PPD®

An introduction to SDTM Trial Design Model (TDM)

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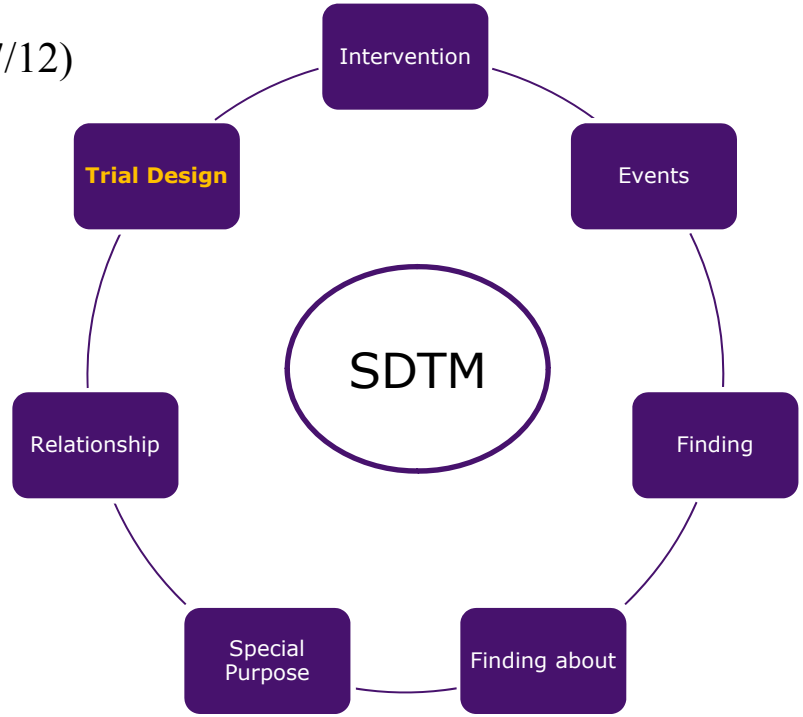
Outline

- About SDTM
- SDTM-TDM basics
- Examples
- Implementation
- Challenges

About SDTM

- The content standard for regulatory submission of case report form **data tabulations** from clinical research studies.
- Current versions:
  - SDTM 1.3 final (16/07/12)
  - SDTMIG 3.1.3 final (16/07/12)



Trial Design

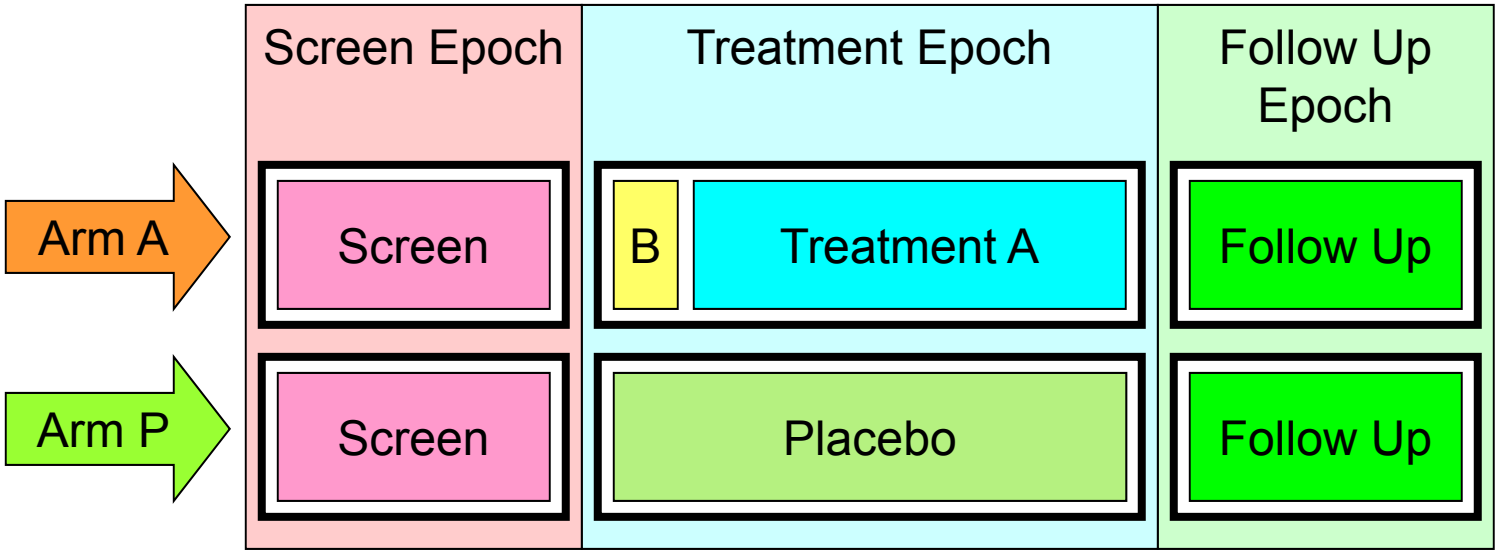
- What is going to be done in a study?
  - information included in the protocol and protocol amendments
  - including planned interventions, assessments, analyses, eligibility criteria, visits etc.
- Planned sequence of events for the study
- Provides ability to compare actual subject progress to the study plan

Trial Design Model

- The Trial Design Model in the SDTM provides a standardized way to describe those aspects of the planned conduct of a clinical trial shown in the study design diagrams of these examples.
  - clearly and quickly grasp the design of a clinical trial
  - understand the rules for how subjects transition through various periods or phases of the trial
  - compare the designs of different trials
  - search a data warehouse for clinical trials with certain features
  - compare planned and actual treatment paths and visits for subjects in a clinical trial.

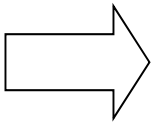
Definition

A two-arm trial comparing Treatment A with pre-treatment B and Placebo



Columns shown with large rectangles “in back” are **epochs**.

Rows marked by arrows are **arms**.

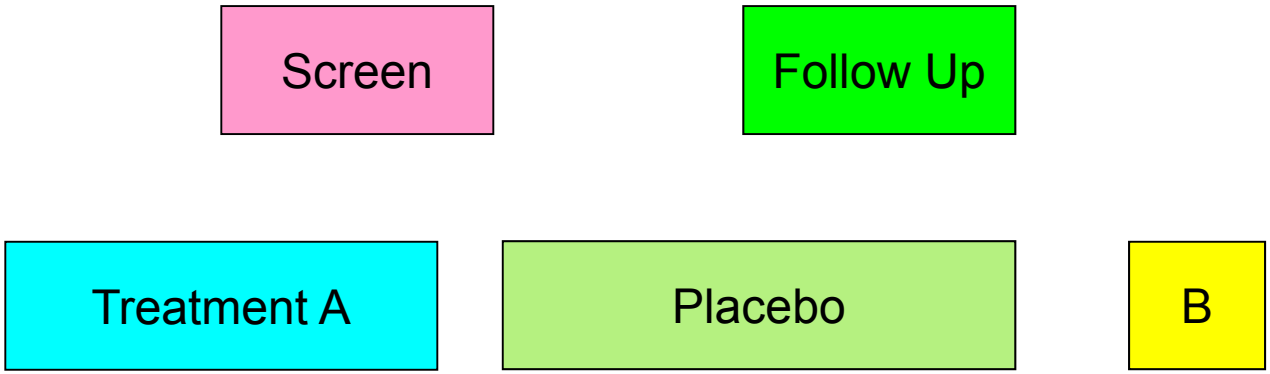


Rectangles with heavy outlines are **study cells**.

Rectangles within the trial cells are **elements.**

Definition

- Element: “a building block that is used to organize activity within the trial.”
  - It involves administering a planned intervention, which may be treatment or no treatment, during a period of time.
  - Elements for which the planned intervention is "no treatment" would include Elements for screening, wash-out, and follow-up.



Definition

- Arm: "a sequence of epochs (time intervals during which treatment is consistent) defining the course of participation for a subject in a trial."
  - a path through the study which describes what activities the subject will be involved
  - equivalent to a treatment group in a parallel design trial
  - each subject is assigned to an Arm

Trail Arm

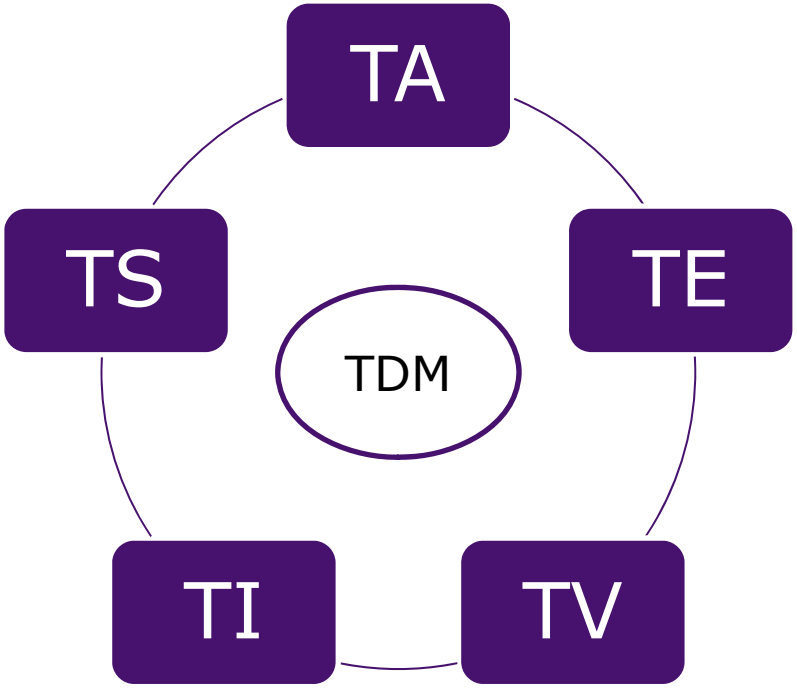
Definition

- Epoch: “an interval of time in the planned conduct of a study during which treatment is constant.” The main purpose of an Epoch is to expose subjects to a treatment, or to prepare for such a treatment period.

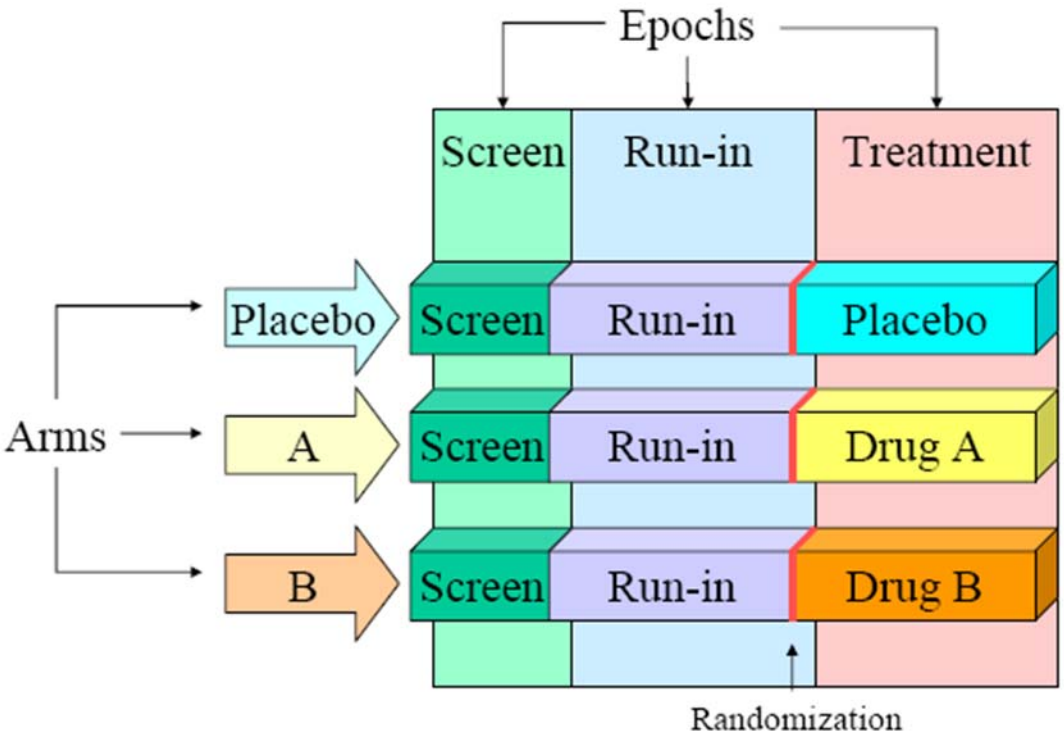
Definition

- Study Cell: Since the trial as a whole is divided into Epochs, each planned path through the trial (i.e., each Arm) is divided into pieces, one for each Epoch. Each of these pieces is called a Study Cell.
  - Combination of Arm and Epoch. Each Study Cell represents an implementation of the purpose of its associated Epoch.
  - For Epochs whose purpose is to expose subjects to treatment, the Study Cells associated with that Epoch expose subjects to particular treatments.

TDM Domain



Example 1: Parallel Trial Design



Trial Design Matrix 1

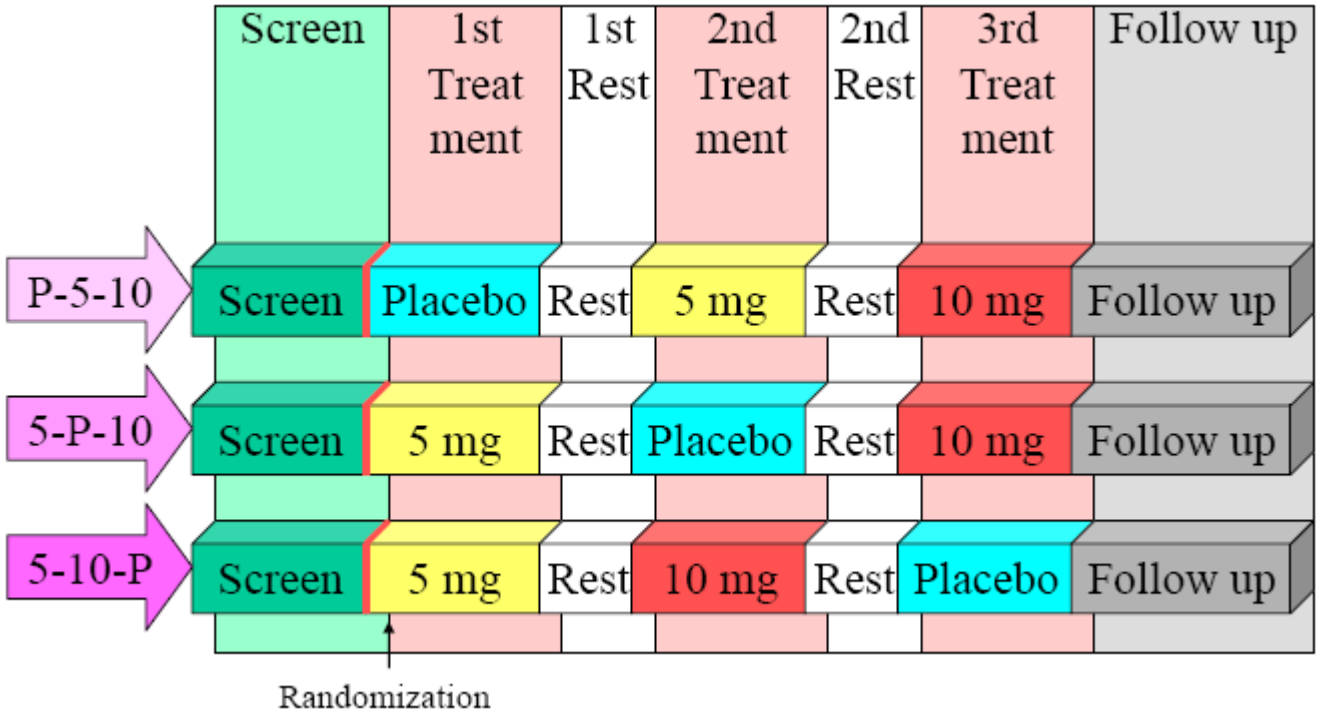
Trial Design Matrix for Example Trial 1

	Screen	Run-in	Treatment
Placebo	Screen	Run-in	Placebo
A	Screen	Run-in	DRUG X
B	Screen	Run-in	Drug B

Trial Arms Dataset for Example Trial 1

Row	STUDYID	DOMAIN	ARMCD	ARM	EPOCH	TAETORD	ETCD	ELEMENT	TABRANCH	TRTRANS
1	EX1	TA	P	Placebo	Screen	1	SCRN	Screen		
2	EX1	TA	P	Placebo	Run-In	2	RI	Run-In	Randomized to Placebo	
3	EX1	TA	P	Placebo	Treatment	3	P	Placebo		
4	EX1	TA	A	A	Screen	1	SCRN	Screen		
5	EX1	TA	A	A	Run-In	2	RI	Run-In	Randomized to Drug A	
6	EX1	TA	A	A	Treatment	3	A	Drug A		
7	EX1	TA	B	B	Screen	1	SCRN	Screen		
8	EX1	TA	B	B	Run-In	2	RI	Run-In	Randomized to Drug B	
9	EX1	TA	B	B	Treatment	3	B	Drug B		

Example 2: Crossover Trial Design



Trial Design Matrix 2

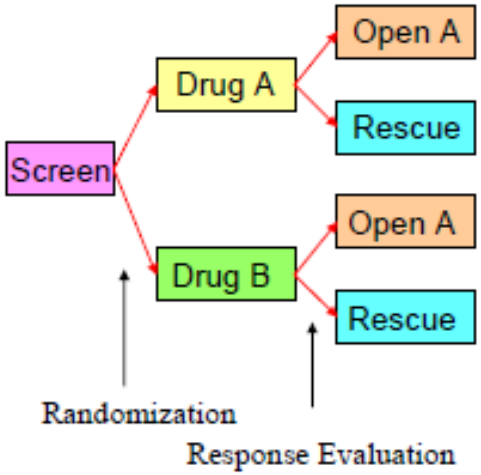
Trial Design Matrix for Example Trial 2

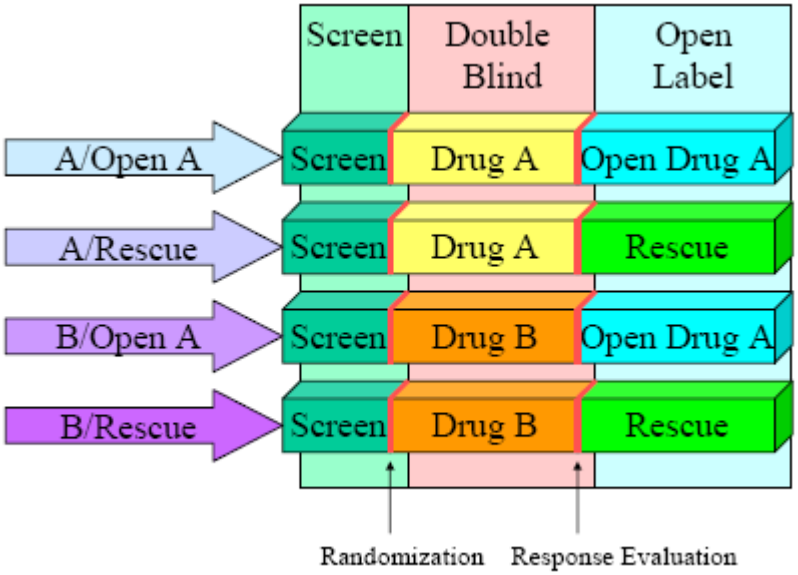
	Screen	First Treatment	First Rest	Second Treatment	Second Rest	Third Treatment	Follow up
P-5-10	Screen	Placebo	Rest	5 mg	Rest	10 mg	Follow-up
5-P-10	Screen	5 mg	Rest	Placebo	Rest	10 mg	Follow-up
5-10-P	Screen	5 mg	Rest	10 mg	Rest	Placebo	Follow-up

Trial Arms Dataset for Example Trial 2

Row	STUDYID	DOMAIN	ARMCD	ARM	EPOCH	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS
1	EX2	TA	P-5-10	Placebo-5mg-10mg	Screen Epoch	1	SCRN	Screen	Randomized to Placebo - 5 mg - 10 mg	
2	EX2	TA	P-5-10	Placebo-5mg-10mg	First Treatment Epoch	2	P	Placebo		
3	EX2	TA	P-5-10	Placebo-5mg-10mg	First Rest Epoch	3	REST	Rest		
4	EX2	TA	P-5-10	Placebo-5mg-10mg	Second Treatment Epoch	4	5	5 mg		
5	EX2	TA	P-5-10	Placebo-5mg-10mg	Second Rest Epoch	5	REST	Rest		
6	EX2	TA	P-5-10	Placebo-5mg-10mg	Third Treatment Epoch	6	10	10 mg		
7	EX2	TA	P-5-10	Placebo-5mg-10mg	Follow-up Epoch	7	FU	Follow-up		
8	EX2	TA	5-P-10	5mg-Placebo-10mg	Screen Epoch	1	SCRN	Screen	Randomized to 5 mg - Placebo - 10 mg	
9	EX2	TA	5-P-10	5mg-Placebo-10mg	First Treatment Epoch	2	5	5 mg		
10	EX2	TA	5-P-10	5mg-Placebo-10mg	First Rest Epoch	3	REST	Rest		
11	EX2	TA	5-P-10	5mg-Placebo-10mg	Second Treatment Epoch	4	P	Placebo		
12	EX2	TA	5-P-10	5mg-Placebo-10mg	Second Rest Epoch	5	REST	Rest		
13	EX2	TA	5-P-10	5mg-Placebo-10mg	Third Treatment Epoch	6	10	10 mg		
14	EX2	TA	5-P-10	5mg-Placebo-10mg	Follow-up Epoch	7	FU	Follow-up		
15	EX2	TA	5-10-P	5mg-10mg-Placebo	Screen Epoch	1	SCRN	Screen	Randomized to 5 mg - 10 mg – Placebo	
16	EX2	TA	5-10-P	5mg-10mg-Placebo	First Treatment Epoch	2	5	5 mg		
17	EX2	TA	5-10-P	5mg-10mg-Placebo	First Rest Epoch	3	REST	Rest		
18	EX2	TA	5-10-P	5mg-10mg-Placebo	Second Treatment Epoch	4	10	10 mg		
19	EX2	TA	5-10-P	5mg-10mg-Placebo	Second Rest Epoch	5	REST	Rest		
20	EX2	TA	5-10-P	5mg-10mg-Placebo	Third Treatment Epoch	6	P	Placebo		
21	EX2	TA	5-10-P	5mg-10mg-Placebo	Follow-up Epoch	7	FU	Follow-up		

Example 3: Multiple Branches Trial Design





Trial Design Matrix 3

Trial Design Matrix for Example Trial 3

	Screen	Double Blind	Open Label
A-Open A	Screen	Treatment A	Open DRUG X
A-Rescue	Screen	Treatment A	Rescue
B-Open A	Screen	Treatment B	Open DRUG X
B-Rescue	Screen	Treatment B	Rescue

Trial Arms Dataset for Example Trial 3

Row	STUDYID	DOMAIN	ARMCD	ARM	EPOCH	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS
1	EX3	TA	AA	A-Open A	Screen	1	SCRN	Screen	Randomized to Treatment A	
2	EX3	TA	AA	A-Open A	Double Blind	2	DBA	Treatment A	Assigned to Open DRUG X on basis of response evaluation	
3	EX3	TA	AA	A-Open A	Open Label	3	OA	Open DRUG X		
4	EX3	TA	AR	A-Rescue	Screen	1	SCRN	Screen	Randomized to Treatment A	
5	EX3	TA	AR	A-Rescue	Double Blind	2	DBA	Treatment A	Assigned to Rescue on basis of response evaluation	
6	EX3	TA	AR	A-Rescue	Open Label	3	RSC	Rescue		
7	EX3	TA	BA	B-Open A	Screen	1	SCRN	Screen	Randomized to Treatment B	
8	EX3	TA	BA	B-Open A	Double Blind	2	DBB	Treatment B	Assigned to Open DRUG X on basis of response evaluation	
9	EX3	TA	BA	B-Open A	Open Label	3	OA	Open DRUG X		
10	EX3	TA	BR	B-Rescue	Screen	1	SCRN	Screen	Randomized to Treatment B	
11	EX3	TA	BR	B-Rescue	Double Blind	2	DBB	Treatment B	Assigned to Rescue on basis of response evaluation	
12	EX3	TA	BR	B-Rescue	Open Label	3	RSC	Rescue		

Implementation

- Specifies the requirements for the design of the study and is a requirement in order for the data to flow into the clinical database.
- Core Contents:
  - Epoch_and_Start_Events Tab
  - Treatment tab
  - Epoch_Tie_Breakers tab
  - Business_Rules tab

Implementation

- epoch and start event function.

A	B	D	G	H	I	J	K
EPOCH	EPOCH Sequence	Treatment Flag	Off Set	Off set Unit	EPOCH Start Event (General Description)	EPOCH Start Event	Start Event Function Name
Screening	10	N			Birth Date	SUPPDM.BRTHDTI	PH_DM_BIRTH_DATE
Metformin Run In	20	N			Visit 2 Date	SUPPSV.SVSTDTI where	PH_SV_DT_V2
Placebo Run In	30	N			Date of first non-zero dose from label A or B	MIN SUPPEX.EXSTDTI where EX.EXSPID IN (A,B) AND	PH_EX_ST_DT_MIN_NZ_A_B
Treatment I	40	Y			Date of first non-zero dose bottles C,D,E,F	MIN SUPPEX.EXSTDTI where EX.EXSPID IN (C,D,E,F) AND	PH_EX_ST_DT_MIN_NZ_CDEF
Post-Treatment I	50	N	5	day	For subjects with a status of discontinued or completed use the maximum Date of the last non-zero dose (Label	MAX SUPPEX.EXENDTI where (EX.EXSPID IN (C,D,E,F) AND SUPPEX.EXNUMDOS <> 0) AND DS.DSSCAT = ('DISCONTINUED') or	PH_EX_EN_DT_MAX_NZ_C2F_DSC_CMP

Implementation

- tie-breaker rules

A	B	C	D	E	F
SDTM Domain Name	Early EPOCH Name	Late EPOCH Name	Assigned To EPOCH Name	Tie-Breaker Qualifier	Tie-Breaker Value
AE	Pre-Study	Treatment	Treatment	None	None
CM	Pre-Study	Treatment	Treatment	STRF	DURING
EX	Pre-Study	Treatment	Treatment	None	None
DS	Pre-Study	Treatment	Treatment	None	None

Implementation

- VALIDATING BUSINESS RULE
  - (1) Import the Setup Specifications by reading in the Epoch_and_Start_Events sheet.
  - (2) Count the total number of distinct epochs listed in the Setup Specification.

```
PROC IMPORT OUT=WORK.MSS
            DATAFILE= "&uatdirxls\&mssfile"
            DBMS=EXCEL REPLACE;
     SHEET="Epoch_and_Start_Events$";
     GETNAMES=YES;
     MIXED=NO;
     SCANTEXT=YES;
     USEDATE=YES;
     SCANTIME=YES;
Run;


data _null_;
      set mss end=eof;
      where epoch ne ' ';
      call symput('epoch'||left( n ),left(epoch));
       call symput('seq'||left(_n_), left(epoch_sequence));
      if eof then call symput('totepoch',left(_n_));
run;
```

Implementation

- VALIDATING BUSINESS RULE
  - (3) The macro reads in the data from the SE domain and transposes it to make one Subject, one record to include all the Actual Elements for each Subject including.

Subject	Trial Epoch	sestdat	sesttime1	sestdti1	seendate1	seentime1	seendti1	Trial Epoch	sestdate2	sesttime2	sestdti2	seendate2	seentime
00200005	Pre-Study	871	.	75254400	17776	47100	1535683500	Treatment	17776	47100	1535683600	17782	72300
00200006	Pre-Study	-3501	.	-302486400	17730	48660	1531920660	Treatment	17730	48660	1531920660	.	.
00200007	Pre-Study	700	.	60480000	17666	70500	1526412900	Treatment	17666	70500	1526412900	17667	70500
00200008	Pre-Study	349	.	30153600	.	.	.	.	.	.	.	.	.
00200018	Pre-Study	3349	.	289353600	17785	54300	1536678300	Treatment	17785	54300	1536678300	.	.

```
%do j=1 %to &totepoch;
    data se&j;
       set uatsddub.se;
       if epoch="&&epoch&j";
           if sestdti ne '' then do;
                 sestdate&j=input(sestdti,is8601da.);
                 sesttime&j=input(scan(sestdti,2,'T'), time8.);
                sestdti&j=sum(input(sestdti,is8601da.)*24*60*60,
                              input(scan(sestdti,2,'T'), time8.));
           end;
                                    data new_se;
                                       merge
                                       %do j=1 %to &totepoch;
                                         se&j
                                       %end;;
                                        by usubjid ;
                                    run;
```

Implementation

- VALIDATING BUSINESS RULE
  - (4) Test to see if there are any Subjects existing in other domains, but without any records in the SE domain. If so, there's a mismatched epoch in the tested domain.

```
data nose_frm_domain;
   merge domain1(in=inae) se1(in=inse);
   by usubjid;
   if inae and not inse;
   myepoch=' ';
   if epoch ne myepoch then flag1="mis-match EPOCH in &domain.domain";
run;
```

Implementation

- VALIDATING BUSINESS RULE
  - (5) Test to see if there's a tie between epochs which need to follow the metadata setup specification.

```
data check_dom;
   merge domain1 new_se1;
   by usubjid;
   length flag $20;
   %if %upcase(&domain)=CM %then %do;
       if upcase(CMSTRF)='DURING' then do;
          if startdt='' then flag='';
           else do;
               if starttime=. or seentime1=. then do;
                   if startdate=seendate1 then flag='tie at epoch1';
              end;
               else do;
                  if startdt=seendti1 then flag='tie at epoch1';
                   else flag='no tie';
               end;
          end;
       end;
        else do;
          flag='no tie';
      end;
       keep usubjid subjid epoch1-epoch4 sestdti1-sestdti4 seendti1-
            seendti4 startdt flag epoch &domain.stdti CMSTRF;
    %end;
```

Implementation

- VALIDATING BUSINESS RULE
  - (6) Derive v-epoch, comparing the derivations and self derivations.

```
data myepoch;
  length myepoch $200.;
  set check_dom;
     if flag='tie at epoch1' then do;
        if epoch2 ne ' ' then myepoch=epoch2;
     end;
     else do;
        if nmiss(seendti1, seendti2, seendti3) =0 then do;
           if sestdti1< &domain.start <=seendti1 then myepoch=epoch1;
            else if sestdti2< &domain.start <=seendti2 then
                  myepoch=epoch2;
           else if sestdti3< &domain.start <=seendti3 then
                  myepoch=epoch3;
                else if &domain.start > sestdti4 then myepoch=epoch4;
               end;
              …
               if &domain.epoch ne myepoch then flag1="mis-match EPOCH in
      &domain. domain";
 run;
```

Challenges

- Create TDM datasets (prospective or retrospective?)
  - finding the information needed for an accurate representation of the study.
  - Creating TDM tables can be as much of an art as it is a science
  - Keep consistency across domains

- Reference:

  - CDISC SDTM Implementation Guide (Version 3.1.3)
  - FDA Guidance for Human Clinical Trials
  - Clinical Trials Terminology Version 2.0, CDISC.
  - CDISC Study Design Model in XML (SDM-XML)

Q&A

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