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Use of SAS® for Risk-Based Monitoring of Survival Endpoints and Adverse Event Data in Clinical Trials

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ABSTRACT

Risk-based monitoring (RBM) could greatly reduce the cost of a clinical trial while protecting safety of a patient and quality of data. Primary endpoints and protocol-required safety measurements are usually identified as critical data for risk assessments. In this paper, we present how to use the basic tools of SAS to detect potential errors for survivals and adverse events data among different sites during centralizing monitoring. The types of errors are generally recognized as more important than others as they could profoundly affect study results and patient safety. This demonstration of RBM could thus enhance the overall efficiency for monitoring activities.

INTRODUCTION

In clinical trials, on-site monitoring is traditionally used to validate trial data quality, reveal abnormal data and identify risk factors. But little evidence has found it has positive effect on bias reduction and precision improvement. Risk-based monitoring (RBM) is a newly developed approach for monitoring sites' performance, which can identify sites with higher risks of bias, errors, deviations and safety issues remotely and effectively.

By revealing abnormally high censoring rate in site-level and too much adverse events in both site-level and subject level, risks reducing the accuracy and precision of survival endpoint and threatening patients' safety can be identified.

A simple test for proportion can be used to detect high censoring rate. One sample one-sided T-test is used to test whether mean of AE per subject in each site exceeds acceptable threshold. Rate Ratio in Poisson Log-linear model was used to examine the SAE rate in each site against a reference rate.

In this paper, we establish SAS macros to perform these simple tests. By calling SAS macros, RBM can reveal risk factors in survival endpoints and adverse event data.

DATASET TEMPLATE

Datasets used to fit macros in this paper should be in accordance with CDISC convention. Requirements of variable attributes are listed in the table below:

Variable Name	Variable Label	Type	Controlled Terms, Code list or Format	CDISC Notes
STUDYID	Study Identifier	Char		Unique identifier for a study.
USUBJID	Unique Subject Identifier	Char		Identifier used to uniquely identify a subject.
AETERM	Reported Term for the Adverse Event	Char		Verbatim name of the event.
AESERN	Serious Event Code Number	Num	Yes=1; No=0	Is this a serious event?
CNSR	Censor	Num	Yes=1; No=0	Defines whether the event was censored.

Table 1. Dataset templates for SAS macros

TEST FOR PROPORTION TO REVEAL ABNORMALLY HIGH CENSORING RATE

In order to reveal abnormally high censoring rate, a simple SAS MACRO containing PROC FREQ can be used to perform a test for proportion. Dataset SED used in this macro should consist with the template mentioned above, and be stored in the library RBM. Parameters used in the macro:

LIBIN, LIBOUT – In and out librefs

DSIN, DSOUT – In and out dataset names

VAR – Variable name to be tested

REFR – Reference censoring rate preset by sponsor

TITLE – Title of printed result table:

```
%macro TestforProportion(libin,libout,dsin,dsout,var,refr,title);

/*Sort dataset by SITEID*/
proc sort data = &libin..&dsin out=&dsin;
          by SITEID;
run;

/*Compare Censoring Rate of each site with the Reference Rate*/
proc freq data = &dsin noprint;
                 by SITEID;

                 /*Set the Reference Rate by calling the macro variable &refr*/
                 tables &var / binomial (p = &refr);

                 /*Output statistics into dataset PROPORTION*/
                 output out = &dsout BINOMIAL;
run;

/*Mark flags for sites with significantly higher censoring rate*/
data &libout..&dsout (keep = SITEID N _BIN_ Riskflag);
                 set &dsout;
                 if  BIN  = 1 then Riskflag = 0;
                 else if (PL_BIN >= 0.05 or PR_BIN >= 0.05) then Riskflag = 0;
                 else Riskflag = 1;
run;

/*Print final result table with risk flag*/
proc print data = &libout..&dsout label;
          title "Risk Flag for &title";
run;

%mend TestforProportion;
```

In this SAS macro, sites with significantly higher (α=0.05) censoring rate compared to a reference censoring rate (acceptable rate according to knowledge and previous experience) pre-set by sponsor will be marked with risk flag (=1). Otherwise, risk flag equals 0.

ONE-SAMPLE ONE SIDE T-TEST MONITORING AE NUMBER

One sample one side T-test is used to test whether the mean of AE per subject in each site exceeds threshold (acceptable risk). The threshold is set by sponsor, taking acceptable risk and length of follow-up time into account. Parameters used in the macro:

LIBIN, LIBOUT – In and out librefs

DSIN, DSOUT – In and out dataset names

AETERM – Verbatim name of the adverse event

M0 – Reference AE number preset by sponsor (acceptable risk)

```
%macro OneSampleTTest(libin,libout,dsin,dsout,aeterm,m0);

/*Calculate total AE per subject in site j*/
proc sql;
    create table &dsin as
        select SITEID,
            SUBJID,
            count(&aeterm) as aebysubj label = 'Total number of AE for each subject'
        from &libin..&dsin
        group by SITEID, SUBJID;
    quit;

/*One sample: one-sided T-Test for testing against a specific mean value*/
proc univariate data = &dsin mu0 = &m0 noprint;
    var aebysubj;
    by SITEID;
    output out = &dsout.01 mean = sitemu PROBT = probttwo;
run;

/*Calculate one side p-value*/
data &dsout.02;
```

```
    set &dsout.01;
    if sitemu <= &m0 then probt = 1-(probttwo/2);
    else probt = probttwo/2;
    keep site sitemu probt;
run;

    /*Generate riskflag*/
data &dsout.03;
    set &dsout.02;
    if probt < 0.05 then riskflag = 1;
    else riskflag = 0;
    label sitemu = "The mean number of AE of each site"
        probt = "The one sided T-test p-value against a specific mean value (&m0)"
        riskflag = "Risk flag for mean number of AE";
run;

proc transpose data = &dsout.03 out = &libout..&dsout
    (drop =  NAME  rename = ( LABEL_ = Items)) prefix = SITEID;
    var sitemu probt riskflag;
    id SITEID;
run;

    /*Output a report*/
ods rtf file = "D:\RBM_AE\Mean_ttest.rtf" bodytitle;

options nonumber nodate ls = 84 missing = " "
formchar = "|----|+|---+=|-/\<>*";

proc report data = &libout..&dsout
        nowindows spacing = 1 headline headskip split = "|";
    title1 "RBM: One sample T-Test";
    title2 "Mean of AE per subject in site j";
    footnote1 "----------------------------------------"
    "----------------------------------------";
    footnote2 "Probt: site j compared to reference value (&m0)";
    footnote3 "Created on &sysdate9..";
run;

ods rtf close;

%mend OneSampleTTest;
```

In this SAS macro, a site with high risk of having too much AE will get a p-valve smaller than the significant level (0.05), then a risk flag will generate for this site (riskflag=1), otherwise riskflag=0.

LOG-LINEAR MODEL FOR MONITORING SAE NUMBER

Rate Ratio in Poisson Log-linear model is used to examine the SAE rate in each site against a reference rate (acceptable risk). In the Poisson Log-linear model, we consider log of SAE rate as outcome, treat sites as qualitative predictors and transform sites into dummy variables to represent sites. Specifically we use macro variable to add one reference site (site=0) with acceptable SAE count into the model.

LIBIN, LIBOUT – In and out librefs

DSIN, DSOUT – In and out dataset names

REFSITE – Reference site name

REFSUBJ – Total subject number in the reference site

REFSAE – Total SAE number in the reference site

```
%macro LogLinear(ibin,libout,dsin,dsout,refsite,refsubj,refsae);

/*Calculate total number of subjects in site j and calculate log_n*/
proc sql;
    create table &dsin.01 as
    select count(distinct SUBJID) as totsubj,
        SITEID,
        log(calculated totsubj) as log_n
    from &libin..&dsin
    group by SITEID;
quit;

/*Calculate total number of SAE in site j*/
proc sql;
    create table &dsin.02 as
```

```
    select SITEID,
        count(aesern) as totSAE label = 'total SAE in site'
    from &libin..&dsin
    where aesern = 1
    group by SITEID;
quit;

data &dsin.03;
    set &dsin.01;
    set &dsin.02;
run;

 data &dsin.04;
           site=&refsite;
           totsubj=&refsubj;
           log_n= log(totsubj);
           totSAE=&refSAE;
run;

data &dsin;
           set &dsin.03;
           set &dsin.04;
run;

/*Log linear model for sum of SAE in each site*/
ods select none;
ods output ParameterEstimates = &dsout.01;

proc genmod data = &dsin;
    class site;
    model totSAE = site / link = log dist = poi offset = log_n;
run;

ods select all;

/*Generate risk site for CI of RR not include 1*/
ods rtf file = "D:\RBM_AE\SAE_RR.rtf" bodytitle;

data &libout..&dsout;
    set &dsout.01;
    RR = exp(estimate);
    LowerRRCL = exp(LowerWaldCL);
    UpperRRCL = exp(UpperWaldCL);
    if level1 ne . and (UpperRRCL > LowerRRCL > 1)
        then Riskflag = Level1;
        title1 "Company "
        " ";
    title2 " RBM: Loglinear Model";
    title3 " Sum of SAE in each site";
    footnote "Created on &sysdate9..";
run;

proc print data = &libout..&dsout;
run;

ods rtf close;

%mend LogLinear(refsite=0,refsubj=,refSAE=);
```

In this SAS macro, RR with 95% confidence interval (CI) is used to compare difference in SAE rate in each site with that in reference site. A suspected site whose lower confidence bound for RR exceeds 1, means this site has too much SAE count compared to reference value. Therefore riskflag = 1, otherwise riskflag=0.

CONCLUSION

By implementing simple statistical methods and SAS tools, Risk-based monitoring (RBM) can take place in clinical trial data monitoring and risk assessment. In this paper, we proposed using test for proportion to monitor high censoring rate in survival endpoint; one-sample one-side T-test to monitor AE and log-linear to monitor the occurrence of SAE. Corresponding SAS macros are also developed for these tests. In summary, simple SAS tools can be used in RBM to detect specific risks in clinical trial data.

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