INTEGO GROUP

Paper SI04

TRIAL DESIGN DATASETS IN ONCOLOGY CLINICAL TRIALS

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AGENDA

- Overview of Trial Design Domains
- Difficulties in oncology
- Trial Visits Domain
- Trial Disease Assessments Domain
- Summary

PART I
OVERVIEW OF TRIAL DESIGN DOMAINS

TRIAL DESIGN MODEL

- Trial design model provides a brief, clear description of the overall plan and design of the study.
- The main concepts of TDM include trial arms, elements, epochs, visits and treatments.
- The specific structure was developed to allow for a standardized way to describe the planned conduct of a clinical trial.

CONTENTS OF TDM

Trial Eligibility and Summary

- **TS** Trial Summary
- **TI** Trial Inclusion/ Exclusion Criteria

Experimental Design

- **TA** Trial Arms
- **TE** Trial Elements

Schedule for Assessments

- **TV** Trial Visits
- **TD** Trial Disease Assessments
- **TM** Trial Disease Milestones

TRIAL ELIGIBILITY AND SUMMARY

Trial Summary

- TS allows to submit a summary of the trial in a structured format.
- Each record corresponds to a parameter, a characteristic of the trial. For example, trial phase, protocol title, and trial objectives.

Trial Inclusion/ Exclusion Criteria

- This trial design domain describes subject eligibility criteria for trial participation.
- Dataset contains one record for each of the inclusion and exclusion criteria for the trial.

EXPERIMENTAL DESIGN

Trial Arms

- This trial design domain contains each planned arm in the trial.

Examples of ending conditions in oncology:
- Date of last infusion of study drug
- Date of Death
- Date of first PD
- X days after the last infusion of study drug
- Discontinuation of Treatment

Trial Elements

- TE contains the definitions of the elements that appear in TA.

Trial elements represent an interval of time that serves a purpose in the trial and are associated with certain activities affecting the subject.

An element has conditions for beginning and ending of the element.

SCHEDULE FOR ASSESSMENTS

Trial Visits

- TV domain contains the planned order and number of visits in the study within each arm.
- Dataset structure can be “One Record per Planned Visit per Arm” or just “One Record per Planned Visit”.

Trial Disease Assessments

- TD provides disease assessment schedule.
- This trial design domain is used for comparison with the actual occurrences to determine whether there was good compliance with the schedule.

Trial Disease Milestones

- The TM dataset describes disease milestones, which are observations or activities anticipated to occur in the course of the disease under study, and which trigger the collection of data.

PART II
DIFFICULTIES IN ONCOLOGY: TRIAL VISITS

DIFFICULTIES IN ONCOLOGY

- Indefinite numbers of repeating elements, indefinite numbers of visits, uneven disease assessment intervals, event-driven assessments schedule.

ISSUES	SOLUTIONS
Indefinite number of elements and visits, requiring constant updates of TV domain	Standard solution: creation of an excel spreadsheet that contains the list of the visits
If done manually, this can lead to unmapped (in time) visits and other errors	Alternative solution is to create a macro that automatically determines the maximum number of repeating visits of interest

% TV_VISITS MACRO: OVERVIEW

- Identify all visits based on all raw datasets that follow the specified pattern
- Derive VISIT, VISITNUM and VISITDY for these visits
- Output the results to an excel spreadsheet for easy copying

```
%macro tv_visits(visit_var      = /* Variable name in raw datasets
                                     that contains visit names */,
                 where_cond     = /* Condition to determine
                                     repeating visits of interest */,
                 out_file       = /* Output excel file path/name*/,
                 rule_visit     = /* Definition of VISIT */,
                 rule_visitnum  = /* Definition of VISITNUM */,
                 rule_visitdy   = /* Definition of VISITDY */);
```

mandatory

optional

% TV_VISITS MACRO: SELECT

```
proc sql noprint;
  select memname into :names separated by
" (keep = &visit_var.) raw."
  from dictionary.tables where libname='RAW';
quit;

data all;
  set raw.&names. (keep = &visit_var.);
run;

proc sort data = all nodupkey;
  by &visit_var.;
  where &where_cond.;
run;
```

	Folder name
1	Cycle 1 Day 1
2	Cycle 10 Day 1
3	Cycle 11 Day 1
4	Cycle 12 Day 1
5	Cycle 13 Day 1
6	Cycle 14 Day 1
7	Cycle 15 Day 1
8	Cycle 16 Day 1
9	Cycle 17 Day 1
10	Cycle 18 Day 1
11	Cycle 19 Day 1
12	Cycle 2 Day 1
13	Cycle 20 Day 1
14	Cycle 21 Day 1
15	Cycle 22 Day 1
16	Cycle 23 Day 1
17	Cycle 3 Day 1
18	Cycle 4 Day 1
19	Cycle 5 Day 1
20	Cycle 6 Day 1
21	Cycle 7 Day 1
22	Cycle 8 Day 1
23	Cycle 9 Day 1

% TV_VISITS MACRO: DERIVE

```
data all2;
   set all;
   %if %length(&rule_visit.)     ^= 0
   %then visit    = &rule_visit.;;
   %if %length(&rule_visitnum.) ^= 0
   %then visitnum = &rule_visitnum.;;
   %if %length(&rule_visitdy.)  ^= 0
   %then visitdy  = &rule_visitdy.;;
run;

proc sort data = all2;
   %if %length(&rule_visitnum.) ^= 0
   %then by visitnum;
   %else by &visit_var.;;
run;
```

	Folder name	visit	visitnum	visitdy
1	Cycle 1 Day 1	CYCLE 1 DAY 1	2	1
2	Cycle 2 Day 1	CYCLE 2 DAY 1	3	21
3	Cycle 3 Day 1	CYCLE 3 DAY 1	4	42
4	Cycle 4 Day 1	CYCLE 4 DAY 1	5	63
5	Cycle 5 Day 1	CYCLE 5 DAY 1	6	84
6	Cycle 6 Day 1	CYCLE 6 DAY 1	7	105
7	Cycle 7 Day 1	CYCLE 7 DAY 1	8	126
8	Cycle 8 Day 1	CYCLE 8 DAY 1	9	147
9	Cycle 9 Day 1	CYCLE 9 DAY 1	10	168
10	Cycle 10 Day 1	CYCLE 10 DAY 1	11	189
11	Cycle 11 Day 1	CYCLE 11 DAY 1	12	210
12	Cycle 12 Day 1	CYCLE 12 DAY 1	13	231
13	Cycle 13 Day 1	CYCLE 13 DAY 1	14	252
14	Cycle 14 Day 1	CYCLE 14 DAY 1	15	273
15	Cycle 15 Day 1	CYCLE 15 DAY 1	16	294
16	Cycle 16 Day 1	CYCLE 16 DAY 1	17	315
17	Cycle 17 Day 1	CYCLE 17 DAY 1	18	336
18	Cycle 18 Day 1	CYCLE 18 DAY 1	19	357
19	Cycle 19 Day 1	CYCLE 19 DAY 1	20	378
20	Cycle 20 Day 1	CYCLE 20 DAY 1	21	399
21	Cycle 21 Day 1	CYCLE 21 DAY 1	22	420
22	Cycle 22 Day 1	CYCLE 22 DAY 1	23	441
23	Cycle 23 Day 1	CYCLE 23 DAY 1	24	462

% TV_VISITS MACRO: EXPORT

```
proc export data    = all2
            outfile = "&out_file."
            dbms    = xlsx
            replace;
run;
```

	A	B	C	D
1	Folder	visit	visitnum	visitdy
2	Cycle 1 Day 1	CYCLE 1 DAY 1	2	1
3	Cycle 2 Day 1	CYCLE 2 DAY 1	3	21
4	Cycle 3 Day 1	CYCLE 3 DAY 1	4	42
5	Cycle 4 Day 1	CYCLE 4 DAY 1	5	63
6	Cycle 5 Day 1	CYCLE 5 DAY 1	6	84
7	Cycle 6 Day 1	CYCLE 6 DAY 1	7	105
8	Cycle 7 Day 1	CYCLE 7 DAY 1	8	126
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15	Cycle 14 Day 1	CYCLE 14 DAY 1	15	273
16	Cycle 15 Day 1	CYCLE 15 DAY 1	16	294
17	Cycle 16 Day 1	CYCLE 16 DAY 1	17	315
18	Cycle 17 Day 1	CYCLE 17 DAY 1	18	336
19	Cycle 18 Day 1	CYCLE 18 DAY 1	19	357
20	Cycle 19 Day 1	CYCLE 19 DAY 1	20	378
21	Cycle 20 Day 1	CYCLE 20 DAY 1	21	399
22	Cycle 21 Day 1	CYCLE 21 DAY 1	22	420
23	Cycle 22 Day 1	CYCLE 22 DAY 1	23	441
24	Cycle 23 Day 1	CYCLE 23 DAY 1	24	462

% TV_VISITS MACRO: THE CALL

```
%tv_visits(
   visit_var      = folder,
   where_cond     = %str(index(upcase(&visit_var.), "CYCLE")) ,
   out_file       = %str(your-path\your-file-name.xlsx),
   rule_visit     = %str(upcase(&visit_var.)),
   rule_visitnum  = %str(input(strip(scan(&visit_var., 2)),
                                    best.) + 1),
   rule_visitdy   = %str(ifn(visitnum=2, 1, (visitnum-2)*21)));
```

special condition for Cycle 1 Day 1 visit to avoid “Day 0”

- Extra optional parameters can be added (i.e., for visit start and end rules).
- The macro can be called several times for different types of repeating visits (chemotherapy cycles, tumor assessments, follow-up visits, etc.)

PART III
TRIAL DISEASE ASSESSMENTS DOMAIN

TD: PURPOSE

- The purpose of the TD domain is to provide information on planned scheduling of disease assessments. It can be used to better describe the logic of assessment schedule when TV is not quite enough.
- This domain was developed specifically with oncology, in particular RECIST, in mind.
- In oncology studies, good compliance with the disease-assessment schedule is essential to reduce the risk of "assessment time bias." The TD domain makes it possible to compare the planned schedule of assessments with the actual one.

TD: STRUCTURE (1)

Variable Name	Variable Label	Type	Format
STUDYID	Study Identifier	Char	
DOMAIN	Domain Abbreviation	Char	
TDORDER	Sequence of Planned Assessment Schedule	Num	
TDANCVAR	Anchor Variable Name	Char	
TDSTOFF	Offset from the Anchor	Char	ISO 8601 duration
TDTGTPAI	Planned Assessment Interval	Char	ISO 8601 duration
TDMINPAI	Planned Assessment Interval Minimum	Char	ISO 8601 duration
TDMAXPAI	Planned Assessment Interval Maximum	Char	ISO 8601 duration
TDNUMRPT	Maximum Number of Actual Assessments	Num	

TD: STRUCTURE (2)

- The structure of the dataset is one record per planned constant assessment period, meaning that each record represents a period with the same pattern of assessments.
- TDANCVAR variable contains **the name of the variable from ADSL** that contains a date used as a reference point for disease assessment schedule. It can be a specifically created ANCHxDT variable or an existing valid ADSL variable.
- TDSTOFF is used when there is an offset between the anchor date and assessment start date.
- TDTGTPAI contains the interval between assessments in the given period.

TD: EXAMPLE

Row	STUDYID	DOMAIN	TDORDER	TDANCVAR	TDSTOFF	TDTGPAI	TDMINPAI	TDMAXPAI	TDNUMRPT
1	ABC123	TD	1	ANCH1DT	P0D	P8W	P53D	P9W	6
2	ABC123	TD	2	ANCH1DT	P48W	P12W	P11W	P13W	?
3	ABC123	TD	3	ANCH2DT	P0D	P12W	P11W	P13W	?

- From this representation we can see that in the first period assessments first occur every 8 weeks for 6 repeats, and then continue every 12 weeks for an indefinite number of repeats (rows 1 and 2).
- In the second period (row 3) assessments occur every 12 weeks.
- The number of repeats for rows 2 and 3 is unknown until the study is completed, so in an ongoing study it should be constantly updated based on the number of repeats available in the data.

%TD_REPEATS MACRO

```
%macro td_repeats(visit_var = , tdorder = , where_cond = );

select-visits-from-all-raw-datasets

proc sql noprint;
  select count(distinct &visit_var.) into :rep&tdorder.
  from all;
quit;
%mend td_repeats;


%td_repeats(visit_var = folder, tdorder = 2, where_cond =
            %str(index(upcase(&visit_var.), "WEEK") and
            input(scan(&visit_var., 2), best.)>48));
```

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PRESENTATION TAKEAWAYS

- Trial Design Domains are different, but not that difficult
- Oncology has some issues in implementing TDM
- Suggested solutions for some of the issues
- Trial Disease Assessments domain provides extra opportunities to accommodate oncology-specific trial design data
- Macros, that can be used to help create some TDM datasets (directly or modified to your own need)

THANK YOU

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