The Creation of Time Deviations

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ABSTRACT
Calculating time deviations are an important edit check to ensure that dates and times are in line with dosing date and times. I will discuss why time deviations are important to data management and pharmacokineticists. I will also discuss a procedure for calculating these time deviations as well a technique to check whether or not your US study was conducted over the beginning or end of daylight savings time. Recognizing this event will prevent unnecessary queries to be generated.

INTRODUCTION
I work in Phase I clinical trials and we deal with pharmacokinetic (PK) data in almost every trial. We receive concentration (blood draw) data at several time points and the pharmacokineticist uses this data to create the PK parameters which are then analyzed. Time deviations are the difference in time (minutes or hours) between when the blood was scheduled to be drawn and when it was actually drawn. Before the pharmacokineticist receives the data, the clinical data manager reviews the time deviations calculated to see if these deviations may be due to errors in the data or actual deviations.

Concentration data is just one example of where time deviations can be calculated. Time deviations can also be used in other data types, such as lab results, ECGs, and vital signs. These data types are found in all phases of clinical trials.

WHY TIME DEVIATIONS
Our programmer creates the time deviations for the concentration data. The time deviations, in the example of PK data, are the number of minutes that the blood draw deviated from the planned interval date and time. Aside from being important to the data cleaning, these are important to the pharmacokineticist. Some PK parameters are dependent on the actual time of collection. It is important that these actual times are collected correctly so the parameters are calculated correctly. In addition, some time points are excluded if they are too far outside of a given window.

THE DATA
Let's look at the data we are going to be working with. In the drug administration dataset, the date and time of the drug administration is recorded.

<table>
<thead>
<tr>
<th>Subject_ID</th>
<th>Visit_No</th>
<th>Dose_Date</th>
<th>Dose_Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>30SEP2006</td>
<td>08:00</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>28OCT2006</td>
<td>07:55</td>
</tr>
</tbody>
</table>

In the blood draw (concentration) data the date, time and scheduled time points are captured.
CREATE THE TIME DEVIATIONS
How do we calculate these time deviations?

MERGING THE DATA
To create the time deviations, the two files must be merged by Subject and Visit.

```plaintext
data blood  
merge blood drug 
by Subject_ID Visit_No 
run;
```

If these time deviations are being used as part of data cleaning, it might be helpful to include “in” statements to help identify any records that do not merge by Subject and Visit.

```plaintext
data blood  
merge blood (in=inblood) 
drug (in=indrug) 
by Subject_ID Visit_No 
if not (inblood and indrug) then FLAG = 'MISMATCH' 
run;
```

CREATE THE TIME DEVIATIONS
Next, we create a numeric date and time variable for both the Dose Date/Time and the Actual Blood Draw Date/Time:

```plaintext
*** Get Numeric Dose Date and Time ***;
Dose_DTM = dhms(input(Dose_Date, date9.), 0, 0, input(Dose_Time, time5.)) ;
*** Get Numeric Actual Blood Draw Date and Time ***;
Actual_DTM = dhms(input(Actual_Date, date9.), 0, 0, input(Actual_Time, time5.)) ;
```

We are given the Scheduled time points (Timept) of when the Blood Draws were supposed to have occurred. We use this information to get hours post dose and add to the Dose Date/Time to calculate the Scheduled Date/Time:

```plaintext
*** Get Scheduled Hours for Blood Draw ***;
if Timept = 'Pre-Dose' then Sch_timept = 0 ;
else if index(Timept, 'HR') > 0 then
    Sch_timept = input(substr(Timept, 1, index(Timept, 'HR')-1), best.) ;
** convert from MIN to HOURS **;
else if index(Timept, 'MIN') > 0 then
    Sch_timept = input(substr(Timept, 1, index(Timept, 'MIN')-1), best.) / 60 ;
*** Get Scheduled Date and Time using Scheduled hours for Blood Draw ***;
Sch_DTM = Dose_DTM + sch_timept*60*60 ;
```
We now use this Scheduled Date/Time and the Actual Blood Draw Date/Time to compute the Time Deviation. We divide by 60 here to convert to minutes for the report:

*** Get Time Deviation ***

\[
\text{Time Dev} = \frac{(\text{Actual DTM} - \text{Sch DTM})}{(60)}
\]

THE RESULTS
For the example data above, our time deviations (in minutes) are:

<table>
<thead>
<tr>
<th>Visit No</th>
<th>Timept</th>
<th>Time_Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-Dose</td>
<td>-5</td>
</tr>
<tr>
<td>1</td>
<td>15MIN Post-dose</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>30MIN Post-dose</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1HR Post-dose</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>24HR Post-dose</td>
<td>-10</td>
</tr>
<tr>
<td>1</td>
<td>36HR Post-dose</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Pre-Dose</td>
<td>-5</td>
</tr>
<tr>
<td>2</td>
<td>15MIN Post-dose</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>30MIN Post-dose</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1HR Post-dose</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>24HR Post-dose</td>
<td>-60</td>
</tr>
<tr>
<td>2</td>
<td>36HR Post-dose</td>
<td>-50</td>
</tr>
</tbody>
</table>

For data cleaning purposes, the clinical data manager might specify acceptable windows for the time deviations. For example, the time points less than 6 hours might allow plus or minus 5 minutes, whereas the time points over 16 hours may allow for a window of plus or minus 10 minutes. We also check that pre-dose (or any check-in) time points occurred before the dosing date. Most of these time deviations look OK with the exception of Visit 2, where we have time deviations of around an hour. Upon closer look at a calendar it is noticed that this visit falls over the end of daylight savings time, thus these last two time points seem to have happened an hour early.

IDENTIFYING DAYLIGHT SAVINGS TIME CHANGES
If the study was conducted in the United States in a state that adjusts for daylight savings time (DST), here is some code to help spot/adjust for the two times of the year when daylight savings begins and ends that could cause problems in time deviations.
*** Daylight savings dates through 2010 ***;
data work.dst;
  input date DATE9. time TIME5. delta 17-18 ;
  format date DATE9. time TIME5. ;
cards;
02APR2006 02:00 1
29OCT2006 02:00 -1
11MAR2007 02:00 1
04NOV2007 02:00 -1
09MAR2008 02:00 1
02NOV2008 02:00 -1
08MAR2009 02:00 1
01NOV2009 02:00 -1
14MAR2010 02:00 1
07NOV2010 02:00 -1
;
run;

*** To create date/time and adjustment (plus/minus) macro variables ***;
data _null_; set work.dst END = eof ;
  CALL SYMPUT(compress('dst' || put(_n_,8.)), compress(put(dhms(date,0,0,time),DATETIME20.))) ;
  CALL SYMPUT(compress('adj' || put(_n_,8.)), compress(put(delta,8.))) ;
  if eof then 
    CALL SYMPUT('dstcnt', compress(PUT(_n_,8.))) ;
run;

*** Macro to compare DST dates to study dates ***;
%MACKRO adjust(dosevar = dose_dtm, actvar = actual_dtm, sched = sch_dtm ) ;
  %DO i = 1 %TO &dstcnt ;
  %IF &i NE 1 %THEN %DO ;
  ELSE
    %END ;
  if &dosevar < "&&dst&i"DT and &actvar > "&&dst&i"DT
   then &sched = &sched + (&&adj&i * 60 * 60) ;
  %END ;
%MEND adjust ;

*** To check for Daylight Savings Time - call adjust macro ***;
%adjust ;

These dates would need to be updated depending on the timing of your study. For longer studies, you may need to include several years of daylight savings changes.

Once these checks are put in place, our time deviations now come out to be:

<table>
<thead>
<tr>
<th>Visit_No</th>
<th>Timept</th>
<th>Time_Param</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-Dose</td>
<td>-5</td>
</tr>
<tr>
<td>1</td>
<td>15MIN Post-dose</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>30MIN Post-dose</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1HR Post-dose</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>24HR Post-dose</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>36HR Post-dose</td>
<td>10</td>
</tr>
</tbody>
</table>
OTHER THINGS TO WATCH OUT FOR

Other problems you may come across and things to look out for while working on time deviations may be:

- Check to see if the clinics are automatically making adjustments for DST.
- How is the date and time collected? Are you starting with character or numeric dates and times?
- What is the date format? Date9.? YYMDD8.?
- Are scheduled time points in minutes or hours?
- What unit (minute, hours) should your final time point be reported in?
- Typically, we drop any unscheduled visits.
- For multi-site international studies, you need to make sure each site is checked for daylight savings time changes.
- When the draw happens on the next calendar day, did the visit date change to the next day, or remain the same? If it is the same date, you need to add an extra day. For example, if merging by study day, sometimes the day 1, 24 hour time point may be associated with study day 2, since it happens the next day. This could affect the merge and the dose date/time at study day 1 would not properly merge.

CONCLUSION

Time deviations for blood draw, lab, ECG, and vital signs data are critical in data cleaning. When programming time deviations there are several issues to be aware of, including when your study is run over a daylight savings time change. This paper talks to the common issues and suggests how you can reduce the impact of them.

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