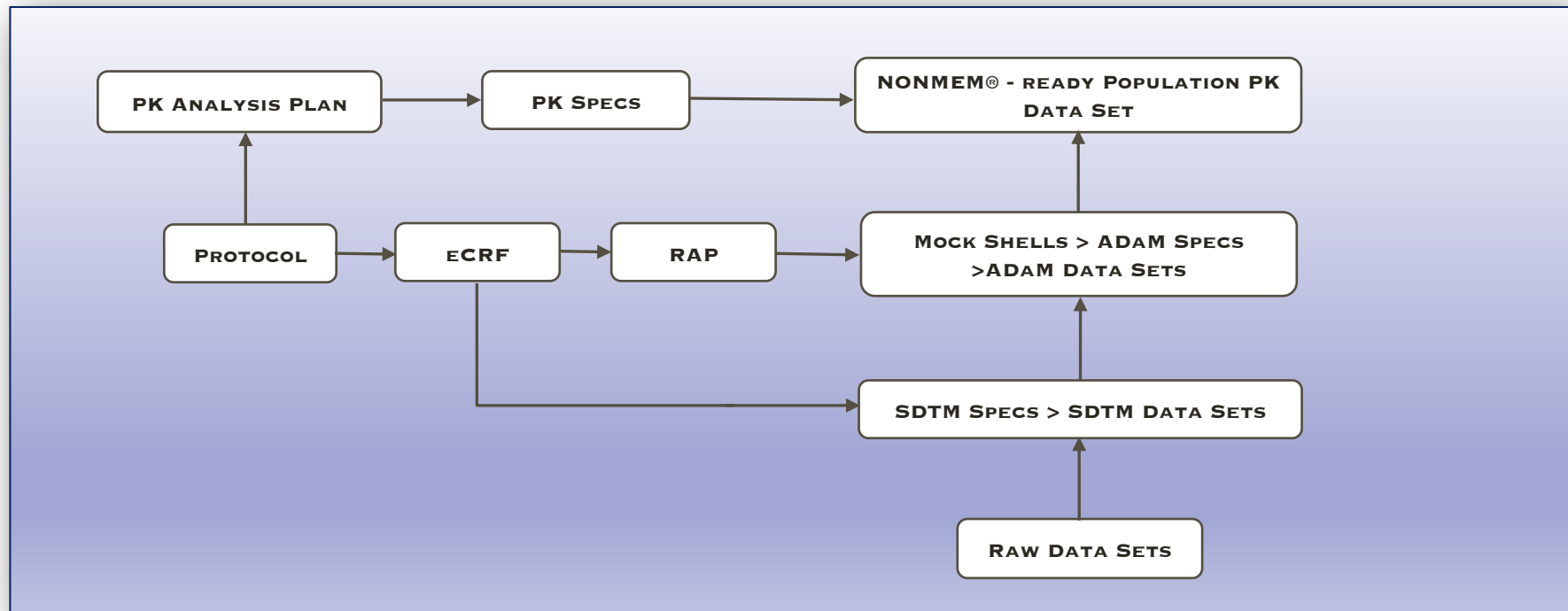
- ROBUST
- EVALUATES ENTIRE POPULATION
ACROSS STUDIES
- DESCRIPTIVE AND PREDICTIVE
- DETERMINES CLEARANCE AND
VOLUME OF DISTRIBUTION
- DETERMINES EFFECTS OF
COVARIATES SUCH AS AGE, SEX,
WEIGHT
- ANALYSIS TIME IS LONGER



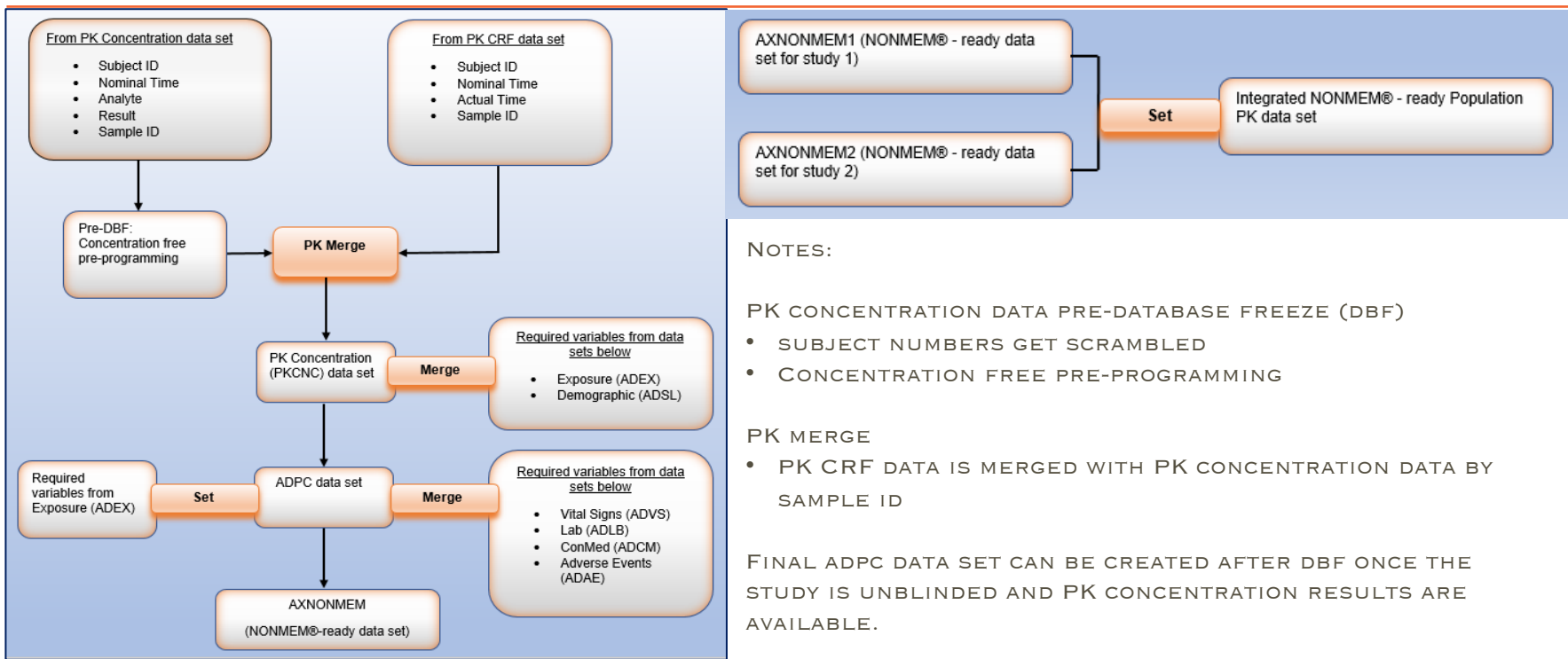
POP PK DATA SET COMPONENTS, STANDARDS, AND VALIDATION

REQUIRED COMPONENTS	1. DOSING DATA 2. PK CONCENTRATION DATA
OPTIONAL COMPONENTS	1. LAB DATA 2. BIOMARKER AND EFFICACY DATA 3. DEMOGRAPHIC DATA 4. CONCOMITANT MEDICATION DATA 5. ADVERSE EVENT DATA
STANDARDS	1. SDTM PC IS IN ONE RECORD PER SUBJECT PER TIME POINT 2. ANALYSIS - READY ADPC IS BASED ON BDS STRUCTURE OF CDISC ADAM 3. NO CDISC ADAM STANDARDS ARE AVAILABLE FOR POP PK DATA SETS
VALIDATION	1. ENSURES THAT DATA IS ACCURATE AND COMPLETE 2. IMPUTATION RULES FOR MISSING AND PARTIAL DATA ARE PROVIDED IN THE STUDY DOCUMENTS 3. CREATE INDEPENDENT VALIDATION CODE AND INCLUDE PROC COMPARE

HIGH LEVEL PROCESS FLOW



DATA SOURCES AND PROCESS FLOW



EXAMPLE OF A POP PK DATA SET

DATATYPE	ID	STUDYID	SUBJID	AGE	SEX	RACE	HT	WT	BMI	CMED	PPI	CRCL	FOOD	SMOKE
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
DOSING	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	1	ABC123456	1	27	M	White	185	87	25.27	Aspirin	No	130.6	No	Non-smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
DOSING	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	147	DEF123456	1	51	F	White	166	55	20.1	Mefenamic Acid	No	90.53	Yes	Smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
DOSING	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
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PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker
PK	253	GHI123456	1	69	M	White	166	62	22.4	Phenytoin	Yes	85.6	Yes	Non-smoker

OPTIONAL COMPONENTS:

- ADL(DEMOGRAPHY): SUBJID, AGE, SEX, RACE, HT, WT, BMI
- SUBUSE (SUBSTANCE USE): SMOKE
- ADCM (CONCOMITANT MEDICATION): CMED
- ADLB (LABORATORY): USED TO DERIVE BASELINE SERUM CREATININE CLEARANCE (CRCL)

EXAMPLE OF A POP PK DATA SET

DATATYPE	ID	STUDYID	SUBJID	CONC	REGIMEN	ROUTE	CMT	EVID	AMT	II	SS	RATE	MDV
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
DOSING	1	ABC123456	1	0	OD	PO	1	1	50	0	0	-2	1
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	1	ABC123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	1	ABC123456	1	231.35	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	802.19	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	837.64	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	539.16	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	267.84	OD	PO	2	0	0	0	0	0	0
PK	1	ABC123456	1	188.52	OD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	.	BD	PO	2	0	0	0	0	0	1
DOSING	147	DEF123456	1	0	BD	PO	1	1	50	12	0	-2	1
PK	147	DEF123456	1	123.6	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	171.19	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	131.55	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	101.69	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	55.59	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	42.08	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	35.05	BD	PO	2	0	0	0	0	0	0
PK	147	DEF123456	1	40.01	BD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	.	OD	PO	2	0	0	0	0	0	1
DOSING	253	GHI123456	1	0	OD	PO	1	1	50	0	0	-2	1
PK	253	GHI123456	1	.	OD	PO	2	0	0	0	0	0	1
PK	253	GHI123456	1	25.11	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	128.07	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	304.09	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	383.85	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	191.94	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	146.67	OD	PO	2	0	0	0	0	0	0
PK	253	GHI123456	1	75.98	OD	PO	2	0	0	0	0	0	0

REQUIRED COMPONENTS: NONMEM® SPECIFIC VARIABLES

- ID – SUBJECT IDENTIFIER
- EVID – EVENT ID
- MDV – MISSING DATA VALUE
- CMT – COMPARTMENT CODE
- AMT – AMOUNT OF DRUG ADMINISTERED
- RATE – RATE OF DRUG INFUSION
- II – INTER-DOSE INTERVAL
- SS – STEADY STATE DATA ITEM

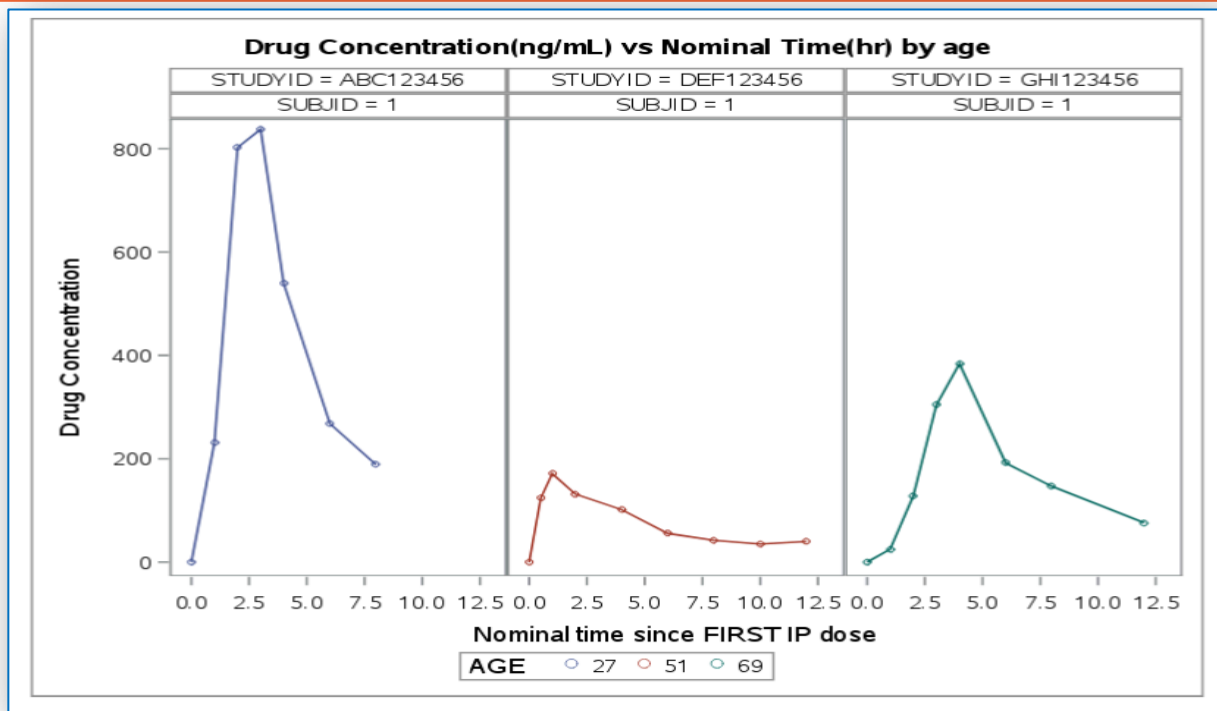
EXAMPLE OF A POP PK DATA SET

DATATYPE	ID	STUDYID	SUBJID	DATETIME	DAY	NDAY	NOMT	NOMTLD	RTFD	RTLD
PK	1	ABC123456	1	11/09/2009 08:55:00	1	.	.	.	-0.08	.
DOSING	1	ABC123456	1	11/09/2009 09:00:00	1	1	0	0	0	0
PK	1	ABC123456	1	11/09/2009 09:15:00	1	1	0.25	0.25	0.25	0.25
PK	1	ABC123456	1	11/09/2009 09:30:00	1	1	0.5	0.5	0.5	0.5
PK	1	ABC123456	1	11/09/2009 10:00:00	1	1	1	1	1	1
PK	1	ABC123456	1	11/09/2009 11:00:00	1	1	2	2	2	2
PK	1	ABC123456	1	11/09/2009 12:00:00	1	1	3	3	3	3
PK	1	ABC123456	1	11/09/2009 13:00:00	1	1	4	4	4	4
PK	1	ABC123456	1	11/09/2009 15:00:00	1	1	6	6	6	6
PK	1	ABC123456	1	11/09/2009 17:00:00	1	1	8	8	8	8
PK	147	DEF123456	1	04/11/2014 08:43:00	1	.	.	.	-0.37	.
DOSING	147	DEF123456	1	04/11/2014 09:05:00	1	1	0	0	0	0
PK	147	DEF123456	1	04/11/2014 09:34:00	1	1	0.5	0.5	0.483	0.483
PK	147	DEF123456	1	04/11/2014 10:04:00	1	1	1	1	0.983	0.983
PK	147	DEF123456	1	04/11/2014 11:04:00	1	1	2	2	1.983	1.983
PK	147	DEF123456	1	04/11/2014 13:04:00	1	1	4	4	3.983	3.983
PK	147	DEF123456	1	04/11/2014 15:04:00	1	1	6	6	5.983	5.983
PK	147	DEF123456	1	04/11/2014 17:04:00	1	1	8	8	7.983	7.983
PK	147	DEF123456	1	04/11/2014 19:04:00	1	1	10	10	9.983	9.983
PK	147	DEF123456	1	04/11/2014 21:01:00	1	1	12	12	11.93	11.93
PK	253	GHI123456	1	11/13/2011 08:59:00	1	.	.	.	-0.02	.
DOSING	253	GHI123456	1	11/13/2011 09:00:00	1	1	0	0	0	0
PK	253	GHI123456	1	11/13/2011 09:30:00	1	1	0.5	0.5	0.5	0.5
PK	253	GHI123456	1	11/13/2011 10:00:00	1	1	1	1	1	1
PK	253	GHI123456	1	11/13/2011 11:00:00	1	1	2	2	2	2
PK	253	GHI123456	1	11/13/2011 12:00:00	1	1	3	3	3	3
PK	253	GHI123456	1	11/13/2011 13:00:00	1	1	4	4	4	4
PK	253	GHI123456	1	11/13/2011 15:00:00	1	1	6	6	6	6
PK	253	GHI123456	1	11/13/2011 17:00:00	1	1	8	8	8	8
PK	253	GHI123456	1	11/13/2011 21:00:00	1	1	12	12	12	12

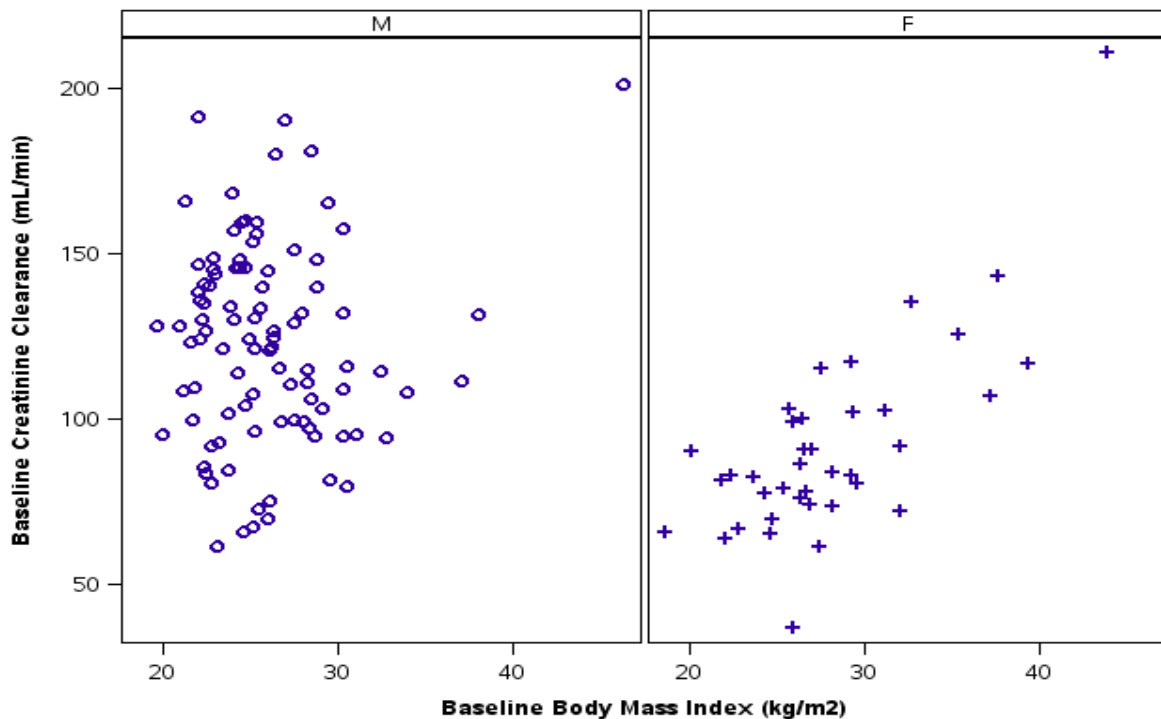
REQUIRED COMPONENTS: TIME DEPENDENT VARIABLES

- DATETIME – DATE AND TIME OF RECORD
- NOMT – NOMINAL TIME SINCE FIRST IP (INVESTIGATIONAL PRODUCT) DOSE
- NOMTLD – NOMINAL TIME SINCE LAST IP DOSE PRIOR TO SAMPLE
- RTFD – RELATIVE TIME FROM FIRST IP DOSE TO CURRENT SAMPLE TIME
- RTLD – RELATIVE TIME FROM LAST IP DOSE TO CURRENT SAMPLE TIME

DRUG CONCENTRATION VS. NOMINAL TIME BY AGE



RELATIONSHIP BETWEEN CREATININE CLEARANCE AND BMI BY SEX



CHALLENGES FROM PROGRAMMING PERSPECTIVE

DATA SET INCONSISTENCIES

1. INCONSISTENT STRUCTURES AND FORMATS
2. LACK OF CONSISTENT INDUSTRY WIDE STANDARDS

FREQUENT CHANGES IN DATA SET SPECIFICATION

1. SPECIFICATION IS CREATED FROM PROTOCOL AND ECRF BEFORE THE REAL DATA IS AVAILABLE
2. THE INITIAL SPECIFICATION DOES NOT COVER ALL DATA SCENARIOS.
3. CHANGES IN SOURCE DATA, RULES, AND DEFINITIONS

AVAILABILITY OF CONCENTRATION DATA

1. PK CONCENTRATION DATA IS AVAILABLE ONLY AFTER DBF.
2. PREPARE PROGRAM CODES USING DUMMY DATA AND GET FAMILIAR WITH THE REAL DATA AS SOON AS IT IS AVAILABLE
3. THE CDM ACTIVITIES ARE NOT ALIGNED WITH POP PK DATA DEVELOPMENT TIMELINES

CHALLENGES FROM PROGRAMMING PERSPECTIVE

DATA PROCESSING TIME

1. THE VOLUME OF THE DATA
2. COMPLEX ALGORITHMS

SCRAMBLING

1. UNREALISTIC DATA
2. INITIAL SETUP IS TIME CONSUMING
3. REQUIRES EXTRA RESOURCES FROM MULTIPLE FUNCTIONS

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THANK YOU!