



DH01 - Incorporating Longitudinal Co-Medication Data into Population Pharmacokinetic (POPPK) Analysis Datasets: A Programmer's Perspective

PHUSE EU Connect 2024 - Data Handling & Data Engineering

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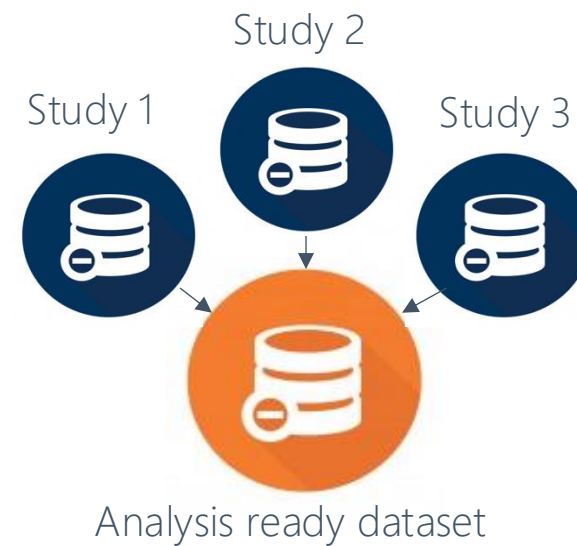
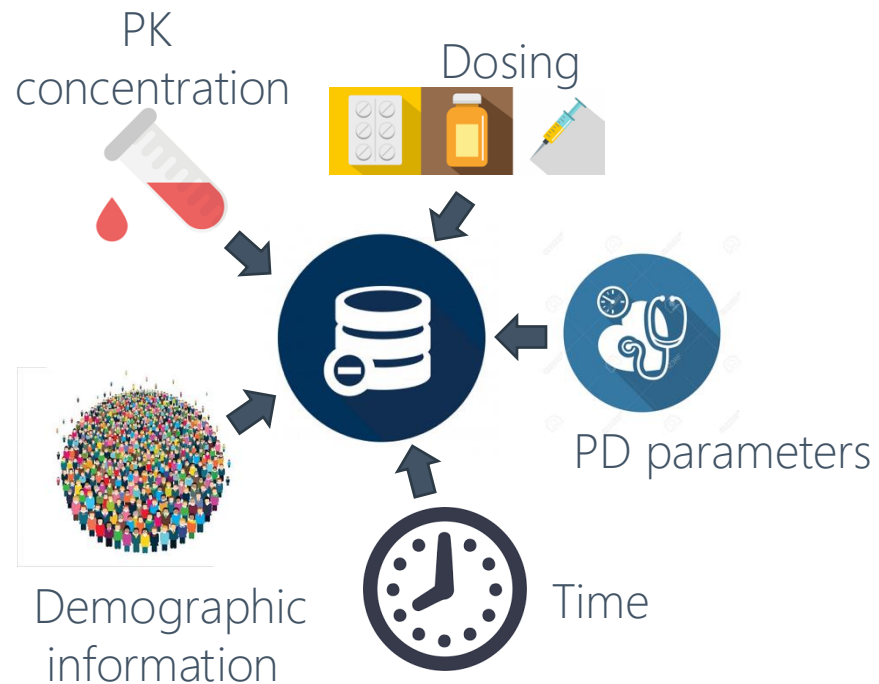
Disclaimer

- All subject data displayed in this presentation is dummy data which is solely included for demonstration purposes.

PPK dataset

Population pharmacokinetic dataset

- A dataset used for modeling of drug levels (pharmacokinetic) in a population by considering the variability in the population (covariates).



Population Pharmacokinetic (POPPK) dataset

Brief introduction

Subject
identifiers

Treatment info.

Time-course info.

PK
concentrations

Subject level
information
(demog., vital signs,
lab. measurements,
etc.)

Dosing
records

PK
observations

STUDYN	SUBJID	TRTAN	TRTPN	NDOSE	DOSE	AMT	NTIME	TIME	DVID	DV	MDV	AGE	BHT	BALT	ADATE	ATIME	USUBJID
12345	987654321	1	1	315	315	.	0	0	1	.	1	37	168	21	2011-06-24	08:56:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	0	0	0	.	1	37	168	21	2011-06-24	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	0.5	0.5	1	203.47	0	37	168	21	2011-06-24	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1	1	1	1584.81	0	37	168	21	2011-06-24	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	1.5	1.5	1	1656.16	0	37	168	21	2011-06-24	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	2	2	1	1365.05	0	37	168	21	2011-06-24	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	3	3	1	1419.27	0	37	168	21	2011-06-24	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	4	4	1	708.63	0	37	168	21	2011-06-24	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	5	5	1	578.77	0	37	168	21	2011-06-24	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	6	6	1	451.77	0	37	168	21	2011-06-24	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	8	8	1	294.8	0	37	168	21	2011-06-24	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	10	10	1	192.05	0	37	168	21	2011-06-24	19:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	12	12	1	114.14	0	37	168	21	2011-06-24	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	16	16	1	57.35	0	37	168	21	2011-06-25	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	24	24	1	19.39	0	37	168	21	2011-06-25	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	36	36	1	7.07	0	37	168	21	2011-06-25	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	48	47.83	1	3.9	0	37	168	21	2011-06-26	08:50:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144	143.92	1	.	1	37	168	21	2011-06-30	08:55:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	144	144	0	.	1	37	168	21	2011-06-30	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	144.5	144.5	1	25.81	0	37	168	21	2011-06-30	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145	145	1	423.23	0	37	168	21	2011-06-30	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	145.5	145.5	1	370.43	0	37	168	21	2011-06-30	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	146	146	1	377.56	0	37	168	21	2011-06-30	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	147	147	1	497.43	0	37	168	21	2011-06-30	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	148	148	1	440.35	0	37	168	21	2011-06-30	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	149	149	1	321.91	0	37	168	21	2011-06-30	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	150	150	1	237.72	0	37	168	21	2011-06-30	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	152	152	1	149.24	0	37	168	21	2011-06-30	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	154	154.02	1	103.72	0	37	168	21	2011-06-30	19:01:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	156	156	1	63.05	0	37	168	21	2011-06-30	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	160	160	1	35.94	0	37	168	21	2011-07-01	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	168	168	1	16.1	0	37	168	21	2011-07-01	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	180	180	1	8	0	37	168	21	2011-07-01	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	.	192	192	1	4.19	0	37	168	21	2011-07-02	09:00:00	ABC12345-987-654-321

Importance of concomitant medication in clinical trials

- Concomitant medication and their effect on drug metabolism.
- Cytochrome P-450 (CYP3A)
 - 50% of all clinically relevant medications are metabolized by CYP3A (*Zhou, 2008*)
- Induction and Inhibition
 - Tramadol, verapamil, and codeine
 - Glucocorticoids, rifampin, phenobarbital

CM-domain

- CDISC-definition: “The CM domain contains data relating to concomitant and prior medications used by the subject, such as those given on an as-needed basis or condition-appropriate medications.”

USUBJID	CMDECD	CMSCAT	CMDOSE	CMDOSU	CMDOSFRQ	CMROUTE	CMSTDTC	CMENDTC	CMSTDY	CMENDY	CMENRF
ABC12345-987-654-321	ROSUVASTATIN	Prior	20 mg	QD		ORAL			.	.	ONGOING
ABC12345-987-654-321	ALLOPURINOL	Prior	300 mg	QD		ORAL	2019-12-30		-63	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	309 mL	ONCE		INTRAVENOUS	2020-01-05	2020-01-05	-57	-57	
ABC12345-987-654-321	SACCHARATED IRON OXIDE	Prior	1 IU	PRN		INTRAVENOUS	2020-01-06	2020-04-18	-56	48	
ABC12345-987-654-321	ACICLOVIR	Prior	400 mg	BID		ORAL	2020-01-07		-55	.	ONGOING
ABC12345-987-654-321	VORICONAZOLE	Prior	200 mg	BID		ORAL	2020-01-07		-55	.	ONGOING
ABC12345-987-654-321	AMOXICILLIN:CLAVULANIC ACID	Prior	. mg	BID		ORAL	2020-01-08		-54	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201 mL	ONCE		INTRAVENOUS	2020-01-08	2020-01-08	-54	-54	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	244 mL	ONCE		INTRAVENOUS	2020-01-12	2020-01-12	-50	-50	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201 mL	ONCE		INTRAVENOUS	2020-01-14	2020-01-14	-48	-48	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	241 mL	ONCE		INTRAVENOUS	2020-02-10	2020-02-10	-21	-21	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	273 mL	ONCE		INTRAVENOUS	2020-02-15	2020-02-15	-16	-16	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	208 mL	ONCE		INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	220 mL	ONCE		INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	INSULIN	Prior	1 OTHER	PRN		SUBCUTANEOUS	2020-02-19		-12	.	ONGOING
ABC12345-987-654-321	INSULIN ASPART	Prior	6 OTHER	TID		SUBCUTANEOUS	2020-02-19		-12	.	ONGOING
ABC12345-987-654-321	METFORMIN	Prior	1000 mg	BID		ORAL	2020-02-19	2020-03-15	-12	14	
ABC12345-987-654-321	HYDROXYCARBAMIDE	Prior	1000 mg	QD		ORAL	2020-02-25	2020-02-28	-6	-3	
ABC12345-987-654-321	FAMOTIDINE	Prior	20 mg	PRN		ORAL	2020-02-25	2020-03-10	-6	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	204 mL	ONCE		INTRAVENOUS	2020-03-01	2020-03-01	-1	-1	
ABC12345-987-654-321	OSELTAMIVIR PHOSPHATE	Prior	75 mg	QD		ORAL	2020-03-01	2020-03-10	-1	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	344 mL	ONCE		INTRAVENOUS	2020-03-03	2020-03-03	2	2	
ABC12345-987-654-321	OTHER DERMATOLOGICALS	Concomitant	1 OTHER	QID		TOPICAL	2020-03-06		5	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	202 mL	PRN		INTRAVENOUS	2020-03-08	2020-03-08	7	7	
ABC12345-987-654-321	MAGNESIUM AMINO ACID CHELATE	Concomitant	266 mg	BID		ORAL	2020-03-09		8	.	ONGOING
ABC12345-987-654-321	PROCHLORPERAZINE	Concomitant	1 OTHER	PRN		ORAL	2020-03-09		8	.	ONGOING
ABC12345-987-654-321	OTHER OPHTHALMOLOGICALS	Concomitant	1 DROP	PRN		INTRAOCULAR	2020-03-09		8	.	ONGOING
ABC12345-987-654-321	GUAIFENESIN	Concomitant	10 mL	QID		ORAL	2020-03-09	2020-03-18	8	17	
ABC12345-987-654-321	BENZONATATE	Concomitant	100 mg	TID		ORAL	2020-03-10		9	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	201 mL	PRN		INTRAVENOUS	2020-03-10	2020-03-10	9	9	
ABC12345-987-654-321	HYDROXYCARBAMIDE	Concomitant	500 mg	QD		ORAL	2020		16	.	ONGOING
ABC12345-987-654-321	SEVELAMER	Concomitant	800 mg	TID		ORAL	2020		18	.	ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	256 mL	PRN		INTRAVENOUS	2020-04-04	2020-04-04	34	34	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	163 mL	PRN		INTRAVENOUS	2020-04-11	2020-04-11	41	41	
ABC12345-987-654-321	LEVOFLOXACIN	Concomitant	500 mg	QD		ORAL	2020-04-17		47	.	ONGOING

How to identify relevant records from the CM-domain

- Understanding drug metabolism
- Identifying full set of co-medications of interest and their relative potency
 - FDA-website
 - Drug Interactions Database (DIDB)
 - Weak/Moderate/Severe inhibition or induction
- (AD)CM-domain
 - CMDECOD, CMTRT, ATC-codes
- Additional factors:
 - Route of administration, administered dose, dosing frequency

Data handling - I

USUBJID	CMDECD	CMSCAT	CMDOSE	CMDOSE	CMDOSEFRQ	CMROUTE	CMSTDT	CMENDT	CMSTDY	CMENDY	CMENRF
ABC12345-987-654-321	ROSUVASTATIN	Prior	20 mg	QD		ORAL					ONGOING
ABC12345-987-654-321	ALLOPURINOL	Prior	300 mg	QD		ORAL	2019-12-30		-63		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	309 mL	ONCE		INTRAVENOUS	2020-01-05	2020-01-05	-57	-57	
ABC12345-987-654-321	SACCHARATED IRON OXIDE	Prior	1 IU	PRN		INTRAVENOUS	2020-01-06	2020-04-18	-56	48	
ABC12345-987-654-321	ACICLOVIR	Prior	400 mg	BID		ORAL	2020-01-07		-55		ONGOING
ABC12345-987-654-321	VORICONAZOLE	Prior	200 mg	BID		ORAL	2020-01-07		-55		ONGOING
ABC12345-987-654-321	AMOXICILLIN;CLAVULANIC ACID	Prior	. mg	BID		ORAL	2020-01-08		-54		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201 mL	ONCE		INTRAVENOUS	2020-01-08	2020-01-08	-54	-54	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	244 mL	ONCE		INTRAVENOUS	2020-01-12	2020-01-12	-50	-50	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	201 mL	ONCE		INTRAVENOUS	2020-01-14	2020-01-14	-48	-48	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	230 mL	ONCE		INTRAVENOUS	2020-01-18	2020-01-18	-44	-44	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	217 mL	ONCE		INTRAVENOUS	2020-01-20	2020-01-20	-42	-42	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	216 mL	ONCE		INTRAVENOUS	2020-01-21	2020-01-21	-41	-41	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	203 mL	ONCE		INTRAVENOUS	2020-01-25	2020-01-25	-37	-37	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	212 mL	ONCE		INTRAVENOUS	2020-02-02	2020-02-02	-29	-29	
ABC12345-987-654-321	METHYLPREDNISOLONE	Prior	32 mg	OTHER		ORAL	2020-02-05		-26		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	219 mL	ONCE		INTRAVENOUS	2020-02-05	2020-02-05	-26	-26	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	302 mL	ONCE		INTRAVENOUS	2020-02-06	2020-02-06	-25	-25	
ABC12345-987-654-321	SULFAMETHOXAZOLE;TRIMETHOPRIM	Prior	1 OTHER	QD		ORAL	2020-02-10		-21		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	241 mL	ONCE		INTRAVENOUS	2020-02-10	2020-02-10	-21	-21	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	273 mL	ONCE		INTRAVENOUS	2020-02-15	2020-02-15	-16	-16	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	208 mL	ONCE		INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	220 mL	ONCE		INTRAVENOUS	2020-02-18	2020-02-18	-13	-13	
ABC12345-987-654-321	INSULIN	Prior	1 OTHER	PRN		SUBCUTANEOUS	2020-02-19		-12		ONGOING
ABC12345-987-654-321	INSULIN ASPART	Prior	6 OTHER	TID		SUBCUTANEOUS	2020-02-19		-12		ONGOING
ABC12345-987-654-321	METFORMIN	Prior	1000 mg	BID		ORAL	2020-02-19	2020-03-15	-12	14	
ABC12345-987-654-321	HYDROXYCARBAMIDE	Prior	1000 mg	QD		ORAL	2020-02-25	2020-02-28	-6	-3	
ABC12345-987-654-321	FAMOTIDINE	Prior	20 mg	PRN		ORAL	2020-02-25	2020-03-10	-6	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Prior	204 mL	ONCE		INTRAVENOUS	2020-03-01	2020-03-01	-1	-1	
ABC12345-987-654-321	OSELTAMIVIR PHOSPHATE	Prior	75 mg	QD		ORAL	2020-03-01	2020-03-10	-1	9	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	344 mL	ONCE		INTRAVENOUS	2020-03-03	2020-03-03	2	2	
ABC12345-987-654-321	OTHER DERMATOLOGICALS	Concomitant	1 OTHER	QID		TOPICAL	2020-03-06		5		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	202 mL	PRN		INTRAVENOUS	2020-03-08	2020-03-08	7	7	
ABC12345-987-654-321	MAGNESIUM AMINO ACID CHELATE	Concomitant	266 mg	BID		ORAL	2020-03-09		8		ONGOING
ABC12345-987-654-321	PROCHLORPERAZINE	Concomitant	1 OTHER	PRN		ORAL	2020-03-09		8		ONGOING
ABC12345-987-654-321	OTHER OPHTHALMOLOGICALS	Concomitant	1 DROP	PRN		INTRAOCULAR	2020-03-09		8		ONGOING
ABC12345-987-654-321	GUAIFENESIN	Concomitant	10 mL	QID		ORAL	2020-03-09	2020-03-18	8	17	
ABC12345-987-654-321	BENZONATATE	Concomitant	100 mg	TID		ORAL	2020-03-10		9		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	201 mL	PRN		INTRAVENOUS	2020-03-10	2020-03-10	9	9	
ABC12345-987-654-321	HYDROXYCARBAMIDE	Concomitant	500 mg	QD		ORAL	2020		16		ONGOING
ABC12345-987-654-321	SEVELAMER	Concomitant	800 mg	TID		ORAL	2020		18		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	256 mL	PRN		INTRAVENOUS	2020-04-04	2020-04-04	34	34	
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	163 mL	PRN		INTRAVENOUS	2020-04-11	2020-04-11	41	41	
ABC12345-987-654-321	LEVOFLOXACIN	Concomitant	500 mg	QD		ORAL	2020-04-17		47		ONGOING
ABC12345-987-654-321	PLATELETS, CONCENTRATED	Concomitant	256 mL	PRN		INTRAVENOUS	2020-04-17	2020	47		
ABC12345-987-654-321	AZACITIDINE		.				2018-08	2019-07	.	.	
ABC12345-987-654-321	DECITABINE		.				2019-08-28	2019-09-01	-187	-183	
ABC12345-987-654-321	VENETOCLAX		.				2019-08-28	2019-09-23	-187	-161	
ABC12345-987-654-321	CYTARABINE		.				2020-01-05	2020-01-13	-57	-49	
ABC12345-987-654-321	VENETOCLAX		.				2020-01-07	2020-02-05	-55	-26	

Data handling - II

- Individual records

USUBJID	CMDECOD	CMSTDTC	CMENDTC	INH	IND
ABC12345-987-654-321	METFORMIN	2020-02-19	2020-03-15	MODERATE	
ABC12345-987-654-321	ACICLOVIR	2020-02-21	2020-03-11	MODERATE	
ABC12345-987-654-321	METFORMIN	2020-03-01	2020-03-21	MODERATE	
ABC12345-987-654-321	HYDROXYCARBAMIDE	2020-02-25	2020-02-28	WEAK	
ABC12345-987-654-321	FAMOTIDINE	2020-02-25	2020-03-10		MODERATE
ABC12345-987-654-321	RITONAVIR	2020-03-01	2020-03-10		STRONG
ABC12345-987-654-321	OSELTAMIVIR PHOSPHATE	2020-03-11	2020-03-21		WEAK

- Summary record

USUBJID	CMSTDTC	CMENDTC	INH	IND
ABC12345-987-654-321	2020-02-19	2020-03-21	MODERATE	
ABC12345-987-654-321	2020-02-25	2020-02-28	WEAK	
ABC12345-987-654-321	2020-02-25	2020-03-10		MODERATE
ABC12345-987-654-321	2020-03-01	2020-03-10		STRONG
ABC12345-987-654-321	2020-03-11	2020-03-21		WEAK

Data handling - III

- Summary record (character variables)

USUBJID	CMSTDTC	CMENDTC	INH	IND
ABC12345-987-654-321	2020-02-19	2020-03-21	MODERATE	
ABC12345-987-654-321	2020-02-25	2020-02-28	WEAK	
ABC12345-987-654-321	2020-02-25	2020-03-10		MODERATE
ABC12345-987-654-321	2020-03-01	2020-03-10		STRONG
ABC12345-987-654-321	2020-03-11	2020-03-21		WEAK

- Summary record (numeric variables)

USUBJID	CMSTDTC	CMENDTC	INH_WEAK	INH_MOD	INH_STR	IND_WEAK	IND_MOD	IND_STR
ABC12345-987-654-321	2020-02-19	2020-03-21	0	1	0	0	0	0
ABC12345-987-654-321	2020-02-25	2020-02-28	1	0	0	0	0	0
ABC12345-987-654-321	2020-02-25	2020-03-10	0	0	0	0	1	0
ABC12345-987-654-321	2020-03-01	2020-03-10	0	0	0	0	0	1
ABC12345-987-654-321	2020-03-11	2020-03-21	0	0	0	1	0	0

Combining the PPK dataset & Co-medication data

STUDYN	SUBJID	TRTAN	TRTPN	NDOSE	DOSE	AMT	NTIME	TIME	DVID	DV	MDV	AGE	BHT	BALT	ADATE	ATIME	USUBJID	CMSTDT	CMENDT	INH_WEEK	INH_MOD	INH_STR	IND_WEEK	IND_MOD	IND_STR
12345	987654321	1	1	315	315	.	0	0	1	.	1	37	168	.	2011-06-19	08:56:00	ABC12345-987-654-321	2011-06-19	2011-06-25	0	1	0	0	0	0
12345	987654321	1	1	315	315	315	0	0	0	.	1	37	168	.	21 2011-06-24	09:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	0.5	0.5	1	203.47	0	37	168	.	21 2011-06-24	09:30:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	1	1	1	1584.81	0	37	168	.	21 2011-06-24	10:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	1.5	1.5	1	1656.16	0	37	168	.	21 2011-06-24	10:30:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	2	2	1	1365.05	0	37	168	.	21 2011-06-24	11:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	3	3	1	1419.27	0	37	168	.	21 2011-06-24	12:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	4	4	1	708.63	0	37	168	.	21 2011-06-24	13:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	5	5	1	578.77	0	37	168	.	21 2011-06-24	14:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	6	6	1	451.77	0	37	168	.	21 2011-06-24	15:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	8	8	1	294.8	0	37	168	.	21 2011-06-24	17:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	10	10	1	192.05	0	37	168	.	21 2011-06-24	19:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	12	12	1	114.14	0	37	168	.	21 2011-06-24	21:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	16	16	1	57.35	0	37	168	.	21 2011-06-25	01:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	24	24	1	19.39	0	37	168	.	21 2011-06-25	09:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	36	36	1	7.07	0	37	168	.	21 2011-06-25	21:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	48	47.83	1	3.9	0	37	168	.	21 2011-06-26	08:50:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	144	143.92	1	.	1	37	168	.	2011-06-28		ABC12345-987-654-321	2011-06-28	2011-06-30	1	0	0	0	0	
12345	987654321	1	1	315	315	315	144	144	0	.	1	37	168	.	21 2011-06-30	08:55:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	144.5	144.5	1	25.81	0	37	168	.	21 2011-06-30	09:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	145	145	1	423.23	0	37	168	.	21 2011-06-30	09:30:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	145.5	145.5	1	370.43	0	37	168	.	21 2011-06-30	10:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	146	146	1	377.56	0	37	168	.	21 2011-06-30	10:30:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	146	146	1	377.56	0	37	168	.	21 2011-06-30	11:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	147	147	1	497.43	0	37	168	.	21 2011-06-30	11:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	147	147	1	497.43	0	37	168	.	21 2011-06-30	12:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	148	148	1	440.35	0	37	168	.	21 2011-06-30	12:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	148	148	1	440.35	0	37	168	.	21 2011-06-30	13:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	149	149	1	321.91	0	37	168	.	21 2011-06-30	14:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	150	150	1	237.72	0	37	168	.	21 2011-06-30	15:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	152	152	1	149.24	0	37	168	.	21 2011-06-30	17:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	154	154.02	1	103.72	0	37	168	.	21 2011-06-30	19:01:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	156	156	1	63.05	0	37	168	.	21 2011-06-30	21:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	160	160	1	35.94	0	37	168	.	2011-07-01		ABC12345-987-654-321	2011-07-01	2011-07-10	0	0	0	0	1	0
12345	987654321	1	1	315	315	.	168	168	1	16.1	0	37	168	.	21 2011-07-01	01:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	168	168	1	16.1	0	37	168	.	21 2011-07-01	09:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	180	180	1	8	0	37	168	.	21 2011-07-01	21:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	
12345	987654321	1	1	315	315	.	192	192	1	4.19	0	37	168	.	21 2011-07-02	09:00:00	ABC12345-987-654-321	.	.	.	.	.	.	.	

Incorporating time-varying co-medication records into the PPK dataset

STUDYN	SUBJID	TRTAN	TRTPN	NDOSE	DOSE	AMT	NTIME	TIME	DVID	DV	MDV	AGE	BHT	BALT	IND_WEAK	IND_MOD	IND_STR	INH_WEAK	INH_MOD	INH_STR	ADATE	ATIME	USUBJID
12345	987654321	1	1	315	315		0	0	1		1	37	168	21	0	0	0	1	1	1	0 2011-06-24	08:56:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	0	0	0		1	37	168	21	0	0	0	1	1	1	0 2011-06-24	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		0.5	0.5	1	203.47	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		1	1	1	1584.81	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		1.5	1.5	1	1656.16	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		2	2	1	1365.05	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		3	3	1	1419.27	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		4	4	1	708.63	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		5	5	1	578.77	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		6	6	1	451.77	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		8	8	1	294.8	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		10	10	1	192.05	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	19:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		12	12	1	114.14	0	37	168	21	0	0	0	1	1	1	0 2011-06-24	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		16	16	1	57.35	0	37	168	21	0	0	1	1	1	1	1 2011-06-25	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		24	24	1	19.39	0	37	168	21	0	0	1	1	1	1	1 2011-06-25	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		36	36	1	7.07	0	37	168	21	0	0	1	1	1	1	1 2011-06-25	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		48	47.83	1	3.9	0	37	168	21	0	0	1	1	1	1	1 2011-06-26	08:50:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		144	143.92	1		1	37	168	21	0	1	1	1	0	0	0 2011-06-30	08:55:00	ABC12345-987-654-321
12345	987654321	1	1	315	315	315	144	144	0		1	37	168	21	0	1	1	1	0	0	0 2011-06-30	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		144.5	144.5	1	25.81	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	09:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		145	145	1	423.23	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	10:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		145.5	145.5	1	370.43	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	10:30:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		146	146	1	377.56	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	11:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		147	147	1	497.43	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	12:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		148	148	1	440.35	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	13:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		149	149	1	321.91	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	14:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		150	150	1	237.72	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	15:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		152	152	1	149.24	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	17:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		154	154.02	1	103.72	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	19:01:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		156	156	1	63.05	0	37	168	21	0	1	1	1	0	0	0 2011-06-30	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		160	160	1	35.94	0	37	168	21	0	1	1	1	0	0	0 2011-07-01	01:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		168	168	1	16.1	0	37	168	21	0	1	1	1	0	0	0 2011-07-01	09:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		180	180	1	8	0	37	168	21	0	1	1	1	0	0	0 2011-07-01	21:00:00	ABC12345-987-654-321
12345	987654321	1	1	315	315		192	192	1	4.19	0	37	168	21	0	1	1	1	0	0	0 2011-07-02	09:00:00	ABC12345-987-654-321

Food for thought

- Lag time of effect
 - Does the start date of co-medication also mean that the clinical effect of the co-medication is immediate?
 - Does the end date of co-medication also mean that the clinical effect of the co-medication is gone?
 - Secondary start- and/or end-date variables to incorporate the 'lag-effect'
- Co-medication which has a different effect when co-administered with other drugs.
 - Lesinurad & allopurinol
 - Individual Lesinurad: moderate inducer
 - Combined administration: weak inducer

Summary

- *Key steps in adding time-varying co-medication data to PPK datasets*
 - *Identifying which co-medication we should be looking out for*
 - *Resolving missing/incomplete start- and end-dates of dosing*
 - *Removing overlapping co-administration records*
 - *Combining with PPK dataset*
 - *Carry-forward co-med data and check for overlap with PPK observation/dosing records*



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