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Evaluating and Correcting Actual and Nominal Relative Time Measurements in Clinical Trials PK data

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ABSTRACT

Pharmacokinetic (PK) data has two types of observations: Dosing and Sampling. Amongst the data items recorded in both of these observation types are the nominal and actual times of dose administration or sample collection. The nominal times are the named times specified on the study case report forms (CRFs) such as VISIT, CYCLE and DAY. The actual times are the chronological times (local to the location of the site) as recorded by the investigating staff at dose administration or sample collection, such as a blood draw. To analyze the PK data there is a need to know the actual and relative differences between these various times. Examples are the nominal and actual time a sample was taken after the first dose or the most recent dose, or how soon a pre-dose sample was collected before a dose was administered. This paper is intended for persons with knowledge of base SAS® and with a basic understanding of Clinical Trials Pharmacokinetic data. There is identification of the different timing variables and discussion, using SAS code examples, of how these variables are evaluated. There is also a discussion of common problems caused by incomplete or missing dates and times and suggested imputation methods for their correction.

INTRODUCTION

PK samples are drawn at nominally pre-determined times to monitor the level of a drug in a patient's blood, therefore there is a need to know the exact actual times of dosing and when a given sample was collected. The actual times must correlate to the CRF labelled planned timepoints. This includes any 'UNSCHEDULED' visits. Relative time and concentration values are used to determine PK parameters such as the time and value of maximum concentration (TMAX/CMAX), half-life, and area under the curve (AUC). The statistics of these parameters can then be compared to theoretical and expected values, or between treatment groups or patient demographics such as age group, gender, and race. The chronological progression of treatment for each patient or group of patients is easily listed or graphically plotted when ordered by increasing relative time measured from the first dose of the study drug.

EXAMPLE OF PK DATA OBSERVATIONS

There are two types of PK observation, *dosing*, and concentration *sampling.* The most important variables in dosing observations are the patient identifier (PAT_ID), the drug being administered (DRUG_ID), the name of the visit (VISIT), the date and time of the start of the drug administration (EXSTDTC), the nominal (planned) and actual (administered) dose amounts, and the dose units of measurement. There is also a numeric flag EVID, which is the event identifier, this is usually 1 for dosing. Other variables which are present in dosing observations, but are not shown in the example below, are the study name, treatment groupings, the method of dosing (e.g., 'pills oral', 'intravenous'), and if there were any problems with the dose administration. If the drug is injected over a period of time, such as an intravenous infusion, an end time (EXENDTC) or a planned and actual dose duration (PTRTDUR/ATRTDUR) are also specified.

Table 1: Example of PK Dosing Observations

PAT_ID	EVID	VISIT	EXSTDTC	DRUG_ID	NOMAMT	ACTAMT	UNIT
504231	1	CYCLE 1 DAY 1	2021-02-22T09:35:00	RO2241	32	32	mg
504231	1	CYCLE 1 DAY 2	2021-02-23T09:17:00	RO2241	32	32	mg
504231	1	CYCLE 1 DAY 3	2021-02-24T10:00:00	RO2241	32	32	mg
504231	1	CYCLE 1 DAY 4	2021-02-25T10:03:00	RO2241	32	32	mg

In concentration sampling observations (EVID is 0) the variables which differ from dosing observations are the identity of the analyte being measured, the timepoint when the sample is planned to be taken (PCTPT), the actual date and time the sample was taken (PCDTC), and the result of the test performed on the analyte. 'BLQ' in the RESULT column indicates below minimum level of quantification, this may be labeled as 'LTR' (less than recordable) or 'QNS' (quantity not sufficient). Other variables which are likely to be present in concentration sampling observations are information about the laboratory where the result is obtained from, assay ranges and normals, the test performed to get the result, and the type of specimen taken from the patient (e.g., 'SERUM', 'PLASMA'). Most PK specimens are blood draws.

Table 2: Example of PK Concentration Sampling Observations

PAT_ID	EVID	VISIT	PCTPT	PCDTC	ANALYTE	RESULT	UNIT
504231	0	CYCLE 1 DAY 1	PREDOSE	2021-02-22T09:24:00	A237	BLQ	ug/mL
504231	0	CYCLE 1 DAY 1	1 HR POST	2021-02-22T10:39:00	A237	4.55	ug/mL
504231	0	CYCLE 1 DAY 1	2 HR POST	2021-02-22T11:33:00	A237	3.38	ug/mL
504231	0	CYCLE 1 DAY 1	4 HR POST	2021-02-22T13:41:00	A237	2.07	ug/mL
504231	0	CYCLE 1 DAY 2	PREDOSE	2021-02-23T08:47:00	A237	0.08	ug/mL
504231	0	CYCLE 1 DAY 2	1 HR POST	2021-02-23T10:14:00	A237	4.82	ug/mL
504231	0	CYCLE 1 DAY 2	2 HR POST	2021-02-23T11:15:00	A237	3.59	ug/mL
504231	0	CYCLE 1 DAY 2	4 HR POST	2021-02-23T13:20:00	A237	1.86	ug/mL

EVENT AND ANALYSIS TIMES

Any dosing or sampling observation is called an *event*. The actual time when an event occurs is the time (and date) recorded by the investigator on the CRF. In PK data the event dates and times of importance (in ADAM data sets) are:

EXSTDTC is the date and time of starting a dose administration. In some studies, only the date is used.

EXENDTC is the date and time the dose administration ended, for medications taken orally the EXENDTC is the same as EXSTDTC or is missing. For intravenous administrations subtracting EXSTDTC from EXENDTC gives the infusion duration (units may have to be converted from seconds or minutes to be in the required units)

PCDTC is the date and time of the collection of the specimen. In 'lab' datasets this may be LBDTC.

If CDISC standards are being followed EXSTDTC, EXENDTC, and PCDTC are all character strings of length 25 in the format

'yyyy-mm-ddThh:mm:ss'

An uppercase ‘T’ is used to separate the date and the time if a time is present. The seconds may be omitted or stored as ‘:00’. The four-digit year is still used for consistency with other data about the patient, such as date of birth or dates of prior surgery, which may be before the year 2000.

To obtain useful event chronological information these character values need to be converted to SAS internal dates, times, and datetimes, called event time variables, the most common of which are listed below.

PCTPT is the planned sample collection time text, usually in hours or minutes since the dose, examples are ’30 MIN POST-DOSE’, ‘2 HR POST DOSE’. The text for a pre-dose sample is usually ‘PRE-DOSE’, and for an unspecified time after dose just ‘POSTDOSE’ or blank. In ‘lab’ data sets this text is LBTPT.

TRTSDTM is the date and time of first dose (Treatment Start Date and Time). This is often found as a SAS internal datetime variable in a patient level data set such as ADSL. Alternatively, TRTSDTM is obtainable by converting the earliest (non-missing) dose date and time (EXSTDTC) to an internal SAS datetime.

The main event time variables derived from EXSTDTC and PCDTC are:

EVNTSDTM is the internal SAS datetime (number of seconds since January 1, 1960)

EVNTDT is the internal SAS date (number of days since January 1, 1960)

EVNTSTTM is the time part of EVNTSDTM

EVNTSDTC is the event date and time as a character string formatted as ‘yyyy-mm-ddThh:mm:ss’

EVNTDTC is the event date as a text string formatted as ‘yyyy-mm-dd’

EVNTSTTC is the event time as a text string formatted as ‘hh:mm:ss’

ETMU / RELTMU is the specified units of relative time measurement (e.g., ‘D’=days, ‘H’=hours)

EVID is a flag indicating 1 for dosing, and 0 for sampling. Some studies may set EVID to 2 for sampling observations which, for whatever reason, are to be excluded from analysis.

Corresponding variables for end times are created when and where required if EXENDTC is available. The derived variables end with ‘EDTM’ or ‘EDTC’. If EXENDTC is not available but an actual dose duration is available end times can be imputed using EVNTSDTM plus the dose duration converted to seconds. For orally administered drugs the duration is taken as zero and the end time is missing (or equal to the start time). The actual dose duration, where applicable, is calculated in hours as

ATRTDUR=(EVNTEDTM-EVNTSDTM)/3600;

The following macro evaluates the event start times. INDS is the name of the input data set and DATEVARC is the character date (e.g., EXSTDTC, PCDTC) and time in the format 'yyyy-mm-ddThh:mm:ss' (is8601dt.). If the date and time are incomplete the missing time parts are imputed as zeroes (eg. if the seconds are missing from the time) and a missing date is imputed as the 15th:

Table 3: Macro to evaluate Actual Event Times from a character date and time in is8601dt. format

```
%macro evntimes(inds= , datevarc=  );

 data &inds(drop=_dt);
   set &inds;
   length evntsttc $8 evntdtc evntsdtc _dt $25;
   format evntdt is8601da. evntsttm is8601tm. evntsdtm is8601dt.;
   if 4<length(&datevarc)<19 then do;
    _dt=trim(left(&datevarc))||substr('YYYY-07-15T00:00:00',
       length(&datevarc)+1);
   end;
   else if length(&datevarc)=19 then do;
    _dt=&datevarc;
   end;
   if _dt ne ' ' then do;
     evntsdtm=input(_dt,is8601dt.);
     evntdt=datepart(evntsdtm);
     evntsttm=timepart(evntsdtm);
     evntsdtc=_dt;
     evntdtc=substr(evntsdtc,1,10);
     if evntsttm ne . then do;
       evntsttc=put(evntsttm,is8601tm.);
     end;
   end;
 run;

%mend evntimes;
```

Another commonly used event time variable is the Event Day, based on the date of the first dose, when EVNTDY=1. EVNTDY is calculated by subtracting the Event Date from the date of first dose, this is the earliest non-missing EVNTDT where EVID=1 or a treatment start date and time in the patient level data, for example TRTSDTM in ADSL. EVNTDY will be negative for events occurring before the date of first dose, such as at screenings. When the event date is on or after the date of first dose one day is added, hence EVNTDY is never zero. This SAS code performs the calculation:

```
EVNTDY = datepart(EVNTSDTM) - datepart(TRTSDTM) +
         (datepart(EVNTSDTM) ge datepart(TRTSDTM));
```

CALCULATED ACTUAL RELATIVE TIMES

Actual Time from First Dose (ACTTMFDS)

In the vast majority of studies actual and nominal times are measured in days or hours. The chosen time unit (in ETMU) must be used for all actual and nominal relative times. The most important timepoint in any clinical trial is the date and time of the first dose administration of the study medication. In all cases this starting time, whether actual or nominal is set as zero, the point from which all other times are measured. In some studies there are multiple study medications, which may begin at different times, in which case the starting point of a second drug may be the time since the administration of the first drug (an offset).

Actual relative times are evaluated using the date and time of first dose (e.g., TRTSDTM 'treatment start date and time' in patient level data) and the event date and time (EVNTSDTM) of the current sampling observation, or subsequent dose. To evaluate the actual relative times the PK observations must be vertically SET together with EVID set as 1 for dosing and 0 for sampling, and then be sorted by the subject identifier (e.g., PAT_ID or USUBJID) and event date and time:

USUBJID EVNTSDTM

Note: This sequencing order assumes all dates and times are complete and are recorded accurately (See the later section 'Handling Problem Dates and Times')

Now ACTTMFDS is calculated by subtracting each event date and time from the date and time of first dose and converting to the applicable units (days or hours). *Note*: ACTTMFDS will be negative for any samples taken prior to the first dose.

ACTTMFDS = (EVNTSDTM - TRTSDTM) / (86400 * (ETMU = 'D') + 3600 * (ETMU = 'H')) ;

Actual Time from the Start of the Most Recent Dose (ACTTMMRD)

The Actual Time since the start of the Most Recent Dose, ACTTMMRD is calculated by subtracting the most recent dose EVNTSDTM (from EXSTDTC) from EVNTSDTM in the current observation and converting the seconds into the units of ETMU.

Points to note about ACTTMMRD are

1) ACTTMMRD for pre-dose samples refers back to the time of the preceding dose, not the dose about to occur except for pre-dose observations before the first dose.
2) ACTTMMRD and ACTTMFDS are negative for observations preceding the first dose.
3) ACTTMMRD is the same as ACTTMFDS for all observations preceding the second dose.
4) ACTTMMRD and all subsequent actual relative time variables are usually set to zero for all dosing (EVID=1) observations.

Actual Time from the Start of the Most Recent Dose, negative values imputed to zero (ACTTMMRZ)

In some studies there is a need to have the first PREDOSE negative actual time taken as zero, so, for example, the first sample result shows at the origin of a graph plotting concentration against actual time.

ACTTMMRZ = (ACTTMMRD > 0) * ACTTMMRD ;

Actual Time from the End of the Most Recent Dose (ACTTMRDE)

ACTTMRDE is calculated in a similar way to ACTTMMRD but using EVNTEDTM, taken from EXENDTC, instead of EVNTSDTM taken from EXSTDTC. End of dose time based relative times are missing for orally administered medications, or where there is no recorded end time or dose duration.

Actual Time from the End of the Most Recent Dose, negative values imputed to zero (ACTTMRDZ)

ACTTMRDZ is calculated in a similar manner to ACTTMMRZ but using the dose end date and time instead of the start date and time.

Actual Time from the Start of the Most Recent Dose with Trough Pre-dose (ACTTMRDP)

This is the Actual Time from the Start of the Most Recent Dose but with pre-dose sample times that are less than a certain time period before the start of the next dose shown as the time before the start of the next dose instead of the time since the prior dose. ACTTMRDP is negative for these pre-dose samples. The period before the start of the next dose during which the dose about occur is taken instead of the prior dose is usually 24 hours, but can be whether the pre-dose was taken on the same day as the dose administration.

Actual Time from the End of the Most Recent Dose with Trough Pre-dose (ACTTRDEP)

This is the Actual Time from the End of the Most Recent Dose with Pre-dose Sample Times that are less than a certain time period before the start of the next dose shown as the time before the start of the next dose. ACTTRDEP is negative for these pre-dose samples.

The following table shows examples of three of these Actual Relative Times using the observations shown in Table 1 and Table2:

Table 4: Examples of Actual Relative Times taken from Table 1 (Dosing) and Table 2 (Samples)

EVID	VISIT	PCTPT	EXSTDTC/PCDTC	ACTTMFDS	ACTTMMRD	ACTTMRDP
0	CYCLE 1 DAY 1	PREDOSE	2021-02-22T09:24	-0.1833	-0.1833	-0.1833
1	CYCLE 1 DAY 1		2021-02-22T09:35	0.0000	0.0000	0.0000
0	CYCLE 1 DAY 1	1 HR POST	2021-02-22T10:39	1.0667	1.0667	1.0667
0	CYCLE 1 DAY 1	2 HR POST	2021-02-22T11:33	1.9667	1.9667	1.9667
0	CYCLE 1 DAY 1	4 HR POST	2021-02-22T13:41	4.1000	4.1000	4.1000
0	CYCLE 1 DAY 2	PREDOSE	2021-02-23T08:47	23.2000	23.2000	-0.5000
1	CYCLE 1 DAY 2		2021-02-23T09:17	23.7000	0.0000	0.0000
0	CYCLE 1 DAY 2	1 HR POST	2021-02-23T10:14	24.6500	0.9500	0.9500
0	CYCLE 1 DAY 2	2 HR POST	2021-02-23T11:15	25.6667	1.9667	1.9667
0	CYCLE 1 DAY 2	4 HR POST	2021-02-23T13:20	27.7500	4.0500	4.0500

Actual Time Reference Dates

Reference or ‘anchor’ dates are the actual date and time (EVNTSDTM) of the dose used to evaluate the corresponding actual relative time. These dates are a sequence of variables, for example, REFDTM1 though REFDTM7, corresponding to each of ACTTMFDS, ACTTMMRD through ACTTRDEP, and are SAS internal date time numeric values with a date time format. For example, the anchor date for ACTTMFDS is TRTSDTM (2021-02-22T09:35:00 in Figure 1). The anchor date for ACTTMMRD is the preceding date and time (EVNTSDTM) of the most recent dose (In Figure 1 the sample at CYCLE 1 DAY 2 1 HR POST at 2021-02-23T10:14:00 would have REFDTM2=2021-02-23T09:17:00 and ACTTMMRD=0.95 hours or 0.03958 days)

CALCULATED NOMINAL RELATIVE TIMES

Nominal Time Sources

A VISIT label, together with any sample timepoint (PCTPT) text defines a nominal time. These labels are printed on the CRFs and hence are fixed at the time the study begins. The most important nominal time is the relative nominal time since the first dose, in this example this will be called NOMTMFDS.

A pre-dose sample (PCTPT=’PREDOSE’ in the above example) is taken soon before a dose is administered to measure the level of any residual drug analyte still in the patient’s blood just prior to receiving the dose. The result should always be ‘BLQ’ prior to the first dose. Post-dose samples are subsequently taken at the CRF PCTPT specified intervals to measure the level of drug analyte at that time since completion of the dose administration. The nominal time is specified in the PCTPT text where applicable.

Nominal Time from First Dose (NOMTMFDS)

NOMTMFDS is easily evaluated from the CRF VISIT and PCTPT texts, since NOMTMFDS is the *planned* time relative to the first dose of the study drug. In many studies dosing is administered in cycles, which are usually of a fixed length for a given drug, common cycle lengths are 21 days or 28 days (a 'Week' has a 'cycle' of 7 days or a multiple of 7 days). Some examples of nominal time evaluation from VISIT are:

CYCLE 1 DAY 1 = 0 (This is the first dose)

CYCLE 1 DAY 2 = 1 (1 day after the first dose, 24 if measured in hours)

CYCLE 1 DAY 3 = 1 (2 days after the first dose, 48 if measured in hours)

CYCLE 2 DAY 1 = 21 (Cycle length is 21 days or 504 hours)

CYCLE 2 DAY 2 = 22 (One 21-day cycle plus 1 day or 528 hours)

WEEK 4 DAY 3 = 30 (7*4-1 + 3 or 720 hours)

In general terms, for a cycle length of CYCLEN, NOMTMFDS is calculated in days or hours, depending on ETMU, as:

NOMTMFDS = ((CYCLE – 1) * CYCLEN + (DAY – 1)) * (1 + 23 * (ETMU = 'H')) ;

Having evaluated NOMTMFDS on the basis of the dosing cycle. the timepoint PCTPT must added where applicable. Pre-dose timepoints are considered as the same nominal time as the dose about to be administered since a pre-dose is 'just before' a dose administration. A pre-dose sample taken several hours before dose administration is just as good as a pre-dose sample taken a few minutes before dose administration if the dosing interval is several days or more. In some studies there is an assumed 'just before' time interval (usually 5 minutes) between the pre-dose sample being collected and the beginning of the dose administration. This time interval, if used, is subtracted from NOMTMFDS at pre-dose visits. For post-dose samples the PCTPT text, if it specifies a time, is used to add the extra time. In the above example, where PCTPT='1 HR POST', one hour or 0.041667 days would be added to NOMTMFDS.

An important point to note is when the time specified in PCTPT is 24 hours of more, the VISIT day also takes this into consideration, and care must be taken not to count the day twice (or more). For example, if VISIT is 'CYCLE 1 DAY 2' and PCTPT is '24 HR POST', DAY should be taken as DAY 1 and not DAY 2. This is because the VISIT 24 hours after the dose is correctly labelled as one day following the dose at VISIT (CYCLE 1 DAY 1).

When defining a specification for nominal times, a key consideration is non 'regular' visits, usually only found in concentration sampling observations. The nominal times for this type of visit is normally pre-defined in the study protocol. Here are the most common examples:

SCREENING: The study specifies screening is performed x days before first dose so NOMTMFDS is set to -x

STUDY DISCONTUATION / TERMINATION / COMPLETION: ‘Termination’ can mean when the patient reaches the end of the planned course of treatment, or when the patient prematurely leaves the study for any reason, such as voluntarily dropping out, disease progression, or death. In some studies the patient may re-join the study at a later time if they meet certain eligibility criteria (a re-challenge), confirmed death is the only case the termination is known to be permanent. Some studies may have patients cross over to a new course of treatment, or may have a ‘follow up’ period where the course of treatment continues after the scheduled completion of the study. A crossover or follow up may also involve a change of medication or dosing schedule, for example placebo patients switch to the study medication, or treatment groups are combined or split. Since so many differing situations can occur following a discontinuation, a discontinuation visit is usually assigned an arbitrary NOMTMFDS value, such as 88888 or 99997. The consideration here is the sort order of the observations when sorted by patient and NOMTMFDS.

FOLLOW-UP: Follow up visits are handled in a similar way to discontinuation visits, NOMTMFDS being based on the sequencing of the possible follow up visits, for example:

FOLLOW-UP 30 DAYS (NOMTMFDS=90030)

FOLLOW-UP 60 DAYS (NOMTMFDS=90060)

FOLLOW-UP 90 DAYS (NOMTMFDS=90090)

As a general rule, PCTPT only has text with time information (e.g., ‘30 min’, ‘2hrs’) when the sample is post-dose and on the same day as the dose. The reasoning is a post-dose sample taken more than 24 hours after the dose will have a result which differs by a very low relative magnitude over one additional hour or less.

UNSCHEDULED: By definition an unscheduled visit has no nominal time, so NOMTMFDS is assigned an arbitrary value such as 99999. Sequencing of UNSCHEDULED visits must be performed using ACTTMFDS. In some cases UNSCHEDULED visits are themselves sequenced (e.g., ‘UNSCHED 1’,’UNSCHED 2’) for a given patient or phase in a study are assigned sequential NOMTMFDS values such as 99991, 99992.

Nominal Time from the Start of the Most Recent Dose (NOMTMMRD)

The second most commonly referenced nominal time is the nominal time relative to the most recent dose, in this example called NOMTMMRD. This is calculated by subtracting NOMTMFDS from the NOMTMFDS of the prior dose after the dosing and sampling observations have been vertically SET together and are then sorted by:

NOMTMFDS DESCENDING EVID

The DESCENDING EVID part of the sort key is so the PREDOSE visits are ordered before their following doses (They have the same VISIT text and hence will likely have the same NOMTMFDS). Post-dose visits will follow their associated dose because of the time added to NOMTMFDS from PCTPT as well as from the visit. In the above example the ‘DAY 2’ ‘PREDOSE’ sample would have NOMTMFDS=1 and NOMTMMRD=1 and the ‘DAY 2’ ‘2 HR POST’ sample would have NOMTMFDS=1.083333 and NOMTMMRD=0.083333.

Points to note about NOMTMMRD are:

1. NOMTMMRD is the same as NOMTMFDS for all samples taken before the second dose
2. NOMTMMRD (and NOMTMFDS) are normally zero for the very first pre-dose sample
3. In some studies there is an assumed time interval (usually 5 minutes) between the pre-dose sample being collected and the beginning of the dose administration. This time interval, if used, is subtracted from NOMTMMRD at all pre-dose visits.
4. NOMTMMRD, unlike NOMTMFDS, should *not* be calculated using the VISIT label, for example setting NOMTMMRD to 21 days because the prior dose should have been a 21-day cycle earlier. This does not allow for the possibility of the scheduled prior dose not being present in the data set. For example, if there was a dose at 'DAY 1' and a dose at 'DAY 3', but the scheduled dose which should have happened at 'DAY 2' was skipped, NOMTMMRD would be 48 hours, not 24 hours. NOMTMFDS would still be 48 hours.'
5. NOMTMMRD and each of the subsequent relative nominal times are usually made equal to NOMTMFDS for non-regular visits such as 'FOLLOW-UP' and 'UNSCHEDULED'.
6. NOMTMMRD and subsequent nominal relative times are usually set to zero for dosing (EVID=1) observations.

Nominal Time from the Start of the Most Recent Dose, negative values imputed to zero (NOMTMMRZ)

This corresponds to ACTTMMRZ for actual times.

NOMTMMRZ = (NOMTMMRD > 0) * NOMTMMRD ;

Nominal Time from the End of the Most Recent Dose (NOMTMRDE)

The nominal end time of a dose is based on the planned dosing duration, such as the infusion duration for an IV administration, which is defined in the study specification. The nominal, or planned, dose duration is usually stored in the numeric variable PTRTDUR and is measured in minutes or hours, in PTRTDURU. Common values for PTRTDUR are 90 minutes for the first dose, 60 minutes for the second dose, and 30 minutes for the third and subsequent doses. Hence NOMTMRDE is NOMTMMRD less the PTRTDUR for the most recent dose.

Nominal Time from the End of the Most Recent Dose, negative values imputed to zero (NOMTMRDZ)

This corresponds to ACTTMRDZ for actual times.

NOMTMRDZ = (NOMTMRDE > 0) * NOMTMRDE ;

Nominal Time from the Start of the Most Recent Dose with Trough Pre-dose (NOMTMRDP)

This is the Nominal Time from the Start of the Most Recent Dose but with pre-dose Sample Times that are less than a nominal day before the start of the next dose shown as the time before the start of the next dose instead of the time since the prior dose. NOMTMRDP is usually zero for these pre-dose samples or may be minus a nominally imputed time interval before the scheduled dose (e.g., 5 minutes or -0.0833 hours)

Nominal Time from the End of the Most Recent Dose with Trough Pre-dose (NOMTRDEP)

This is the Nominal Time from the Start of the Most Recent Dose less PTRTDUR with Pre-dose Sample Times that are less than a nominal day before the start of the next dose shown as the time before the start of the next dose. NOMTRDEP is usually zero for these pre-dose samples or may be minus a nominally imputed time interval before the scheduled dose (e.g., 5 minutes or -0.0833 hours).

Table 5: Examples of Nominal Relative Times taken from Table 1 (Dosing) and Table 2 (Samples)

EVID	VISIT	PCTPT	EXSTDTC/PCDTC	NOMTMFDS	NOMTMMRD	NOMTMRDP
0	CYCLE 1 DAY 1	PREDOSE	2021-02-22T09:24	0.0000	0.0000	0.0000
1	CYCLE 1 DAY 1		2021-02-22T09:35	0.0000	0.0000	0.0000
0	CYCLE 1 DAY 1	1 HR POST	2021-02-22T10:39	1.0000	1.0000	1.0000
0	CYCLE 1 DAY 1	2 HR POST	2021-02-22T11:33	2.0000	2.0000	2.0000
0	CYCLE 1 DAY 1	4 HR POST	2021-02-22T13:41	4.0000	4.0000	4.0000
0	CYCLE 1 DAY 2	PREDOSE	2021-02-23T08:47	24.0000	24.0000	0.0000
1	CYCLE 1 DAY 2		2021-02-23T09:17	24.0000	0.0000	0.0000
0	CYCLE 1 DAY 2	1 HR POST	2021-02-23T10:14	25.0000	1.0000	1.0000
0	CYCLE 1 DAY 2	2 HR POST	2021-02-23T11:15	26.0000	2.0000	2.0000
0	CYCLE 1 DAY 2	4 HR POST	2021-02-23T13:20	28.0000	4.0000	4.0000

IMPUTED RELATIVE TIMES

An imputed relative time (e.g., IMPTMFDS, IMPTMMRD) is taken as the actual relative time unless the actual relative time is missing, in which case the imputed relative time is set to the nominal relative time. If both the actual and nominal relative times are missing the imputed relative time is also missing.

Using the code below, if ACTTMFDS has a non-zero and non-missing value IMPTMFDS is set to ACTTMFDS, if ACTTMFDS is zero IMPTMFDS is also set to zero, or if ACTTMFDS is missing IMPTMFDS is set to NOMTMFDS. The other imputed relative times are calculated in the same manner with the corresponding actual and nominal relative times.

IMPTMFDS = ifn (ACTTMFDS , ACTTMFDS , 0 , NOMTMFDS) ;

For UNSCHEDULED visits IMPTMFDS may be set to ACTTMFDS, regardless of NOMTMFDS, when IMPTMFDS is used as a sort key which includes any UNSCHEDULED observations.

The Actual Relative times and the corresponding Nominal Relative times should be approximately the same. The difference in magnitude between the ACTTMFDS and NOMTMFDS is stored in a variable ACTNOMDF (or RELTMDIF). This can be evaluated as:

ACTNOMDF = ifn (nmiss (ACTTMFDS , NOMTMFDS) , . , abs (ACTTMFDS – NOMTMFDS)) ;

HANDLING 'PROBLEM' DATES AND TIMES

So far, the assumption has been made that all dates and times have been correctly recorded, unfortunately in practice there are instances where dates and times are incomplete or erroneous, or incorrectly sequenced.

The main errors which occur when entering data onto the CRF are:

1. An Event Date such as EXSTDTC, EXENDTC, PCDTC, or LBDTC is omitted and is hence missing.
2. The time part of a date and time combination is missing.
3. Date parts are transposed, for example, the month and day are switched (e.g., 2020-03-01 is recorded as 2021-01-03) *Note:* Different countries have different date formats.
4. Time hours and minutes are transposed, for example '17:05:00' is recorded as '05:17:00'
5. Times may have been rounded to the nearest five minutes or the nearest hour or quarter hour, for example '08:57:00' is recorded as '09:00:00'.
6. Clocks and watches may be fast or slow and different clocks or watches may have been used to record two successive event times.
7. A patient may not always record the time they take their medication correctly
8. A date or time field may be filled with non or incorrectly formatted chronological data (e.g., '********',99:99:99')
9. Non-local time zone time input, 'spring forward' and 'fall back' time changes mean incorrect hour or number of hours
10. An incorrect CRF was used to record dosing or sampling information, for example the intended 'CYCLE 1 DAY 2' data was entered on the CRF with a VISIT 'CYCLE 2 DAY 1'.

Incorrect dates and times can cause improper sequencing, for example an end date may be before a start date, or visit texts (and hence nominal times) or actual times may be duplicated.

Data capture technology and data cleansing effectively prevent or subsequently correct incidences of missing, duplicated, or erroneous data, but amongst large volumes of data (often thousands of observations) a few mishaps are still bound to take place. When these problems occur dates and times may be imputed using other related dates and times and knowledge of the study protocol. Below are described the most common imputation methods. *Note:* The exact imputation rules may be study and data set specific.

Methods of checking for possible incorrect dates are:

1. Obvious errors such as non-date or non-time characters
2. Missing or blank dates and times
3. An unrealistically large discrepancy between the actual date and time and the nominal date and time.
4. End times too soon or too long after start times, or equal to, or before start times.
5. A pre-dose sample after the corresponding dose, or a post-dose sample before its corresponding dose, or incorrectly sequenced post-dose times (e.g., a '30 min' post-dose is later than the '1 hr' post-dose)
6. Date and time are inconsistent with the corresponding visit and timepoint text.
7. Unlikely times, such as taking a medicine dose at 3am – though this is still possible.
8. A date which is a holiday or a Sunday, when a clinic is normally closed. *Note:* Holidays and days of religious observance are country and culture dependent.

Quite often observations with such erroneous values are flagged for exclusion from analysis, with an exclusion reason code. They may be corrected in subsequent data cleansing, so the data should be reviewed every time it is updated.

Missing dosing start date (EXSTDTC) or dosing start date has missing or incomplete time (seconds can be zero or missing).

Note: In some studies where the dosing time scale is lengthy (eg. once a month) times may not be used, only dates.

If there is a sampling time (PCDTC or LBDTC) for the dose on the same day, the dose start time may be imputed by taking the pre-dose sampling time and adding five minutes (300 seconds). This is the assumed time interval between collecting the pre-dose sample and beginning the administration of the dose. If a pre-dose sample is unavailable a post-dose sample may be used by subtracting the nominal time of that post-dose sample and also subtracting the actual dose duration ATRTDUR if available, otherwise the planned dose duration (PTRTDUR). For example, if the first post-dose sample is at PCTPT='30 MIN POST' and the dose duration is 60 minutes, 90 minutes is subtracted from EVNTSDTM to obtain an imputed dose start time. Care must be taken to ensure the imputed dose time is not earlier than the pre-dose sample time.

If there is an end of dose date (EVNTEDTM from EXENDTC) available, EXSTDTC (EVNTSDTM) may be imputed by subtracting the actual dose duration (ATRTDUR) from EXENDTC. If ATRTDUR is not available the planned duration PTRTDUR can be used instead. *Note:* The pre-dose sample time, if available, should be used in preference to the dose end time, since there is the possibility, after

subtracting the dose duration from the end date, the imputed dose start time could be earlier than the pre-dose sample time.

If the dose end date is required for the study and is missing or incomplete, or obviously incorrect, such as being before the dose start time or an unrealistically long time after the start date it can be imputed from the dose start time. This imputation is to add the dose duration ATRTDUR, or PTRTDUR if ATRTDUR is not available.

A prior dose time may be used as an imputed time for a missing dose time if the study protocol is for the patient to receive the dose at 'the same time' each day of dosing. Care must be taken, though, to ensure the imputed dose time is not before the pre-dose sample time or after or too close to the first post-dose sample time.

If all of the start time of dose, end time of dose, and sample collection time are missing or incomplete and there is no prior dose time to work with the time has to be assumed from the planned dosing schedule. For example, if the patient is scheduled to take their dose 'before breakfast' a time of '08:00:00' is assigned for the dose start time and '07:55:00' for a corresponding pre-dose sample. 'At bed time' may be considered as 10pm (22:00:00). Some studies have two doses daily, such as an 'am dose' and a 'pm dose', corresponding imputed times can hence be assigned.

Note: Imputation rules are often different for other data set types in the same study with incomplete or missing dates and times. An example is imputed start and end times for adverse events (AE data),

Concentration sampling date (PCDTC/LBDTC) is missing or has an incomplete time.

The concentration sampling time, if the sample is pre-dose, can be imputed by subtracting five minutes from the dosing start time. If a complete dosing start date and time is unavailable, imputation may be performed by subtracting the dose duration and five minutes from the dose end date. ie: dose end date from EXENDTC less (ATRTDUR+5 minutes).

If no prior dosing date and time is available a prior sample date and time (PCDTC or LBDTC) may be used for imputation along with time indicated in timepoint text (PCTPT or LBTPT). For example a '48 HR POST' sample may be set to the date and time of a preceding '24 HR POST' sample plus 24 hours (add one day to the date).

Missed Doses

If a dose is missed the respective dosing observation may be absent or there may be an actual dose amount value (e.g., AMT) of zero or missing. There are some fields such as EXADJ in the dosing data which, if they have any text, describe one or more problems why the dose was missed (or incomplete). For medications taken orally there may be a 'number of pills/capsules taken' field which would be zero or missing if the medication was not taken, (or a larger than expected value if too many pills were taken).

Study protocol determines whether zero or missed does are counted or not. Generally missed doses would not cause time variable errors, though nominal relative times other than NOMTMFDS must still be

calculated using the preceding and/or next doses (not using the VISIT label for the dose that should have occurred).

Pre-dose Sampling After the Dose Administration

Rules for handling an improper sequence of events generally depend on the study protocol and whether the pre-dose sample was taken more or less than 24 hours 'after' the dose.

Post-dose Sampling Before the Dose Administration

Just like with a pre-dose after a dose a post-dose may have had an incorrectly recorded date and or time placing it before instead of after the dose date and time. When sequencing post-dose samples the nominal time (NOMTMFDS), rather than the actual time (EVNTSDTM or ACTTMDS) should be used as the sort key.

Different studies have different imputation rules, but one way to more accurately sequence PK data is to use the imputed date and time IMPTMFDS in the sort key, since IMPTMFDS will hold the 'better' of ACTTMFDS or NOMTMFDS. Another method is to create a flag to indicate a pre-dose sample, dose, or post-dose sample. For example:

PREPOST = 3 – 2 * (index (upcase (PCTPT) , 'PRE') > 0) - (EVID = 1) ;

Here, PREPOST would be 1 for pre-dose, 2 for dosing, and 3 for post-dose. The data can now be sorted by

USUBJID EVNTDY PREPOST EVNTSDTM

This would achieve correct sequencing but the actual times would still be inaccurate.

CONCLUSION

Accurate recording of dose start, dose end, and sample times is critical for achieving meaningful analysis of the PK data, in terms of when events happened, the duration of events, and the ordering of their occurrences. When events happen relative to each other, as well as on an absolute scale is also important. Much information about the conduct and effectiveness of treatment is easily visualized when plotted on a graph showing analyte concentration with respect to relative actual and nominal times

Improvements in data capture technology and data cleansing techniques have lessened error rates and made inconsistencies easier to identify. Improvements have also been made in data collection on a global scale.

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RECOMMENDED READING

- *Introduction to Population Pharmacokinetic / Pharmacodynamic Analysis with Non-Linear Mixed Effects Models. By Joel S. Owen & Jill Fiedler-Kelly © 2014 John Wiley & Sons Inc., Hoboken, New Jersey, USA.*

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