Advancing Clinical Trial Analysis: Bridging Gaps in Hierarchical Composite Endpoints Implementation

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Meet the Speaker

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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *The author has no real or apparent conflicts of interest to report.*

Agenda

1. Summary of Hierarchical Composite Endpoints (HCEs)
2. Implementation of HCEs in ADaM
3. Suggesting a Standardized CDISC Implementation of HCEs
4. Setting up working group

Summary of Hierarchical Composite Endpoints (HCEs)

Theory and Use

Hierarchical Composite Endpoints

- Ordinal ranking of two or more individual endpoints
  - From e.g most severe to least severe
  - Choose most severe event for each subject
- Complex and novel
  - Clinically & programmatically
  - CDISC adherence
  - ADaM implementation incomplete
  - Increased recent usage
- Win statistics and Maraca plot
- Can include endpoints of different types
  - Death events. Laboratory values. Symptom summary score
  - Time-to-Event (within an event)
    - Sooner event is worse

Outcome	Rank	TTE / Value
"Worst"	1	yy
"2nd Worst"	2	yy
…	…	…
"Best"	n	zz

Implementation of HCEs in ADaM

Practical example

Key Details

Kidney HCE. Two treatment groups. Fixed follow-up. No dropouts

Rank	Outcome	Subcategorization	Favorability	Source
1	Death	Timing (later is better)	Worst	ADTTE
2	Dialysis	Timing		ADTTE
3	Sustained eGFR<15	Timing		ADTTE
4	Sustained >=57% eGFR decline	Timing		ADTTE
5	Sustained >=50% eGFR decline	Timing		ADTTE
6	Sustained >=40% eGFR decline	Timing		ADTTE
7	Individual rate of change of GFR	Actual values (higher is better)	Best	ADLB

Hierarchical Composite Endpoints Specification (1/2)

Variable Name	Variable Label	Codelist/ Controlled Terms	Source / Derivation
name	*description*	*valid values or codes and decodes*	*where the variable came from in the source data or how the variable was derived*
SUBJID	Subject Identifier for the Study		ADSL.SUBJID
TRTP	Planned Treatment	A, P	ADSL.TRT01P
AVAL	Analysis Value		First, identify participants with any of the 1-6 dichotomous events by selecting the PARAM value in ADTTE corresponding to this event. Then select the most severe event of a participant and the corresponding timing of the event from ADTTE.AVAL. If ADTTE.PARAM="All-cause death" and ADTTE.CSNR=0 then ADHCE.AVAL = 0*ADTTE.PADY + ADTTE.AVAL Else if ADTTE.PARAM="Dialysis" and ADTTE.CSNR=0 then ADHCE.AVAL = 1*ADTTE.PADY + ADTTE.AVAL and so on. Here we are using the numeric rank (minus one) of each type of an event, 0 for death, 1 for dialysis and so on, following the order of the outcomes. If the participant did not experience any of the outcomes in 1-6 then these participants fall into category 7. Select records from ADLB with PARAM = "Rate of change of GFR" AVAL will be derived as, ADHCE.AVAL = 6*ADTTE.PADY + ADLB.AVAL – m+1, where m is the minimum of all values ADLB.AVAL(PARAM = "Rate of change of GFR") for participants who did not have any of the dichotomous events.

PADY – Last study day included in the analysis (duration of the fixed follow-up)

Hierarchical Composite Endpoints Specification (2/2)

Variable Name	Variable Label	Codelist / Controlled Terms	Source / Derivation
name	*description*	*valid values or codes and decodes*	*where the variable came from in the source data or how the variable was derived*
HCEGR1	HCE Group 1	"Death", "Dialysis", "eGFR < 15", "eGFR >= 57%", "eGFR >= 50%", "eGFR >= 40%", "eGFR"	If the result comes from ADTTE, then set to ADTTE.PARAM Else if ADLB.PARAM = "Rate of change of GFR" then HCEGR1 = "eGFR"
HCEGR1N	HCE Group 1 (N)		if HCEGR1 = "Death" then HCEGR1N = 1 Else if HCEGR1 = "Dialysis" then HCEGR1N = 2 Else if HCEGR1 = "eGFR < 15" then HCEGR1N = 3 Else if HCEGR1 = "eGFR >= 57%" then HCEGR1N = 4 Else if HCEGR1 = "eGFR >= 50%" then HCEGR1N = 5 Else if HCEGR1 = "eGFR >= 40%" then HCEGR1N = 6 Else if HCEGR1 = "eGFR" then HCEGR1N= 7
PADY	Primary Analysis Day		ADSL.PADY

Hierarchical Composite Endpoints

- Most severe event chosen per subject
- PADY: Primary Analysis Day
- AVAL for subsequent outcome immediately follows previous one
- AVAL (in derivation): TTE or value of continuous outcome variable
- HCEGR1: Most severe outcome per subject
- Additional core BDS variables

AVAL	HCEGR1
0*PADY+AVAL	Death
1*PADY+AVAL	Dialysis
…..	
n*PADY+AVAL-m+1	eGFR

Outcome	Rank	TTE / Value
“Worst”	1	yy
“2nd Worst”	2	yy
…	…	…
“Best”	n	zz

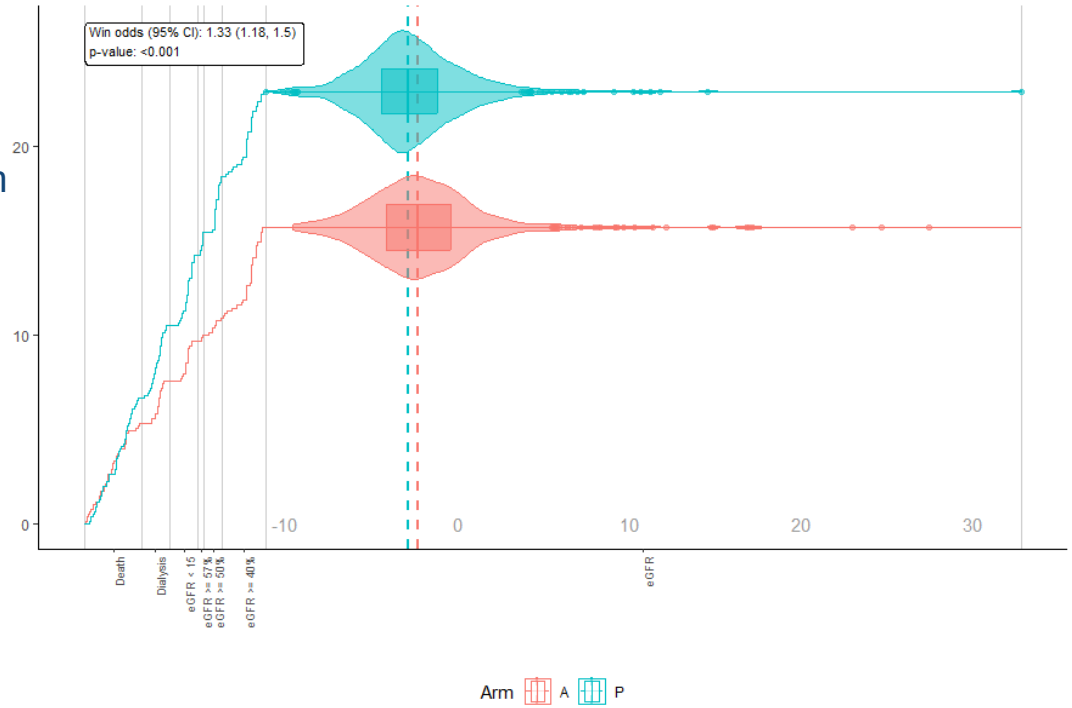
Hierarchical Composite Endpoints

SUBJID	TRTP	AVAL	HCEGR1	HCEGR1N	PADY	PARAM	PARAMCD
001	A	20	Death	1	100	Kidney hierarchical composite endpoint	KHCE
002	B	120	Dialysis	2	100	Kidney hierarchical composite endpoint	KHCE

Subject 001: Died on day 20
Subject 002: eGFR>=50% decline on day 10. Dialysis on day 20

Maraca Plot

- Win odds
  - Each patient's outcome in the active treatment arm is compared to each patient's outcome in the placebo arm
  - Results in a win, a tie or a loss
  - Proportion of wins plus half of all ties



Suggesting a Standardized CDISC Implementation of HCEs

Core ideas and considerations

Core Ideas

- TTE: BDS + Additional TTE variables
  - Specific details for certain variables (e.g. AVAL)
- HCE: BDS + Additional HCE variables (incorporating TTE variables)
  - Needs to consider the differences in possible endpoint data
- Possible endpoint data types:
  - Binary/categorical
    - Time-to-event
  - Numerical (lab values)
- Cover all possible combinations of endpoints

Table 3.3.6.1 Time-to-Event Variables for BDS Datasets

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core
STARTDT	Time-to-Event Origin Date for Subject	Num		Perm
STARTDTM	Time-to-Event Origin Datetime	Num		Perm
STARTDTF	Origin Date Imputation Flag	Char	(DATEFL)	Cond
STARTTMF	Origin Time Imputation Flag	Char	(TIMEFL)	Cond

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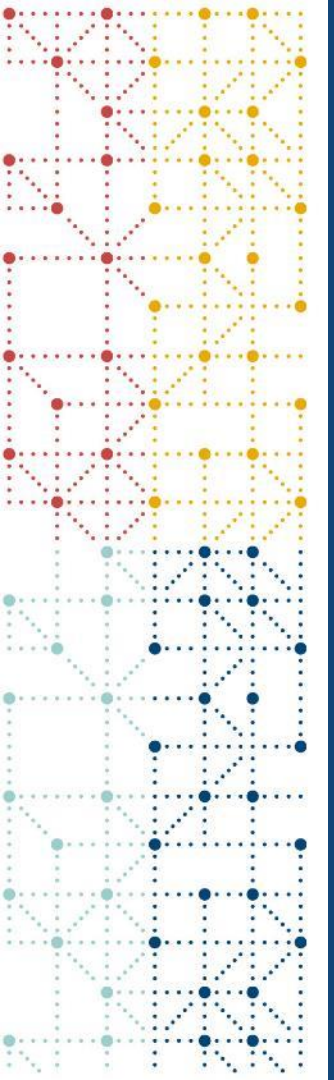
CDISC Analysis Data Model Implementation Guide (1.3 Final)

Variable Name	Variable Label	Type	Codelist/ Controlled Terms	Core
CNSR	Censor	Num		Cond
EVNTDESC	Event or Censoring Description	Char		Perm
CNSDTDSC	Censor Date Description	Char		Perm

Considerations

- Pairwise comparisons in ADaM dataset
- Cases without fixed follow-up
- Separate document or append to existing? Both?
  - ADaM BDS for TTE Analyses
    - Addition
  - Examples in Commonly Used Statistical Analysis Methods
- Simplicity and extensibility
- R-implementation
  - PHUSE US 2024 presentation



Setting up working group

Collaboration is needed

HCE Working Group

- Create CDISC HCE implementation documents
  - Approach dependent on outcome of collaboration
- Combine experience from:
  - Theory
  - Existing CDISC documents
  - Clinical trial experience
- Working Group structure, timeline and "mode of action" TBD

Thank You!