An Approach for Deriving a Timing Variable in SDTM Standards

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ABSTRACT

Time since Last Dose is a variable that relates adverse events to study medication administrations. This variable is very useful information for data analysis and e-Submissions. But, the derivations are complicated, and if the rules are not clearly defined it makes a hard task even harder. To meet the standards of CDISC SDTM, Merck & Co., has created business rules for deriving important variables for analysis and e-Submissions. Time since Last Dose is one of these derived variables. To implement the rules and to perform User Acceptance Testing on the derived data, we developed SAS® programs and macros for this important timing variable.

Keywords: timing variable, CDISC, SDTM, business rule

Introduction

As the CDISC Study Data Tabulation Model (SDTM) has been endorsed by the FDA and is gaining acceptance within the pharmaceutical industry, many companies are re-engineering their internal processes to adopt the new model. This paper provides a concept of how to derive a timing variable - Time since Last Dose which is commonly used for data analysis and e-Submissions in SDTM standards. The derivation rules, SAS® programs, and macros will be provided to illustrate the derivation process. These macros can also be used as convenient tools to calculate and display timing/duration in ISO 8601 format.

Time since Last Dose (referred to as variable named AEDOSDUR) is commonly used to relate AE information with study medication administration. The latest Study Medication administration date (any date between medication start date (EXSTDTC) and medication stop date (EXENDTC) where the number of doses is greater than zero prior to the AE Start Date (AESTDTC) is also known as the last previous dose date. Time will not be considered in any date/time variables at this point. The duration will be displayed in ISO 8601 format. This paper uses the basic ISO 8601 format nYnMnD, when time is not considered.

In basic and extended ISO 8601 format, the complete representation for duration shall be nYnMnDTnHnMnS or nW. The number of years shall be followed by the designator [Y], the number of months by [M], the number of weeks by [W], and the number of days by [D]. The part including time components shall be preceded by the designator [T]; the number of hours shall be followed by [H], the number of minutes by [M] and the number of seconds by [S]. In the examples [n] represents one or more digits, constituting a positive integer or zero.

In this paper the following rules apply for reduced precision:
a) If the number of years, months, days, hours, minutes or seconds in any of these expressions equals zero, the number and the corresponding designator may be absent; however, at least one number and its designator shall be present, the removal of leading non-zero components is not allowed.

b) The designator T shall be absent if all of the time components are absent.

Derivation Rules:

Assuming both the AE Start Date (AESTDTC) and Study Medication Dose Start Date (EXSTDTC) are not null, the following rules are defined for derivation:

- AEDOSDUR is calculated by comparing the AE start date to the medication date that is immediately prior or equal to the AE start date. Duration is calculated as AE Start Date - Latest Medication Date +1 when Time is not considered.
- If Study Medication End Date (EXENDTC) is null, the Study Medication Start Date (EXSTDTC) is used in the calculation.
- If AESTDTC is between EXSTDTC and EXENDTC, the duration is:
    YYYY-MM-DD/P1D where YYYY-MM-DD is AESTDTC.
- When AESTDTC is after study medication periods, the correct usage is:
    YYYY-MM-DD/PnYnMnD where YYYY-MM-DD is the last EXENDTC.
- For AESTDTC prior to study medication, the syntax is:
    PnYnMnD/YYYY-MM-DD where YYYY-MM-DD is the first EXSTDTC.
- If duration = 0, it will be displayed as YYYY-MM-DD/P0D

Program Flow:

1) Read in AE data with SDTM variables USUBJID, AESEQ, AESTDTC, etc., use macro %DTCtoDTN to convert AESTDTC to numeric date AESTDTN.

2) Read in EX data with SDTM variables USUBJID, EXNUMDOS (Number of Daily Doses), EXSTDTC, EXENDTC, etc., use macro %DTCtoDTN to convert EXSTDTC to EXSTDTN and EXENDTC to EXENDTN.

3) Merge AE with EX to identify AESTDTN between EXSTDTN and EXENDTN records. Flag the data with AEFLAG = "during."

4) Find AE between two discontinued dosing periods by comparing AESTDTN with the previous EXENDTN (PREVEDTN) and the next EXSTDTN to get PREVEDTN < AESTDTN < EXENDTN records.

5) Find the minimum EXSTDTN (first dose date FDOSEDTN) and the maximum EXENDTN (last dose date LDOSEDTN) for each patient and allocate the remaining AE records to get AESTDTN < FDOSEDTN or AESTDTN > LDOSEDTN data, and flag the data with AEFLAG = "before" and "after" respectively.

6) Apply macro %DurIS8601 to calculate an ISO 8601 format duration for each pair of dates and assemble the reference dates and durations based on the format described in the rules above.

Input and Output:

Input data **AE**:

USUBJID	AESEQ	AETERM	AESTDTC
0999-099_000300001	1	calcium decreased	2007-12-20
0999-099_000300001	2	travelling sickness	2007-12-14
0999-099_000300001	3	travel sickness	2007-12-15
0999-099_000300001	4	nausea	2008-01-23
0999-099_000300001	5	very mild bilateral ankle swelling	2008-02-16
0999-099_001100001	1	polyuria	2007-08-26
0999-099_001100001	2	hyperactivity	2007-08-26
0999-099_001100001	3	influenza	2007-11-13
0999-099_001100001	4	chest cold	2007-12-26
0999-099_002000017	1	viral gastroenteritis	2007-09-06
0999-099_002000017	2	bilateral otitis media	2007-11-19
0999-099_002000017	3	nasal congestion	2007-11-19
0999-099_002000017	4	left arm hematoma	2007-11-28
0999-099_002000017	5	sinusitis	2008-01-05
0999-099_002000017	6	iron deficiency	2007-10-24

Input data **EX**:

USUBJID	EXSPID	EXSTDTC	EXENDTC	EXNUMDOS
0999-099_000300001	A	2007-12-11	2007-12-19	1
0999-099_000300001	B	2007-12-11	2007-12-18	1
0999-099_000300001	C	2007-12-20	2007-12-20	0
0999-099_000300001	D	2007-12-20	2007-12-20	0
0999-099_000300001	C	2007-12-21	2008-01-31	1
0999-099_000300001	D	2007-12-22	2008-01-31	1
0999-099_000300001	A	2007-12-06	2007-12-06	0
0999-099_000300001	B	2007-12-06	2007-12-06	0
0999-099_000300001	A	2007-12-07	2007-12-10	0
0999-099_000300001	B	2007-12-07	2007-12-10	0
0999-099_000300001	C	2008-01-31	2008-02-14	1
0999-099_000300001	D	2008-01-31	2008-02-14	1
0999-099_001100001	A	2007-09-27	2007-09-27	1
0999-099_001100001	B	2007-09-27	2007-09-27	1
0999-099_001100001	A	2007-09-28	2007-10-08	1
0999-099_001100001	B	2007-09-28	2007-10-08	1
0999-099_001100001	C	2007-10-09	2007-10-09	1
0999-099_001100001	D	2007-10-09	2007-10-09	1
0999-099_001100001	C	2007-10-10	2007-11-19	1
0999-099_001100001	D	2007-10-10	2007-11-12	1
0999-099_001100001	D	2007-11-13	2007-11-13	1
0999-099_001100001	D	2007-11-14	2007-11-19	0

USUBJID	EXSPID	EXSTDTC	EXENDTC	EXNUMDOS
0999-099_001100001	C	2007-11-20	2007-11-20	1
0999-099_001100001	D	2007-11-20	2007-11-20	1
0999-099_001100001	C	2007-11-20	2008-01-04	1
0999-099_001100001	D	2007-11-20	2007-12-10	2
0999-099_001100001	D	2007-12-11	2008-01-04	1
0999-099_002000017	A	2007-10-03	2007-10-03	1
0999-099_002000017	B	2007-10-03	2007-10-03	1
0999-099_002000017	C	2007-10-17	2007-10-17	1
0999-099_002000017	D	2007-10-17	2007-10-17	1
0999-099_002000017	A	2007-10-04	2007-10-04	1
0999-099_002000017	B	2007-10-04	2007-10-04	1
0999-099_002000017	A	2007-10-05		1
0999-099_002000017	B	2007-10-05	2007-10-16	1
0999-099_002000017	C	2007-10-18	2007-11-28	1
0999-099_002000017	D	2007-10-18	2007-11-28	1
0999-099_002000017	C	2007-11-29	2008-01-14	1
0999-099_002000017	D	2007-11-29	2008-01-14	1

Output data **AENEW**

USUBJID	AESEQ	AETERM	AESTDTC	AEDOSDUR
0999-099_000300001	1	calcium decreased	2007-12-20	2007-12-19/P1D
0999-099_000300001	2	travelling sickness	2007-12-14	2007-12-14/P1D
0999-099_000300001	3	travel sickness	2007-12-15	2007-12-15/P1D
0999-099_000300001	4	nausea	2008-01-23	2008-01-23/P1D
0999-099_000300001	5	very mild bilateral ankle swelling	2008-02-16	2008-02-14/P2D
0999-099_001100001	1	polyuria	2007-08-26	P1M1D/2007-09-27
0999-099_001100001	2	hyperactivity	2007-08-26	P1M1D/2007-09-27
0999-099_001100001	3	influenza	2007-11-13	2007-11-13/P1D
0999-099_001100001	4	chest cold	2007-12-26	2007-12-26/P1D
0999-099_002000017	1	viral gastroenteritis	2007-09-06	P27D/2007-10-03
0999-099_002000017	2	bilateral otitis media	2007-11-19	2007-11-19/P1D
0999-099_002000017	3	nasal congestion	2007-11-19	2007-11-19/P1D
0999-099_002000017	4	left arm hematoma	2007-11-28	2007-11-28/P1D
0999-099_002000017	5	sinusitis	2008-01-05	2008-01-05/P1D
0999-099_002000017	6	iron deficiency	2007-10-24	2007-10-24/P1D

From output data AENEW, the records highlighted in blue are AEs occurring before study medication. To the left of '/' is the duration between AE start date (AESTDTC) and first medication date in ISO 8601 format. To the right of "/" is first medication date.

The records highlighted in yellow are AEs that occurred two days after last study medication. The duration is displayed on the right side of '/', and the last medication date is displayed on the left.

The record highlighted in pink is AE that occurred between two discontinued medication periods with non 0 doses (after the last period ended at 2007-12-19 and before the next period start at 2007-12-21). The left side of AEDOSDUR is the latest EXSTDTC before the AE start date, which is 2007-12-19, and the right side is the duration of the latest EXENDTC and AESTDTC which is one day.

The remaining AEs are during study medication periods; duration is one day 'P1D' and AESTDTC is displayed on the left.

Macros

%DTCtoDTN (dtcvar)

This macro can serve as a convenient tool to convert the complete character date in ISO 8601 format to SAS® numeric date format in SAS® data step. Parameter **dtcvar** is the input DTC variable, and can be any complete character date in ISO 8601 format (i.e. AESTDTC, BRTHDTC, EXSTDTC, etc.). The output variable name will adopt the input name. For example, input AESTDTC will output AESTDTN.


```
%macro DTCtoDTN(dtcvar);
  ** Get text part of DTC variable name before 'DTC' **;
      %let dtnvar = %substr(&dtcvar, 1, %length(&dtcvar)-3);
      &var.DTN = input(&dtcvar, is8601da.);
      format &var.DTN is8601da.;
%mend DTCtoDTN;
```


%Display_DurIS8601 (yeardur, mondur, daydur, dur)

This macro assembles the calculated year, month and day periods and displays them in ISO 8601 format PnYnMnD - this macro works in a SAS® data step.
Parameters **yeardur**, **mondur** and **daydur** are positive integers or zeros representing each 'n' in PnYnMnD which break down a duration into year, month, and day accordingly. Parameter **dur** is the output variable name for PnYnMnD when the macro is called. 'P' represents "period". If all periods (**yeardur**, **mondur**, **daydur**) are 0, then '0D' will be displayed.

```
%macro Display_DurIS8601 (yeardur, mondur, daydur, dur);
      if &yeardur > 0 then nY = put(&yeardur, best.)||'Y';
      if &mondur > 0 then nM = put(&mondur, best.)||'M';
      if &daydur > 0 then nD = put(&daydur, best.)||'D';

      length &dur $20.;
      &dur = compress(nY||nM||nD);

      ** if all durations are 0 then display as '0D' **
      if &dur = '' then &dur = '0D';
      drop nY nM nD;
```

```
%mend;
```

%DURIS8601 (sdate, edate)

This macro calculates duration of two SAS® dates and displays the duration in ISO 8601 format.
Parameter **sdate** is the start date and **edate** is the end date; **edate** must be greater than or equal to **sdate -**
this macro works in a SAS® data step.

```
%macro DurIS8601(sdate, edate);
      syear = year(&sdate);
      smonth = month(&sdate);
      sday = day(&sdate);
      eyear = year(&edate);
      emonth = month(&edate);
      eday = day(&edate);

      *** Calculate PMONTH (previous month) and PYEAR (year associated with PMONTH)
          based on &edate, if month of &edate is January then the previous month of
          &edate will be December of previous year **;
      ...

      *** Calculate month, day and year duration between &sdate and &edate ***;
      *** if end month is after start month ***;
      if emonth >= smonth then do;
        mondur = emonth - smonth;
        yeardur = eyear - syear;
      end;

      *** if end month is before start month ***;
      else if emonth < smonth then do;
        mondur = sum(mondur, 12);
        yeardur = yeardur - 1;
      end;

      *** if end day after start day ***;
      if eday >= sday then do;
        daydur = eday - sday;
      end;

      *** if end day before start day ***;
      else if eday < sday then do;
        daydur = mdy(emonth,sday,eyear) - mdy(pmonth,sday,pyear) + (eday - sday);
        mondur = mondur - 1;
      end;

      *** Disaplay duration in ISO 8601 format ***;
      %Display_DurIS8601(yeardur, mondur, daydur, dur);
%mend DurIS8601;
```

Conclusion

This paper offers one approach for defining and deriving the timing variable Time since Last Dose. The SAS® program is developed based on the derivation rules we specified in the paper. The macros can be considered as convenient tools when handling CDISC compliant data that involves ISO 8601 format.

Appendix

Partial Listing of the source code for the derivation of Time since last dose (AEDOSDUR)

```
** Read in AE data **;
data ae;
  set rawdir.ae(keep=usubjid aeseq aeterm aebodsys aedecod aestdtc aeendtc);
  %DTCtoDTN(aestdtc);
run;


** Read in EX data **;
data ex;
  set rawdir.ex;
  %DTCtoDTN(exstdtc);
  %DTCtoDTN(exendtc);
  ** impute EXENDTN based on the rule **;
  if exendtn = . then exendtn = exstdtn;
run;


** Find distinct start date and stop date by patient **;
...

** Find minimum start date and maximum end date by patient **;
...

** Find AE occurred during drug period, assign AEFLAG = 'during' **;
proc sql;
  create table aeinex as
  select ae.*, exstdtc, exstdtn, exendtc, exendtn, 'during' as aeflag, fdosedtn,
         ldosedtn
  from ae, ex2
  where ae.usubjid = ex2.usubjid and ae.aestdtn between exstdtn and exendtn
  order by usubjid, aeseq, exstdtn
  ;
quit;

** Get earliest EXSTDTN if an AE is mapped to multiple EX periods **;
...

** Find previous end date PREVEDTN for current drug period **;
...


** Find AE occurred between two drug periods **;
```

7

```sas
proc sql;
  create table aebtex as
  select ae.*, exstdtc, exstdtn, prevedtc, prevedtn, 'between' as aeflag, fdosedtn,
         ldosedtn
  from ae, ex3
  where ae.usubjid = ex3.usubjid and . < prevedtn < aestdtn < exstdtn
  order by usubjid, aeseq
  ;
quit;

* The remaining AEs before first dose or after last dose **;
proc sql;
  create table aenoex as
  select ae.usubjid, aeseq, aeterm, aebodsys, aedecod, aestdtc, aeendtc, aestdtn
  from ae
  except
  select in.usubjid, aeseq, aeterm, aebodsys, aedecod, aestdtc, aeendtc, aestdtn
  from aefinex in
  except
  select bt.usubjid, aeseq, aeterm, aebodsys, aedecod, aestdtc, aeendtc, aestdtn
  from aebtex bt
  ;
quit;

proc sql;
**** AE before first dose date ****;
  create table beforeex as
  select ae.*, fdosedtn, ldosedtn, 'before' as aeflag
  from aenoex ae, exminmax ex
  where ae.usubjid = ex.usubjid and . < ae.aestdtn < fdosedtn
  ;

*** AE after last dose date ***;
  create table afterex as
  select ae.*, fdosedtn, ldosedtn, 'after' as aeflag
  from aenoex ae, exminmax ex
  where ae.usubjid = ex.usubjid and ae.aestdtn > ldosedtn > .
  ;
quit;


*** Combine all data, calculate and display AEDOSDUR ***;
data aenew;
  set aefinex aebtex beforeex afterex;
  length aedosdur $50;
  if aeflag = 'during' then AEDOSDUR = put(aestdtn, is8601da.)||'/'||'P1D';
  else if aeflag = 'between' then do;
    %DurIS8601(prevedtn, aestdtn);
    aedosdur = put(prevedtn, is8601da.)||'/P'||dur;
  end;
  else if aeflag = 'before' then do;
    %DurIS8601(aestdtn, fdosedtn);
    aedosdur = 'P'||trim(dur)||'/'||put(fdosedtn, is8601da.);
  end;
  else if aeflag = 'after' then do;
    %DurIS8601(ldosedtn, aestdtn);
    aedosdur = put(ldosedtn, is8601da.)||'/P'||dur;
```

8

```
    end;
    keep usubjid aeseq aeterm aebodsys aedecod aestdtc aeendtc aedosdur;
run;

proc sort data=aenew;
    by usubjid aeseq aestdtc;
run;
```

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