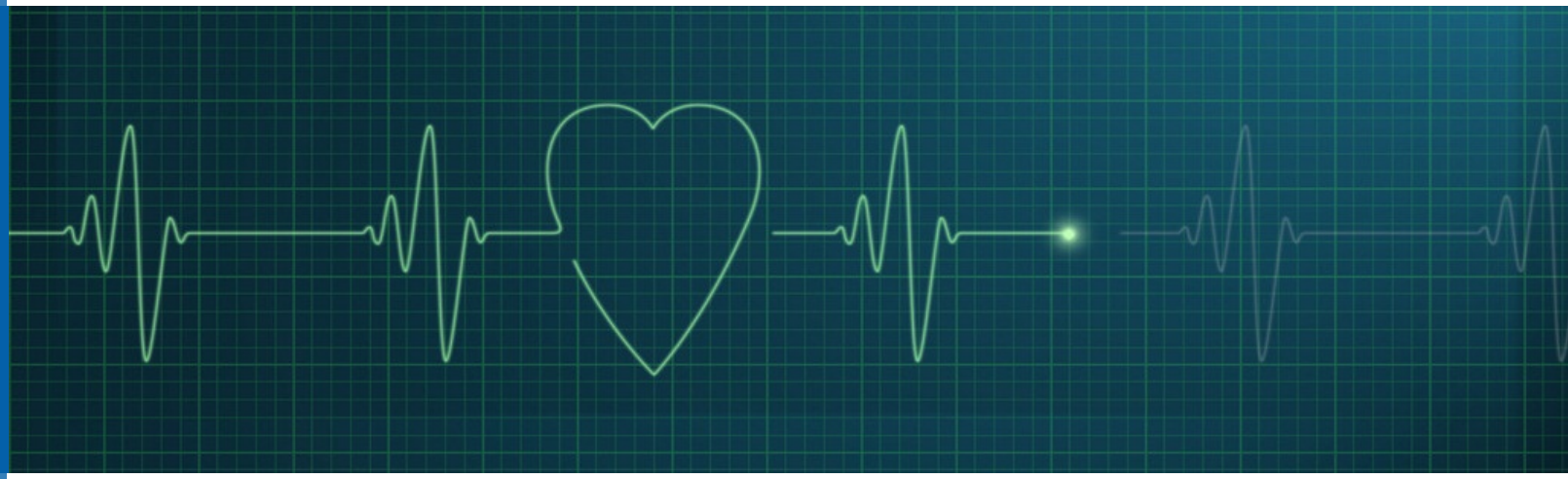
Cardiovascular Disease



Recurrent Events

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Outline

- ❑ Background
- ❑ Analysis Needs
- ❑ Challenge
- ❑ Solutions

Background

Concept 1. Recurrent Event

Concept 2. Cardiovascular Endpoint

Concept 3. Composite Endpoint

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Background

Concept 1. Recurrent Event

An event that occurs more than once per subject over time.

Examples: multiple relapse from remission for leukemia patients, repeated heart attacks, recurrence of bladder cancer tumors

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Background

Concept 2. Cardiovascular Endpoint

- Death
- Heart Failure Event (HF)
- Transient Ischemic Attack (TIA) and Stroke
- Myocardial Infarction (MI)
- Unstable Angina Hospitalization Event (UA)

etc.

Background

Concept 3. Composite Endpoint

Example 1. Composite endpoint of CV death and HF hospitalization;

Example 2. Composite endpoint of CV death, MI and Stroke.

Example 3. Composite endpoint of CV death, MI, stroke and HF hospitalization

etc.

Analysis Needs

```
PROC PHREG DATA=<DATA SET NAME> OPTION;
  CLASS ...;
  MODEL (<START VALUE>, <STOP VALUE>)*CNSR(1) = <COVARIATES LIST>;
  ID USUBJID;
  ESTIMATE ...;
  LSMEANS ...;
RUN;
```

Statistical model

USUBJID	Event Index	Start value	End value	Indicator (0=event, 1=censor)
001	1	0	T1	0
001	2	T1	T2	0
001	3	T2	T3	0
001	...			
001	4	Tk	Tk+1	1
...	...			
002	1	0	T1	0
002	2	T1	T2	0

Expected analysis ready data structure

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Challenge

How to prepare an ADaM for this expected data structure???

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Challenge

USUBJID	Event Index	Start value	End value	Indicator (0=event, 1=censor)
001	1	0	T1	0
001	2	T1	T2	0
001	3	T2	T3	0
001	...			
001	4	Tk	Tk+1	1
...	...			
002	1	0	T1	0
002	2	T1	T2	0

Challenge

USUBJID	Event Index	Start value	End value	Indicator (0=event, 1=censor)
001	1	0	T1	0
001	2	T1	T2	0
002	1	0	T1	0
002	2	T1	T2	0

One record for each subject, each event.
However two analysis values associated.

Potential Solutions

Solution 1. Go with a strict BDS structure?

-> Only to keep AVAL for the stop value;

-> start value to be populated at reporting level

Potential Solutions

Solution 2. Go with an ODS structure?

-> with ASTVAL / AENVAL “invented”

Our Solution

Go with a TTE structure.

-> non-BDS compliant, despite BDS-like.

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Our Solution

Metadata

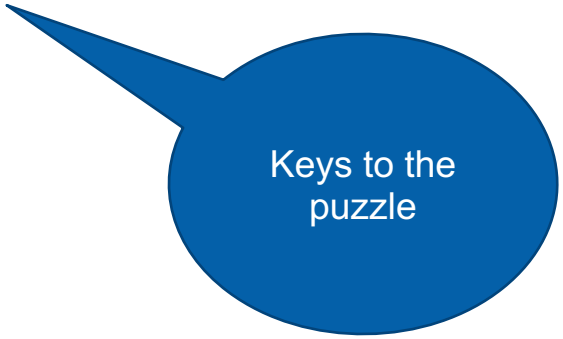
Dataset	Description	Class	Structure	Purpose	Keys
ADTTRE	Recurrent of HFHOSP and CV Death	BDS	One record per subject per parameter per censor indicator per event occurrence	Analysis	STUDYID, USUBJID, PARAMCD, ENUM, CNSR

Variable	Label	Type	Format	Comment
CNSR	Censor	Num		0 for Event, 1 for Censor
CNSDTDSC	Censor Date Description	Char		
EVNTDESC	Event or Censoring Description	Char		
ASEQ	Analysis Sequence Number	Num		Event order
STARTDT	Time to Event Origin Date for Subject	Num	e8601da.	Start date (RANDDT if first occurrence; else ADT of previous event)
ADT	Analysis Date	Num	e8601da.	Stop date -> source for stop value
STARTVAL	Analysis Start Value	Num		Start value
AVAL	Analysis Value	Num		Stop value

Our Solution

Metadata

Variable	Label	Comment
ASEQ	Analysis Sequence Number	Event order
STARTVAL	Analysis Start Value	Start value
AVAL	Analysis Value	Stop value = ADT–RANDDT (+1)



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Our Solution

Data Examples

Composite endpoint of CV death and HF hospitalization (HFHOSP)

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Our Solution

Data Examples

Subject 001 has no HFHOSP, and died due to CV cause

adenp

USUBJID	CEREFID	CEEVAL	CETERM	CEOCCUR	CESTDTC	ASTDT
001	ABC001A	CEC ADJUDICATOR	Death	Y	2017-01-10	2017-01-10

adsl

USUBJID	RANDFL	RANDDT	LSTALVDT	DTHCAUS
001	Y	2017-01-01	2017-01-05	CV

adttrre

USUBJID	CEREFID	RANDFL	DTHCAUS	STARTDT	ADT	CNSR	ASEQ	STARTVAL	AVAL
001	ABC001A	Y	CV	2017-01-01	2017-01-10	0	1	0	9

Our Solution

Data Examples

Subject 002 has no HFHOSP, and died due to “NON-CV”

adenp

USUBJID	CEREFID	CEEVAL	CETERM	CEOCCUR	CESTDTC	ASTDT
002	ABC002A	CEC ADJUDICATOR	Death	Y	2017-01-10	2017-01-10

adsl

USUBJID	RANDFL	RANDDT	LSTALVDT	DTHCAUS
002	Y	2017-01-01	2017-01-05	NON-CV

adttrre

USUBJID	CEREFID	RANDFL	DTHCAUS	STARTDT	ADT	CNSR	ASEQ	STARTVAL	AVAL
002	ABC002A	Y	NON-CV	2017-01-01	2017-01-10	1	1	0	9

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Our Solution

Data Examples

Subject 003 has no HFHOSP, and still alive at the study cutoff date (Nov 02, 2017)

adenp

USUBJID	CEREFID	CEEVAL	CETERM	CEOCCUR	CESTDTC	ASTDT
003	ABC003A	CEC ADJUDICATOR	HF hospitalization	N		.

adsl

USUBJID	RANDFL	RANDDT	LSTALVDT	DTHCAUS
003	Y	2017-01-01	2017-11-02	

adttrre

USUBJID	CEREFID	RANDFL	DTHCAUS	STARTDT	ADT	CNSR	ASEQ	STARTVAL	AVAL
003	ABC003A	Y		2017-01-01	2017-11-02	1	1	0	305

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Data Examples

Subject 004 has 2 HFHOSP, and then a CV death

adenp

USUBJID	CEREFID	CEEVAL	CETERM	CEOCCUR	CESTDTC	ASTDT
004	ABC004A	CEC ADJUDICATOR	HF hospitalization	Y	2017-01-05	2017-01-05
004	ABC004B	CEC ADJUDICATOR	HF hospitalization	Y	2017-02-01	2017-02-01
004	ABC004C	CEC ADJUDICATOR	Death	Y	2017-02-10	2017-02-10

adsl

USUBJID	RANDFL	RANDDT	LSTALVDT	DTHCAUS
004	Y	2017-01-01	.	CV

adttrre

USUBJID	CEREFID	RANDFL	DTHCAUS	STARTDT	ADT	CNSR	ASEQ	STARTVAL	AVAL
004	ABC004A	Y	CV	2017-01-01	2017-01-05	0	1	0	4
004	ABC004B	Y	CV	2017-01-05	2017-02-01	0	2	4	31
004	ABC004C	Y	CV	2017-02-01	2017-02-10	0	3	31	40

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Our Solution

Data Examples

Subject 005 has 2 HFHOSP, and alive at the study cutoff date (Nov 02, 2017)

adenp

USUBJID	CEREFID	CEEVAL	CETERM	CEOCCUR	CESTDTC	ASTDT
005	ABC005A	CEC ADJUDICATOR	HF hospitalization	Y	2017-01-05	2017-01-05
005	ABC005B	CEC ADJUDICATOR	HF hospitalization	Y	2017-02-01	2017-02-01

adsl

USUBJID	RANDFL	RANDDT	LSTALVDT	DTHCAUS
005	Y	2017-01-01	2017-11-02	

adttrre

USUBJID	CEREFID	RANDFL	DTHCAUS	STARTDT	ADT	CNSR	ASEQ	STARTVAL	AVAL
005	ABC005A	Y		2017-01-01	2017-01-05	0	1	0	4
005	ABC005B	Y		2017-01-05	2017-02-01	0	2	4	31
005		Y		2017-02-01	2017-11-02	1	3	31	305

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Our Solution

Points to Consider

1. Reported event versus adjudication
2. Partial event date
3. Censoring dates
4. Study cutoff date
5. Traceability
6. What if the components (CV death and HFHOSP) are on the same date?

Our Solution

Extensions

1. Extensible to other composites, which is to be defined with a different PARAM & PARAMCD
2. Extensible to endpoint reported by investigators (not CEC), to support sensitivity analyses

Thank you

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