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A Macro to Mark Invalid PK Data Observations for Exclusion

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ABSTRACT

This paper describes a macro for identifying and marking observations in a SAS® PK dataset, containing dosing and related PK sampling observations, as invalid and marking them with a an exclusion code and exclusion reason test. This paper is intended for SAS programmers with a basic or higher level of expertise and familiarity with PK data.

INTRODUCTION

PK observations in a SAS data set contain study drug dose administration or PK sampling analysis data. This macro checks the PK observations and finds and marks observations for exclusion from analysis tables and figures due to confirmed or possible invalid data. Examples of such invalid data are: a pre-dose sample having a later time than the dose to which it refers, duplicated observations, excessive difference between a nominal time and its corresponding actual time, and no doses recorded for a given patient. The macro uses a flag variable with a code identifying the exclusion criteria met and a text string containing a description of the exclusion. Exclusions have an order of precedence where an observation meets two or more of the criteria. As well as setting the exclusion flag and text, a note of the exclusion and its description is written to the SAS log file with the observation numbers _n_ and the BY variables (sort key) and their values. Observations not matching any of the exclusion criteria (the 'normal' situation) have a flag that is missing and a blank text.

EXAMPLE OF PK DATA

An example of some observations of PK data is shown below. There are two types of PK observation, *dosing*, and concentration *sampling.* These are indicated with an Event ID flag named EVID, 1 for a dosing observation and 0 for a PK sample, usually a blood draw. A dose administration of PK sample collection is referred to as an Event. The date and time of the event is EVNTSDTM, a SAS internal numeric datetime. The Dosing Cycle for this study is 21 days (504 hours)

PATNUM	COHORT	EVID	VISIT	CYCLE	DAY	VISITDY	ATPTDY	ATPTN	ATPT	NRELTM	ARELTM	ARELTMU	EVNTSDTM	EVNTSDT	ASTPT	ANACTAMT	ANACTAMU	AVAL	AVALC	AVALU	LOQFL
601	A5	0	TC8	CYCLE 1	DAY 1	1	1	1	PREDOSE	1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL			.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1	DAY 1	1	1	1			0.0	0.00	hr	17MAR2021:13:02	1			16	16 mg	.			.
601	A5	0	TC8	CYCLE 1	DAY 1	1	1	1	30 MIN POST	2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL			455	455	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 1	1	1	1	2 HR POST	3	2.0	1.85	hr	17MAR2021:14:53	1	R55	ug/mL			442	442	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 1	1	1	1	4 HR POST	4	4.0	3.90	hr	17MAR2021:16:56	1	R55	ug/mL			428	428	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 1	1	1	1	8 HR POST	5	8.0	8.22	hr	17MAR2021:21:15	1	R55	ug/mL			417	417	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 2	1	2	2	24 HR POST	6	24.0	24.13	hr	18MAR2021:13:10	2	R55	ug/mL			380	380	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 3	1	3	3	48 HR POST	7	48.0	47.75	hr	19MAR2021:12:47	3	R55	ug/mL			348	348	ug/mL	60
601	A5	0	TC8	CYCLE 1	DAY 8	1	8	8	POSTDOSE	8	168.0	172.05	hr	24MAR2021:17:05	8	R55	ug/mL			223	223	ug/mL	60
601	A5	0	TC8	CYCLE 2	DAY 1	2	1	22	PREDOSE	1	504.0	502.78	hr	07APR2021:11:49	22	R55	ug/mL			.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 2	DAY 1	2	1	22			504.0	503.33	hr	07APR2021:12:22	22			22	22 mg	.			.
601	A5	0	TC8	CYCLE 2	DAY 1	2	1	22	30 MIN POST	2	504.5	505.27	hr	07APR2021:12:46	22	R55	ug/mL			621	621	ug/mL	60
601	A5	0	TC8	CYCLE 2	DAY 8	2	8	29	POSTDOSE	8	672.0	674.95	hr	14APR2021:15:59	29	R55	ug/mL			240	240	ug/mL	60
601	A5	0	TC8	CYCLE 3	DAY 1	3	1	43	PREDOSE	1	1008.0	1004.08	hr	28APR2021:09:07	43	R55	ug/mL			.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 3	DAY 1	3	1	43			1008.0	1004.22	hr	28APR2021:09:15	43			22	22 mg	.			.
601	A5	0	TC8	CYCLE 3	DAY 1	3	1	43	30 MIN POST	2	1008.5	1004.77	hr	28MAY2021:09:48	43					625	625	ug/mL	.
601	A5	0	TC8	CYCLE 3	DAY 8	3	8	50	POSTDOSE	8	1176.0	1176.66	hr	04MAY2021:15:42	50	R55	ug/mL			272	272	ug/mL	60
601	A5	0	TC8	CYCLE 4	DAY 1	4	1	64	PREDOSE	1	1512.0	1515.48	hr	25MAY2021:16:31	64	R55	ug/mL			.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 4	DAY 1	4	1	64			1512.0	1515.97	hr	25MAY2021:17:00	64			22	22 mg	.			.
601	A5	0	TC8	CYCLE 4	DAY 1	4	1	64	30 MIN POST	2	1512.5	1516.52	hr	25MAY2021:17:33	64					622	622		.
601	A5	0	TC8	CYCLE 4	DAY 8	4	8	71	POSTDOSE	8	1680.0	1675.85	hr	31MAY2021:08:53	71	R55	ug/mL			264	264	ug/mL	60

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PATNUM    - Patient Identifier
COHORT    - Study Treatment Group (e.g. 'Med A', 'Med B', 'Med C')
EVID      - Event Identifier, 0 for PK sampling, 1 for dosing
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DRUG     - Study Drug Identifier
VISIT    - Planned Visit Test (e.g. 'SCREENING', 'CYCLE 1 DAY 1', 'WEEK 2 DAY 1')
CYCLE    - Dosing Cycle, periods of a set number of days
DAY      - Day within the cycle 1 though cycle length in days
VISITDY  - Day of visit. Day 1 is the first day of the study.
ATPT     - Sampling Analysis Time Point (e.g. '30 MIN POSTDOSE', '2 HOURS POST DOSE'). This can be blank.
ATPTN    - Sampling Analysis Time Point sequence number (e.g. 1='PRE-DOSE', 2='30 MIN POSTDOSE')
NRELTIM1 - Nominal Relative Time of Sample or Dose, ie: planned dose timepoint in the study
ARELTIM1 - Actual Relative Time of Sample or Dose, relative to the start of the study
ETMU     - Elapsed Time Units, units of measurement for NRELTM1 and ARELTM1 (e.g. 'day','hr')
EVNTSDTM - Event date/time, numeric SAS internal datetime. A character version named EVNTSDTC is needed to run the EXCLSET macro.
EVNTDAY  - Day in the study the event took place
ASTYP    - Analyte Identifier
ASTYPU   - Analyte concentration units of measurement (e.g. ug/mL)
NOMAMT   - Planned dose amount
ACTAMT   - Actual dose amount administered
ACTAMTU  - Actual dose amount units of measurement
AVAL     - Sampling analyte concentration numeric result (missing when result is 'BLQ')
AVALC    - Sampling analyte concentration character result (e.g. '12.4','105','BLQ')
AVALU    - Result concentration units of measurement (e.g. ug/mL)
LLOQ     - Lowest level of analyte concentration that is readable (Equal to BLQ)
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REASONS FOR EXCLUDING OBSERVATIONS

There are several causes of erroneous PK data which may result in inaccurate reporting on tables, and figures. Most involve the dose or analyte amount and the date or time of the dosing or sampling event. The decision to exclude a PK observation is based on a combination of study specific criteria and the opinion of the Lead Scientist as to whether the accuracy of tabulated or plotted results is compromised. Here is a list of the main sources of error:

PILLS ORAL DOSING ERRORS

Patient forgot to or refused to take their medicine

Patient took their medicine too early or too late, actual dose time ARELTM1 not close to the planned dose time NRELTM1

Patient took their medicine before instead of after, or after instead of before, a meal (affects rate of absorption in the gastrointestinal tract)

Patient did not take all of their pills or took too many pills or took incorrect strength pills (incorrect dose amount – ACTAMT did not match planned dose amount NAMT)

Adverse event. (e.g. Patient could not swallow the medicine or vomited after taking the medicine)

Dose amount or time omitted or not recorded correctly on the Case Report Form (CRF)

IVF INJECTION ERRORS

Patient missed their appointment or refused treatment

Patient determined as unable to have the infusion or injection (e.g. failed a drug test, feeling unwell)

Infusion/Injection site reaction/infection

Infusion Interruption or discontinuation (e.g. Adverse Event, problem with IV system)

Incorrect dose amount or incorrect concentration administered (e.g. recorded as ug instead of mg)

Dose amount or time omitted or not recorded correctly on the CRF

DATE AND TIME ERRORS

Date or time not recorded (missing)

Month and Day transposed

Time rounded to nearest 5 or 10 minutes or nearest hour

Different time sources (e.g. wall-clock slow, investigators watch fast)

Improper am/pm conversion to military time

Missing month or day or missing minutes

Non-date or time characters

Too large or too small a time range or window or end date or time before start date or time

HANDLING EXCLUSIONS

These exact details do not need to be specified, what is important is what is recorded (or not recorded) on the CRF. Each exclusion case is assigned a code, usually a sequence number or letter, and an explanatory text. PK observations marked for exclusion are *not* included in tables or graphs, because the results shown may be visibly distorted. Observations marked for exclusion *are* shown on listings, the applicable row of the listing is subscripted with the exclusion code, (or sequentially as a, b, c…) and the corresponding text is shown as a footnote on each page of the listing. Footnotes may include text for exclusions that did not occur, indicating the exclusion condition has been taken into consideration when checking the data. This provides a means of auditing the listed data and correlating it with other (non-PK) listings such as Adverse Events, Patient Disposition, and Missed Doses.

COMMON EXCLUSION CASES

Listed below are the main reasons for excluding observations. The order of precedence is important, for example a non BLQ pre-dose result is a specific case of a Missing or Invalid Result. These events are listed in order of precedence, once an exclusion condition is matched no further exclusion checks are performed.

PATIENT HAS NO RECORDED DOSE

If a given patient has no record of receiving a dose of the study medication any PK sample observations for this patient have no meaning.

PATIENT HAS NO POST-DOSE SAMPLES

A profile of the level of an analyte related to the study medication cannot be produced so the preceding dose observation should be excluded. A related pre-dose observation, if any, is still kept.

PRE-DOSE SAMPLE AFTER DOSE

This is a case of events occurring in an incorrect order. The cause can be an incorrect or incomplete time entered on the CRF. In this example the time of the PREDOSE sample was incorrectly recorded as 12:35 instead of 11:49.

PATNUM	COHORT	EVID	DRUG	VISIT	CYCLE	DAY	VISITDY	ATPT	ATPTN	NRELTM1	ARELTM1	ETMU	EVNTSDTM	EVNTDAY	ASTYP	ASTYPU	NOMAMT	ACTAMT	ACTAMTU	AVAL	AVALC	AVALU	LLOQ
601	A5	1	TC8	CYCLE 2 DAY 1	2	1	22			504.0	503.33	hr	07APR2021:12:22	22			22	22	mg	.			.
601	**A5**	**0**	**TC8**	**CYCLE 2 DAY 1**	**2**	**1**	**22**	**PREDOSE**	**1**	**504.0**	**502.78**	**hr**	**07APR2021:12:35**	**22**	**R55**	**ug/mL**				**.**	**BLQ**	**ug/mL**	**60**
601	A5	0	TC8	CYCLE 2 DAY 1	2	1	22	30 MIN POST	2	504.5	505.27	hr	07APR2021:12:46	22	R55	ug/mL				621	621	ug/mL	60

NON-BLQ PRE-DOSE RESULT

The very first pre-dose sample, before the very first dose of the study medication, should have no measurable amount of any related analytes. Subsequent doses should, generally, have pre-dose samples with less than the lowest detectable amount of analyte(s), though in some studies a higher amount of pre-dose concentration is valid for the second and subsequent doses. This problem may arise due to incorrect or incomplete dates and times on the CRF, or an incorrectly recorded result. In this example a result, AVAL, is 27 and AVALC is '27', not 'BLQ' or 'LTR' at the very first PRE-DOSE, when no analyte should be present. For the second and subsequent doses PRE-DOSE AVAL can be non-missing but should be below a maximum limit dependent on the study, dose, and time since the prior dose. In some studies all PREDOSE results have to be BLQ.

P	C					V			N	A		E		E			A					
A	O			V		C	S		A	E		V		N	A	S		O	C	T		A	A	
T	H	E	D	I		Y	I	A	T	L	L	E		S	T	S	T		M	T	A	A	V	V	L
N	O	V	R	S		Y	D	T	T	P	T	T	T	D	D	T	Y		A	A	M	V	A	A	L
U	R	I	U	I		L	A	D	P	T	M	M	M	T	A	Y	P		M	M	T	A	L	L	O
M	T	D	G	T		E	Y	Y	T	N	1	1	U	M	Y	P	U		T	T	U	L	C	U	Q
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**		**1**	**1**	**1**	**PREDOSE**	**1**	**0.0**	**-2.12**	**hr**	**17MAR2021:10:55**	**1**	**R55**	**ug/mL**				**27**	**27**	**ug/mL**	**60**
601	A5	1	TC8	CYCLE 1 DAY 1		1	1	1			0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	30 MIN	POST 2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL				455	455	ug/mL	60

MISSING OR INVALID RESULT

A given sample result is missing or not in the expected range. In the following example the result (AVAL/AVALC) at the '30 MIN POST' timepoint is too small, there is a post-dose BLQ result preceding a non-BLQ post dose result, and the result at '4HR POST' is too large (may have been recorded in incorrect units).

P	C					V			N	A		E		E			A					
A	O			V		C	S		A	E		V		N	A	S		O	C	T		A		
T	H	E	D	I		Y	I	A	T	L	L	E		S	T	S	T		M	T	A	A	V	L
N	O	V	R	S		Y	D	T	T	P	T	T	T	D	D	T	Y		A	A	M	V	A	L
U	R	I	U	I		L	A	D	P	T	M	M	M	T	A	Y	P		M	M	T	A	L	L	O
M	T	D	G	T		E	Y	Y	T	N	1	1	U	M	Y	P	U		T	T	U	L	C	U	Q
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	PREDOSE		1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL			.		BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1 DAY 1		1	1	1				0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	30 MIN	POST	2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL			.		BLQ	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	2 HR	POST	3	2.0	1.85	hr	17MAR2021:14:53	1	R55	ug/mL			442		442	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	4 HR	POST	4	4.0	3.90	hr	17MAR2021:16:56	1	R55	ug/mL			419200		419200	ug/mL	60

EXCESSIVE DIFFERENCE BETWEEN NOMINAL AND ACTUAL TIMES

Since correct dosing and sampling times are critical for accurate reporting the actual dose time or sample time should approximate to the corresponding nominal time. This is particularly significant within the first 72 hours of a dose, when a small time difference is a relatively large percentage of the elapsed time since dosing. For example, a deviation of four hours on the first day after dosing is much more significant than a deviation of that same number of hours a week after dosing. A maximum allowable deviation is normally specified in the Study Protocol. This issue does not apply to nominal times that are not chronological times, such as UNSCHEDULED, EARLY TERMINATION, and FOLLOW-UP, though follow-up at time intervals (e.g. FOLLOW-UP 3 MONTHS, FOLLOW-UP 6 MONTHS) must be in the appropriate order of sequence. Serious mismatches between the actual and nominal time can result in observations being out of sequence. The example below shows the '4HR POST' observation having an incorrectly recorded event date of April 17 2021, instead of March 17 2021. This results in an Actual Relative Time of 747 hours and 54 minutes instead of 3 hours and 54 minutes (an additional 31 days x 24 hours). The nominal time for the visit is 4 hours, hence there is a difference between the nominal and actual times of 743 hours and 54 minutes instead of just six minutes (16:56-13.02).

P	C					V			N	A		E		E			A					
A	O			V		C	S		A	E		V		N	A	S		O	C	T		A	A	
T	H	E	D	I		Y	I	A	T	L	L	E		S	T	S	T		M	T	A	A	V	V	L
N	O	V	R	S		Y	D	T	T	P	T	T	T	D	D	T	Y		A	A	M	V	A	A	L
U	R	I	U	I		L	A	D	P	T	M	M	M	T	A	Y	P		M	M	T	A	L	L	O
M	T	D	G	T		E	Y	Y	T	N	1	1	U	M	Y	P	U		T	T	U	L	C	U	Q
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	PREDOSE		1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL				.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1 DAY 1		1	1	1				0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	30 MIN	POST	2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL				455	455	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	2 HR	POST	3	2.0	1.85	hr	17MAR2021:14:53	1	R55	ug/mL				442	442	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1		1	1	1	8 HR	POST	5	8.0	8.22	hr	17MAR2021:21:15	1	R55	ug/mL				417	417	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 2		1	2	2	24 HR	POST	6	24.0	24.13	hr	18MAR2021:13:10	2	R55	ug/mL				380	380	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 3		1	3	3	48 HR	POST	7	48.0	47.75	hr	19MAR2021:12:47	3	R55	ug/mL				348	348	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 8		1	8	8	POSTDOSE		8	168.0	172.05	hr	24MAR2021:17:05	8	R55	ug/mL				223	223	ug/mL	60
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**		**1**	**1**	**1**	**4 HR**	**POST**	**4**	**4.0**	**747.50**	**hr**	**17APR2021:16:56**	**31**	**R55**	**ug/mL**				**428**	**428**	**ug/mL**	**60**

DUPLICATED DATES OR TIMES

Two dosing or sampling results recorded as being at the same time. Incomplete or missing times, for example the minutes missing from two samples taken within the same hour. Missing times can be imputed from other times, such as the time of the preceding or following sample.

PATNUM	COHORT	EVID	DRUG	VISIT	CYYLE	DAY	VISITDY	ATPT	ATPTN	NRELTM1	ARELTM1	ETMU	EVNTSDTM	EVNTDAY	ASTYP	ASTYPU	NOMAMT	ACTAMT	ACTAMTU	AVAL	AVALC	AVALU	LLOQ
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	PREDOSE	1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL				.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1 DAY 1	1	1	1			0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	30 MIN POST	2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL				455	455	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	2 HR POST	3	2.0	1.85	hr	17MAR2021:14:53	1	R55	ug/mL				442	442	ug/mL	60
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**	**1**	**1**	**1**	**4 HR POST**	**4**	**4.0**	**3.90**	**hr**	**17MAR2021:16:56**	**1**	**R55**	**ug/mL**				**428**	**428**	**ug/mL**	**60**
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**	**1**	**1**	**1**	**8 HR POST**	**5**	**8.0**	**3.90**	**hr**	**17MAR2021:16:56**	**1**	**R55**	**ug/mL**				**417**	**417**	**ug/mL**	**60**
601	A5	0	TC8	CYCLE 1 DAY 2	1	2	2	24 HR POST	6	24.0	24.13	hr	18MAR2021:13:10	2	R55	ug/mL				380	380	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 3	1	3	3	48 HR POST	7	48.0	47.75	hr	19MAR2021:12:47	3	R55	ug/mL				348	348	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 8	1	8	8	POSTDOSE	8	168.0	172.05	hr	24MAR2021:17:05	8	R55	ug/mL				223	223	ug/mL	60

DUPLICATED VISIT AND NOMINAL TIME POINT

Two sampling observations have the same VISIT text and Timepoint text. (They will also have the same calculated nominal times).

PATNUM	COHORT	EVID	DRUG	VISIT	CYYLE	DAY	VISITDY	ATPT	ATPTN	NRELTM1	ARELTM1	ETMU	EVNTSDTM	EVNTDAY	ASTYP	ASTYPU	NOMAMT	ACTAMT	ACTAMTU	AVAL	AVALC	AVALU	LLOQ
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	PREDOSE	1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL				.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1 DAY 1	1	1	1			0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	30 MIN POST	2	0.5	0.55	hr	17MAR2021:13:35	1	R55	ug/mL				455	455	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	2 HR POST	3	2.0	1.85	hr	17MAR2021:14:53	1	R55	ug/mL				442	442	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	4 HR POST	4	4.0	3.90	hr	17MAR2021:16:56	1	R55	ug/mL				428	428	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	8 HR POST	5	8.0	8.22	hr	17MAR2021:21:15	1	R55	ug/mL				417	417	ug/mL	60
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 2**	**1**	**2**	**2**	**24 HR POST**	**6**	**24.0**	**24.13**	**hr**	**18MAR2021:13:10**	**2**	**R55**	**ug/mL**				**380**	**380**	**ug/mL**	**60**
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 2**	**1**	**3**	**3**	**24 HR POST**	**6**	**24.0**	**47.75**	**hr**	**19MAR2021:12:47**	**3**	**R55**	**ug/mL**				**348**	**348**	**ug/mL**	**60**
601	A5	0	TC8	CYCLE 1 DAY 8	1	8	8	POSTDOSE	8	168.0	172.05	hr	24MAR2021:17:05	8	R55	ug/mL				223	223	ug/mL	60

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DATE, TIME, OR VISIT MISSING

The date or time is blank or has non-date time characters, or there is no VISIT text. Timepoint text can be missing for samples taken a significant time after the dose was administered, for example, one hour is a significant fraction of the first few hours after dosing, but is not a significant fraction of several days. Sample timepoint text should be missing for dosing observations. Missing timepoint text where there is supposed to be timepoint text will impact the calculated nominal time causing it to differ significantly from the actual time.

PATNUM	COHORT	EVID	DRUG	VISIT	CYYLE	DAY	VISITDY	ATPT	ATPTN	NRELTM1	ARELTM1	ETMU	EVNTSDTM	EVNTDAY	ASTYP	ASTYPU	NOMAMT	ACTAMT	ACTAMTU	AVAL	AVALC	AVALU	LLOQ
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	PREDOSE	1	0.0	-2.12	hr	17MAR2021:10:55	1	R55	ug/mL				.	BLQ	ug/mL	60
601	A5	1	TC8	CYCLE 1 DAY 1	1	1	1		.	0.0	0.00	hr	17MAR2021:13:02	1			16	16	mg	.			.
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**	**1**	**1**	**1**	**30 MIN POST**	**2**	**0.5**	**.**	**hr**	**.**	**1**	**R55**	**ug/mL**				**455**	**455**	**ug/mL**	**60**
601	**A5**	**0**	**TC8**	**CYCLE 1 DAY 1**	**1**	**1**	**1**		**3**	**2.0**	**1.85**	**hr**	**17MAR2021:14:53**	**1**	**R55**	**ug/mL**				**442**	**442**	**ug/mL**	**60**
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	4 HR POST	4	4.0	3.90	hr	17MAR2021:16:56	1	R55	ug/mL				428	428	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 1	1	1	1	8 HR POST	5	8.0	8.22	hr	17MAR2021:21:15	1	R55	ug/mL				417	417	ug/mL	60
601	**A5**	**0**	**TC8**	**.**	**1**	**2**	**2**	**24 HR POST**	**6**	**24.0**	**24.13**	**hr**	**18MAR2021:13:10**	**2**	**R55**	**ug/mL**				**380**	**380**	**ug/mL**	**60**
601	A5	0	TC8	CYCLE 1 DAY 3	1	3	3	48 HR POST	7	48.0	47.75	hr	19MAR2021:12:47	3	R55	ug/mL				348	348	ug/mL	60
601	A5	0	TC8	CYCLE 1 DAY 8	1	8	8	POSTDOSE	8	168.0	172.05	hr	24MAR2021:17:05	8	R55	ug/mL				223	223	ug/mL	60

MACRO CODE

This macro, EXCLSET, takes as input a PK dataset (INDS) like the one shown in the example and a variable which is a character representation of the event date and time in the format “yyyymmddThh:mm” (e.g. EVNTSDTM stored as EVNTSDTC with a length of $25). and may or may not include the seconds in the time part. The contents of the input dataset (INDS) are unchanged except for the observation sort order and the addition of the two variables EXCLFLN and EXCLREAS. EXCLFLN is the exclusion code number and is 0 if no exclusions apply. EXCLREA is the corresponding exclusion reason text and is blank if no exclusions apply. The order of precedence of exclusion causes is the sequential order of the exclusion codes, if two or more exclusions apply to the same observation only the first is specified.

```
%macro exclset(inds=,          /* Input dataset name */
               patid=usubjid,  /* Patient ID, character or numeric */
               drugid=,        /* Drug name (character) or numeric id */
               areltm1=afrlt,  /* Actual relative time from first dose */
               nreltm1=nfrlt,  /* Nominal relative time from first dose */
               tpttxt=,        /* Sample timepoint text (e.g. '1HR POST')*/
               actamt=amt,     /* Actual dose amount administered */
               resultn=aval,   /* Sample concentration result (numeric) */
               resultc=avalc); /* Sample concentration result (character)*/


%local reastxt1 reastxt2 reastxt3 reastxt4 reastxt5 reastxt6 reastxt7
reastxt8 reastxt9 ulimit tfract;

%let reastxt1=Patient has No Recorded Doses for the Drug;
%let reastxt2=Patient has No Post Dose samples;
%let reastxt3=Pre-dose Sample After Dose;
%let reastxt4=Post-dose Sample Before Dose;
%let reastxt5=Non-BLQ First Pre-dose;
%let reastxt6=Missing Post-dose Result or Result Outside of Expected Range;
%let reastxt7=Excess Nominal and Actual Relative Dates or Times Difference;
%let reastxt8=Duplicated Sample Nominal Time;
%let reastxt9=Duplicated Sample Actual Time;

%let ulimit=300*&actamt; /* Upper limit of dose amount */
%let tfract=0.25;  /* Maximum variance between actual and nominal time */



 data &inds; /* Indicate predose=1, dose=2, postdose=3, and if BLQ/LTR */
   set &inds;
   prepost=3-evid-2*(index(upcase(&tpttxt),'PRE')>0 or
     upcase(&tpttxt)='PRIOR TO DOSE');
   fblqn=(upcase(&resultc) in ('BLQ','BQL','LTR','QNS') or
     index(&resultc,'<')>0);
 run;

 proc sort data=&inds; /* Get the date+time of the next scheduled dose */
   by &patid &drugid descending &nreltm1 descending prepost;
 run;

 data &inds;
   set &inds;
   by &patid &drugid descending &nreltm1 descending prepost;
   retain nxtreltm 0;
```

```
  if first.&drugid then do;
    nxtreltm=.;
  end;
  if prepost=2 then do;
    nxtreltm=areltm1;
  end;
run;

proc sort data=&inds;  /* Get the date+time of the prior scheduled dose */
  by &patid &drugid &nreltm1 prepost;
run;

data &inds;
  set &inds;
  by &patid &drugid &nreltm1 prepost &areltm1;
  retain prireltm 0;
  if first.&drugid then do;
    prireltm=.;
  end;
  if prepost=2 then do;
    prireltm=areltm1;
  end;
run;

proc sort data=&inds;
  by &patid &drugid descending evid descending &actamt;
run;

data &inds; /* Indicate if patient had no measurable doses */
  set &inds;
  by &patid &drugid descending evid descending &actamt;
  retain f1 0;
  if first.&drugid then do;
    f1=(evid=0 or (evid=1 and &actamt le 0));
  end;
run;

proc sort data=&inds;
  by &patid &drugid descending prepost descending &resultn;
run;

data &inds; /* Indicate if patient had no measureable post dose samples */
  set &inds;
  by &patid &drugid descending prepost descending &resultn;
  retain f2 0;
  if first.&drugid then do;
    f2=(prepost in (1,2) or (prepost=3 and &resultn le 0));
  end;
run;

proc sort data=&inds;
  by &patid &drugid &nreltm1 prepost &areltm1;
run;

data &inds(drop=i f1-f9 fblqn prepost nxtreltm prireltm);
  set &inds;
  by &patid &drugid &nreltm1 prepost &areltm1;
```

```
    array excflags {9} f1 f2 f3 f4 f5 f6 f7 f8 f9;
    length exclrea $200;
    excflags{3}=(prepost=1)*(&areltm1>nxtreltm>.);
    excflags{4}=(prepost=3)*(&areltm1 le prireltm or prireltm=.);
    excflags{5}=(prepost=1)*(prireltm=.)*(fblqn=0);
    excflags{6}=(prepost=3)*(&resultn=. or &resultn ge &ulimit or fblqn=1);
    excflags{7}=((&areltm1>(&nreltm1*(1+&tfract)))+
     (&areltm1<(&nreltm1*(1-&tfract))))*(&nreltm1 ne 0);
    excflags{8}=(first.prepost=0);
    excflags{9}=(first.&drugid=0 and prepost=lag(prepost) and
     &areltm1=lag1(&areltm1));
    exclfln=0;
    do i=1 to dim(excflags);
      if exclfln=0 and excflags{i}=1 then do;
        exclfln=i;
        exclrea=scan("&reastxt1!&reastxt2!&reastxt3!&reastxt4!&reastxt5!
         &reastxt6!&reastxt7!&reastxt8!&reastxt9",exclfln,'!');
      end;
    end;
  run;

%mend exclset;
```

EXAMPLE LISTING OUTPUT

In the example listing segments below patient 601 has all valid observations. Patient 613 had a PREDOSE sample and a 30 MIN POST sample taken but there is no recording of the dose given, that is no non-missing dose amount in the drug expose data (An observation should be present in the Exposure as Collected (EC) data showing the dose was scheduled but not performed). Patient 619 only had a PRE-DOSE sample taken, there were no Post Dose samples recorded. If this patient had not had a dose the exclusion code would have been ‘a’ instead of ‘b’. Patient 633 has a PRE-DOSE sample collection time later than the dose time (and the first post-dose time). Patient 640 has a non-BLQ sample result at the very first PRE-DOSE sample, where a BLQ result would be expected. Patient 653 has a missing result and a result not in the expected range, below LLOQ (60 ug/mL). Patient 662 has an actual relative sample collection time (2.57 hours) that deviates significantly from the nominal (planned) collection time of 30 minutes. Patient 669 has observations with duplicated VISIT and TIMEPOINT texts. Patient 672 has a duplicated actual relative sample collection time.

Listing Of PK Concentration at PK Sampling Timepoints
Protocol: TC8-001

Treatment	Subject Number	Administered Dose (mg)	Visit and Timepoint		Nominal Time (hr) from First Dose	Actual Time (hr) from First Dose	R55-Analyte Serum Concentration (ug/mL)
Cohort A5	601	16	CYCLE 1 DAY 1	PREDOSE	0.0	-2.12	BLQ
			CYCLE 1 DAY 1	30 MIN POST	0.5	0.55	455
			CYCLE 1 DAY 1	2 HR POST	2.0	1.85	442
			CYCLE 1 DAY 1	4 HR POST	4.0	3.90	428
			CYCLE 1 DAY 1	8 HR POST	8.0	8.22	417
			CYCLE 1 DAY 2	24 HR POST	24.0	24.13	380
			CYCLE 1 DAY 3	48 HR POST	48.0	47.75	348
			CYCLE 1 DAY 8	POSTDOSE	168.0	172.05	223

Listing Of PK Concentration at PK Sampling Timepoints
Protocol: TC8-001

Treatment	Subject Number	Administered Dose (mg)	Visit and Timepoint	Nominal Time (hr) from First Dose	Actual Time (hr) from First Dose	R55-Analyte Serum Concentration (ug/mL)
		22	CYCLE 2 DAY 1 PREDOSE	504.0	502.78	BLQ
			CYCLE 2 DAY 1 30 MIN POST	504.5	505.27	621
			CYCLE 2 DAY 8 POSTDOSE	672.0	674.95	240
		22	CYCLE 3 DAY 1 PREDOSE	1008.0	1004.08	BLQ
			CYCLE 3 DAY 1 30 MIN POST	1008.5	1004.77	625
			CYCLE 3 DAY 8 POSTDOSE	1176.0	1176.66	272
		22	CYCLE 4 DAY 1 PREDOSE	1512.0	1515.48	BLQ
			CYCLE 4 DAY 1 30 MIN POST	1512.5	1516.52	622
			CYCLE 4 DAY 8 POSTDOSE	1680.0	1675.85	264
Cohort A5	613	.	CYCLE 1 DAY 1 PREDOSE	0.0	-0.66	BLQ (a)
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.48	BLQ (a)
Cohort A5	619	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.44	BLQ (b)
Cohort A5	633	16	CYCLE 1 DAY 1 PREDOSE	0.0	1.14	BLQ (c)
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.49	438
			CYCLE 1 DAY 1 2 HR POST	2.0	2.07	417
Cohort A5	640	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.39	79 (d)
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.50	458
			CYCLE 1 DAY 1 2 HR POST	2.0	2.02	440
Cohort A5	653	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.31	BLQ
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.68	. (e)
			CYCLE 1 DAY 1 2 HR POST	2.0	1.94	23 (e)
Cohort A5	662	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.35	BLQ
			CYCLE 1 DAY 1 30 MIN POST	0.5	2.57	441 (f)
			CYCLE 1 DAY 1 2 HR POST	2.0	2.02	444
Cohort A5	669	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.38	BLQ
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.45	450
			CYCLE 1 DAY 1 2 HR POST	2.0	1.98	437
			CYCLE 1 DAY 1 2 HR POST	2.0	4.07	422 (g)
Cohort A5	672	16	CYCLE 1 DAY 1 PREDOSE	0.0	-0.59	BLQ
			CYCLE 1 DAY 1 30 MIN POST	0.5	0.45	450
			CYCLE 1 DAY 1 2 HR POST	2.0	0.45	437 (h)

Limit of Quantitation = 60.0 ug/mL
BLQ = Below Limit of Quantitation, LTR = Lower than Reportable, N/A = Not Applicable,
N/C = Not Calculable
(a) No recorded valid doses for the patient
(b) No post-dose PK samples recorded for this patient
(c) Pre-dose has a sample collection time later than the dose time
(d) Non-BLQ Pre-dose PK sample
(e) Missing result or result not in expected range
(f) Actual sample collection time deviates significantly from the corresponding nominal time
(g) Duplicated Visit and Timepoint in the same dosing cycle
(h) Duplicated actual sample collection time

CONCLUSIONS

This macro code is a quick method of flagging PK data observations which may distort the accuracy of tables and figures produced from these data. The flagged observations should be included in listings with the reason for the exclusion, so these observations can be identified easily. This macro also ensures consistency when applied to a group of related studies. The included example code is not exhaustive and exact specifications are often study dependent and subject to change by the Lead Scientist.

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PharmaSUG 2022 Paper Selection Committee

RECOMMENDED READING

- Paturi, Durga Kalyani, May 2022, "Paper AP-146, Merging Pharmacokinetic (PK) Sample Collection and Dosing Information for PK Analysis Based on Study Design and Lessons Learned" Proceedings of Pharmasug 2022, Austin, TX. Available at: https://www.pharmasug.org/proceedings/2022/AP/PharmaSUG-2022-AP-146.pdf
- Veramed, 5th Floor Regal House, 70 London Road, Twickenham, London, TW1 3QS, UK. September 24, 2020. "Four Mistakes to avoid when getting started in programming with Pharmacokinetic (PK) data". Available at: https://www.veramed.co.uk/guide/4-mistakes-pk

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