

Identifying and Verifying Treatment-Emergent Adverse Events and Concomitant Medications by Date Specificity

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ABSTRACT

In clinical trials, treatment-emergent adverse events and concomitant medications are often identified in a similar manner: Event start and end dates are compared to reference start and end dates. However, partial dates can add many complications. The Statistical Analysis Plan (SAP) provides instruction for the handling of partial dates. This presentation will offer a method for using date specificity as a tool to address potential shortcomings of the methodology provided in the SAP.

INTRODUCTION

The correct identification of treatment-emergent adverse events and concomitant medications is pivotal to the safety and efficacy of a study. The precise definitions of treatment-emergent adverse events and concomitant medications may vary between different studies. Typically, the intent is to identify adverse events that begin during treatment as treatment-emergent, and medications that are taken during treatment as concomitant. Obviously, a treatment-emergent adverse event can indicate that the study drug is causing a harmful effect. This could potentially end a study. Similarly, concomitant medications can bias the efficacy of the study drug. The SAP may outline rules to impute dates that do not always correctly identify the event. In addition to the rules provided in the SAP, we use a macro called %MCONTEAE (Macro for Concomitant medications and Treatment-Emergent Adverse Events). %MCONTEAE uses the specificity of the event and reference start and end dates to highlight discrepancies with the identification methods provided in the SAP. Additionally, %MCONTEAE performs data integrity checks and handles other issues related to partial date processing.

HOW IT WORKS

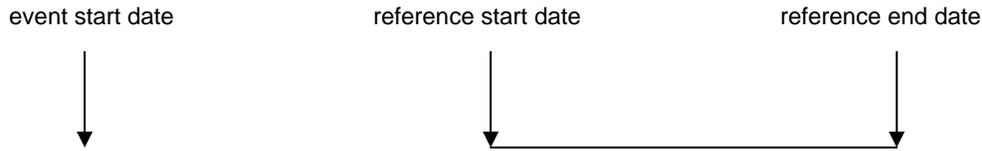
%MCONTEAE takes the following parameters:

- DTA = Dataset name.
- EVT = Event type – CON (concomitant medication) or TEAE (treatment-emergent adverse event).
- EVTSTDT = Name of variable containing event start date (must be character). Represents adverse event start date or medication start date.
- EVTENDT = Name of variable containing event end date (must be character). Represents adverse event end date or medication end date.
- REFSTDT = Name of variable containing reference start date (can be character or numeric). May represent treatment start date, period start date, etc.
- REFENDT = Name of variable containing reference end date (can be character or numeric). May represent treatment end date, period end date, etc.
- RESVAR = Name of variable to contain result ('Y' indicates treatment-emergent or concomitant, null indicates not treatment-emergent or not concomitant).
- CMPPVAR = Name of variable to which the result will be compared (optional).

%MCONTEAE takes a conservative approach, assuming all adverse events are treatment-emergent and all medications are concomitant unless there is sufficient specificity to the event start/end and/or reference start/end dates to prove at least one of the three scenarios illustrated in Figure 1. After performing a series of bullet proof error checks, the heart of %MCONTEAE opens a DATA step and examines each scenario. To simplify the code and to conform to good programming practices, each scenario is examined with calls to a supplemental macro called %MCMPDATE. These calls to %MCMPDATE are also illustrated in Figure 1. %MCMPDATE takes the following parameters:

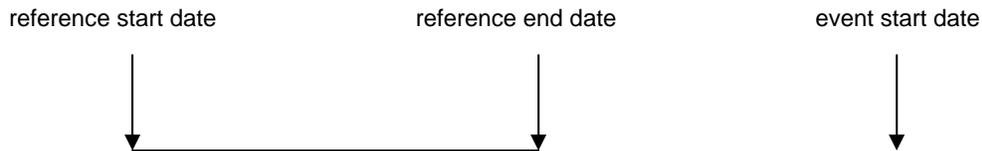
- EVTDT = Event date. The event start or end date, passed from EVTSTDT or EVTENDT in %MCONTEAE.
- REFDT = Reference date. The reference start or end date, passed from REFSTDT or REFENDT in %MCONTEAE.
- SIGN = '<' or '>'. The type of comparison to be done between the event date and the reference date.
- OUTCM = Name of variable to contain the result. Passed from RESVAR in %MCONTEAE.

Scenario 1: Event start date comes before reference start date. This eliminates the possibility that an adverse event is treatment-emergent. However, it does not eliminate the possibility that a medication is concomitant.



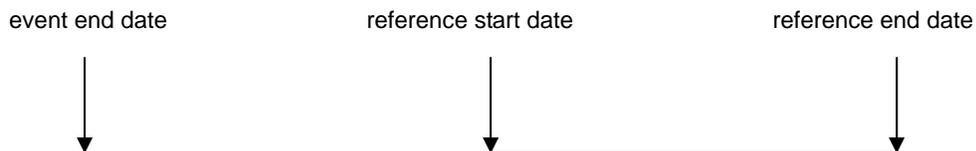
```
%if %UPCASE(&evt)=TEAE %then %MCMPPDATE(evt dt=&evtstdt, refdt=&refstdt, sign=<,
outcm=&resvar);
```

Scenario 2: Event start date is after reference end date. This eliminates the possibility that an adverse event is treatment-emergent or a medication is concomitant.



```
if &resvar='Y' then %MCMPPDATE(evt dt=&evtstdt, refdt=&refenddt, sign=>,
outcm=&resvar);
```

Scenario 3: Event end date is before reference start date. This eliminates the possibility that an adverse event is treatment-emergent or a medication is concomitant.



```
if &resvar='Y' then %MCMPPDATE(evt dt=&evtenddt, refdt=&refstdt, sign=<,
outcm=&resvar);
```

Figure 1. Scenarios examined by %MCONTEAE with the respective calls to %MCMPPDATE

Data integrity checks are performed in a similar manner within %MCONTEAE to verify that the reference start date is not after the reference end date or the event start date is not after the event end date. These are data issues that would corrupt the identification of the event. Note that the result variable is always initially set to 'Y'. Because Scenario 1 cannot eliminate the possibility that a medication is concomitant, this scenario is only examined if the

value of the EVT parameter specified in the call to %MCONTEAE is TEAE. %MCONTEAE maximizes efficiency by only executing calls to %MCMPDATE when the result variable has not yet been proven null.

Analysis datasets are programmed according to the Analysis Data Model (ADaM). ADaM datasets are derived from the Study Data Tabulation Model (SDTM) data, to which the Case Report Form (CRF) data has been converted. SDTM requires dates and datetimes to be stored according to the international standard ISO 8601. Therefore, %MCONTEAE assumes ISO 8601 format. The Clinical Data Interchange Standards Consortium (CDISC) SDTM Implementation Guide Version 3.1.2 defines ISO 8601 format as follows:

- YYYY-MM-DDThh:mm:ss

where:

- [YYYY] = four-digit year
- [MM] = two-digit representation of the month (01-12, 01=January, etc.)
- [DD] = two-digit day of the month (01 through 31)
- [T] = (time designator) indicates time information follows
- [hh] = two digits of hour (00 through 23) (am/pm is NOT allowed)
- [mm] = two digits of minute (00 through 59)
- [ss] = two digits of second (00 through 59)

For example, full and partial dates are represented in ISO 8601 as follows:

November 19, 2007 20:54:18	Complete date/time	2007-11-19T20:54:18
November 19, 2007 20:54	Unknown seconds	2007-11-19T20:54
November 19, 2007 20	Unknown minutes and seconds	2007-11-19T20
November 19, 2007	Unknown time	2007-11-19
November, 2007	Unknown day and time	2007-11
2007	Unknown month, day, and time	2007

%MCMPDATE functions with a do-while loop, making use of ISO 8601 format:

```
%MACRO MCMPDATE( evtdt=, refdt=, sign=, outcm= );

    i = 1;

    do while( SCAN(TRANSLATE(&evtdt, '-', 'T', '-', ':'), i, '-') ne ' ' and
              SCAN(TRANSLATE(&refdt, '-', 'T', '-', ':'), i, '-') ne ' ' and i lt 7 );

        if SCAN(TRANSLATE(&evtdt, '-', 'T', '-', ':'), i, '-') &sign
           SCAN(TRANSLATE(&refdt, '-', 'T', '-', ':'), i, '-') then do;
            &outcm= ' ';
            i=6;
        end;

        else if SCAN(TRANSLATE(&evtdt, '-', 'T', '-', ':'), i, '-') ne
                SCAN(TRANSLATE(&refdt, '-', 'T', '-', ':'), i, '-') then i=6;

        i=i+1;

    end;

%MEND MCMPDATE;
```

The SAS® TRANSLATE function is very useful to convert the 'T' and ':' to '-', thereby ensuring uniform delimiters for the processing of the do-while loop. The do-while loop will only execute for as long as both dates have a component for the level of the iteration. As soon as the condition of the scenario being examined has been met, the result variable is set to null and the loop will no longer execute. If the condition of the scenario being examined has not been met AND the components of both dates are NOT equal, the loop will no longer execute. This approach facilitates the processing and minimizes the overhead of additional variables often created during these types of calculations.

Note that %MCONTEAE assumes that missing date components are hierarchical. It is conceivable for a higher level component of the date, such as the year, to be missing, but a lower level component, such as the month, to not be missing. In such cases, a conservative approach, which is consistent with the function of %MCONTEAE, would simply identify an adverse event as treatment-emergent and a medication as concomitant.

As previously mentioned, the variables specified in the REFSTDT and REFENDT parameters of %MCONTEAE may be character or numeric. For the purposes of partial date processing, they must be character. However, in the process of programming analysis datasets, reference start and end dates have often been derived, and already exist in numeric form. As a courtesy to the user, %MCONTEAE will convert numeric values to character. It is necessary to determine if the numeric represents a date or a datetime so the conversion can be handled appropriately. To make this determination, %MCONTEAE examines the suffix of the variables specified in REFSTDT and REFENDT. If these variables are numeric, then the suffix 'DT' indicates date, and the suffix 'DTM' indicates datetime. According to the CDISC ADaM Implementation Guide Version 1.0, these suffixes are the standard for numeric date and datetime variables. If neither suffix is present, a message will be sent to the log to alert the user and %MCONTEAE will stop executing. Of course, all conversions are to ISO 8601 format.

PROCESS IMPROVEMENTS

%MCONTEAE functions on a strictly conservative philosophy: Unless there is sufficient specificity to the event start/end dates or reference start/end dates to prove that an adverse event is not treatment-emergent or a medication is not concomitant, then a positive identification will be made. The intent of many clinical trials is also often conservative. However, the SAP often provides rules for the imputation of partial dates. As an example, here are the imputation rules from an actual SAP:

When a patient has missing or partial date information for adverse events or concomitant medications, the following algorithm will be applied to the partial date information:

- For dates without a specific day of the month given (e.g., JAN 2001) the day will be imputed to 15.
- For dates without a specific day or month (e.g., 2001) the day will be imputed to the last day of the month and the month will be imputed to June.

The SAP then goes on to define a treatment-emergent adverse event as follows:

All adverse events with an onset date no earlier than the treatment start date and no later than the treatment end date will be considered treatment-emergent.

There are potential problems with these rules. If, for example, we know the following:

- An adverse event began in January of 2001.
- The adverse event ended on January 5, 2001.
- The treatment started on January 7, 2001.
- The treatment ended on January 11, 2001.

The imputation rules outlined above would impute the adverse event start date to January 15, 2001. This would push the adverse event outside the treatment interval, and could potentially lead, in some cases, to a false negative. Note that the definition of treatment-emergent adverse event did not mention the adverse event end date. It is not uncommon for the SAP to only mention the onset date. In this case, the adverse event end date of January 5, 2001 is before the treatment start date of January 7, 2001, and would therefore indicate that the adverse event is not treatment-emergent. %MCONTEAE requires both event start and end dates to remind the user of their potential importance. If a dataset does not have a variable for the end date, then a dummy variable can be created and set to null as a placeholder for %MCONTEAE to function.

Suppose the imputation rules outlined above were enhanced by the following rule:

- For adverse event start dates that could be before or after the treatment start date, ensure that any imputed date occurs no earlier than the treatment start date.

Now, the adverse event start date would be imputed to the treatment start date of January 7, 2001, and a false positive would result!

In some cases, situations as those discussed above may be oversights of the SAP. In other cases, there may be reasons for the rules provided in the SAP. The CMPVAR parameter in %MCONTEAE enables a comparison between the results obtained using date specificity and the results obtained using other imputation methods. If a variable is specified in the optional CMPVAR parameter, then a dataset that lists the records where the value of the variable specified in the RESVAR parameter contains a different result is generated. Any discrepancies are at least worth noting to verify that the methodology provided in the SAP is really the desired approach. The worst case scenario is for an adverse event to not be identified as treatment-emergent when in fact it was caused by the study drug, or a medication to not be identified as concomitant when in fact it did bias the efficacy of the study drug.

CONCLUSION

A macro such as %MCONTEAE is very useful for handling partial dates to determine if an adverse is treatment-emergent or a medication is concomitant. When date specificity is outlined in the SAP, such a macro can eliminate many of the nightmares associated with partial dates. When specific imputation rules are outlined in the SAP, such a macro provides a handy tool to quickly generate results based on date specificity. These results can be used to raise questions and to verify that the methodology in the SAP is not an oversight.

REFERENCES

CDISC ADaM Implementation Guide Version 1.0
CDISC SDTM Implementation Guide (Version 3.1.2)

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