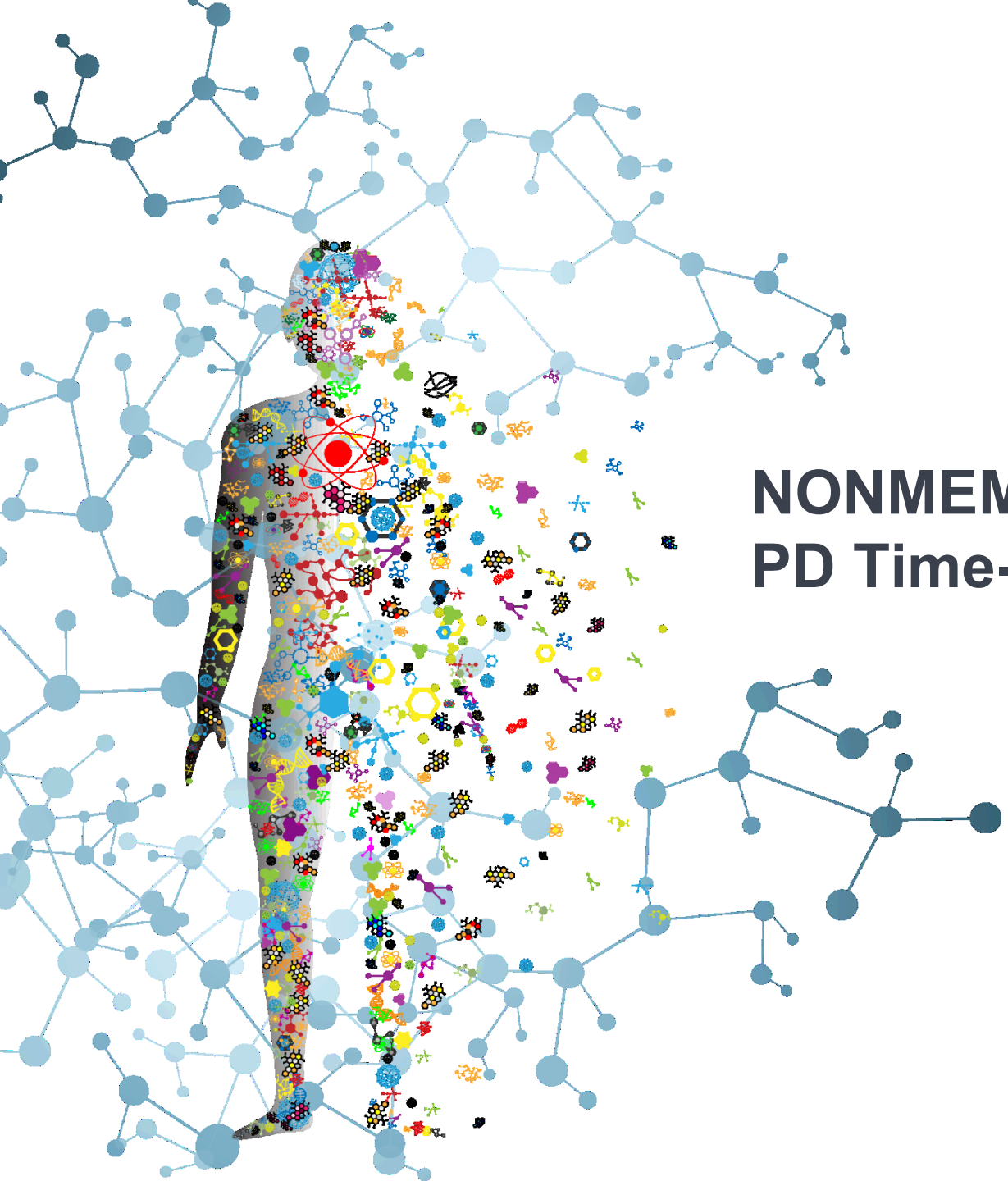


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# NONMEM to NLME: PD Time-to-Event Data

# Agenda

- Model Description
- Input Data
- Exploratory Data Analysis
- Model in NM-TRAN and PML Code
- Demo
- Summary
- Q&A


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# NONMEM to NLME: time-to-event

- Model Description
  - Structural Model
    - Survival Model
  - Error model
    - No error model – no deterministic model
  - Structural Parameters
    - PD: D50
  - Random Effect
    - Variance: negligible
  - Engine
    - Laplacian

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# time-to-event: Input Data

## NONMEM

| | ID | TIME | Event | MDV | DOSE |
|---|---|---|---|---|---|
| 1 | 1 | 0 | . | 1 | 0 |
| 2 | 1 | 286 | 1 | 0 | 0 |
| 3 | 2 | 0 | . | 1 | 0 |
| 4 | 2 | 252 | 1 | 0 | 0 |
| 5 | 3 | 0 | . | 1 | 0 |
| 6 | 3 | 28 | 1 | 0 | 0 |
| 7 | 4 | 0 | . | 1 | 0 |
| 8 | 4 | 34 | 1 | 0 | 0 |
| 9 | 5 | 0 | . | 1 | 0 |
| 10 | 5 | 6 | 1 | 0 | 0 |
| 11 | 6 | 0 | . | 1 | 0 |
| 12 | 6 | 68 | 1 | 0 | 0 |
| 13 | 7 | 0 | . | 1 | 0 |
| 14 | 7 | 580 | 1 | 0 | 0 |
| 15 | 8 | 0 | . | 1 | 0 |
| 16 | 8 | 46 | 1 | 0 | 0 |
| 17 | 9 | 0 | . | 1 | 0 |
| 18 | 9 | 176 | 1 | 0 | 0 |

## NLME

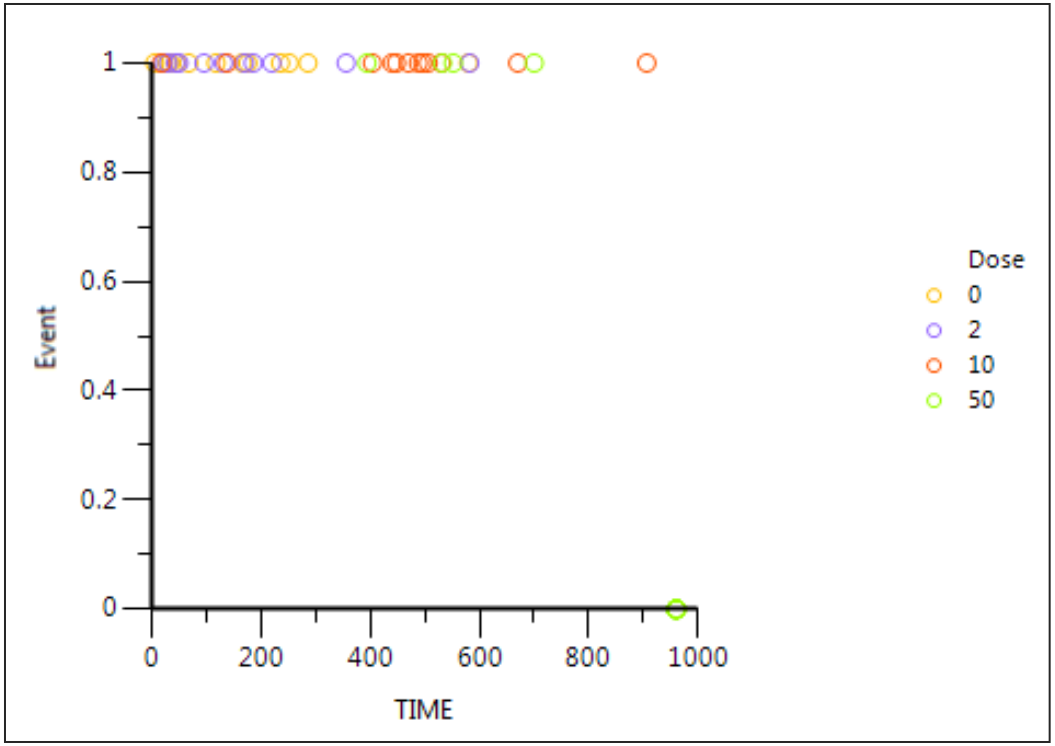
| | ID | TIME | Event | DOSE |
|---|---|---|---|---|
| 1 | 1 | 286 | 1 | 0 |
| 2 | 2 | 252 | 1 | 0 |
| 3 | 3 | 28 | 1 | 0 |
| 4 | 4 | 34 | 1 | 0 |
| 5 | 5 | 6 | 1 | 0 |
| 6 | 6 | 68 | 1 | 0 |
| 7 | 7 | 580 | 1 | 0 |
| 8 | 8 | 46 | 1 | 0 |
| 9 | 9 | 176 | 1 | 0 |
| 10 | 10 | 236 | 1 | 0 |
| 11 | 11 | 166 | 1 | 0 |
| 12 | 12 | 118 | 1 | 0 |
| 13 | 13 | 186 | 1 | 2 |
| 14 | 14 | 50 | 1 | 2 |
| 15 | 15 | 220 | 1 | 2 |
| 16 | 16 | 960 | 0 | 2 |
| 17 | 17 | 96 | 1 | 2 |
| 18 | 18 | 22 | 1 | 2 |
| 19 | 19 | 132 | 1 | 2 |

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# Plot: time-to-event

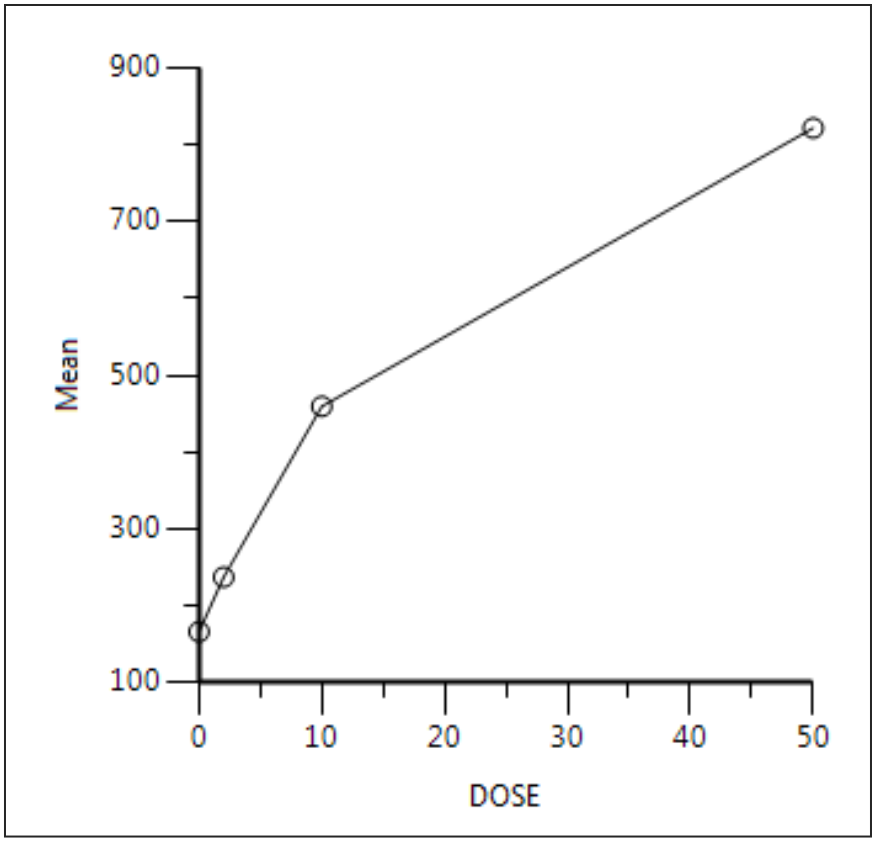
- Event versus Time:




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# Plot: time-to-event

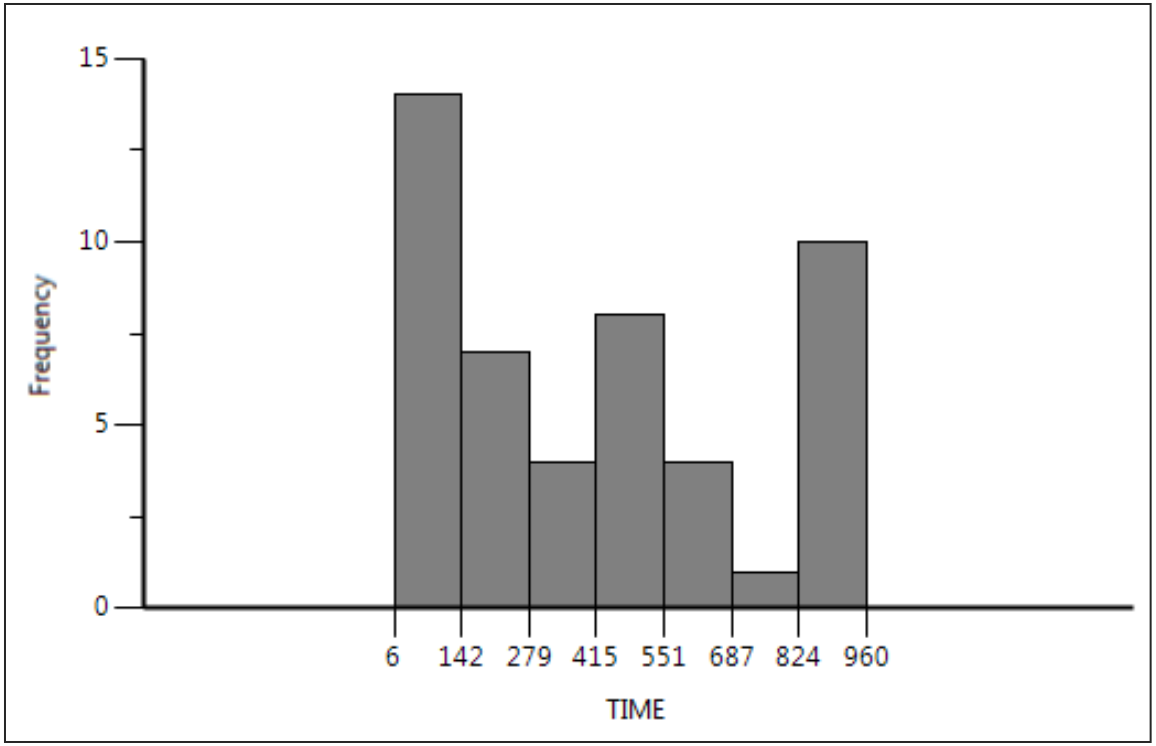
- Mean Event Time versus Dose:




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# Plot: time-to-event

- Frequency of Events over Time:




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# NONMEM to NLME: time-to-event

## NONMEM

```
;Input
$INPUT ID TIME Event=DV DOSE
$SUBR ADVAN=6 TOL=9
$MODEL
COMP=(CUMHAZ)
$DES
DADT(1)=THETA(1)*(1-
DOSE/(DOSE+THETA(2)))
$PK
HAZ=THETA(1)*(1-
DOSE/(DOSE+THETA(2)))
D50=THETA(2)
DUM=THETA(3)+Eta(1)
```

## NLME

```
#Input
fcovariate(DOSE())

stparm(haz = tvhaz * (1-
DOSE/(DOSE+D50))*exp(nhaz))
stparm(D50 = tvD50 * exp(nD50))
```

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# NONMEM to NLME: time-to-event

## NONMEM

```
; Estimation Code
IF (DV.EQ.0) THEN
Y=EXP(-CUMHAZ)
ENDIF

IF (DV.EQ.1) THEN
HAZNOW=THETA(1)*(1-
DOSE/(DOSE+THETA(2)))
Y=EXP(-CUMHAZ)*HAZNOW
ENDIF
```

## NLME

```
event(censor, haz)
```

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# NONMEM to NLME: time-to-event

## NONMEM

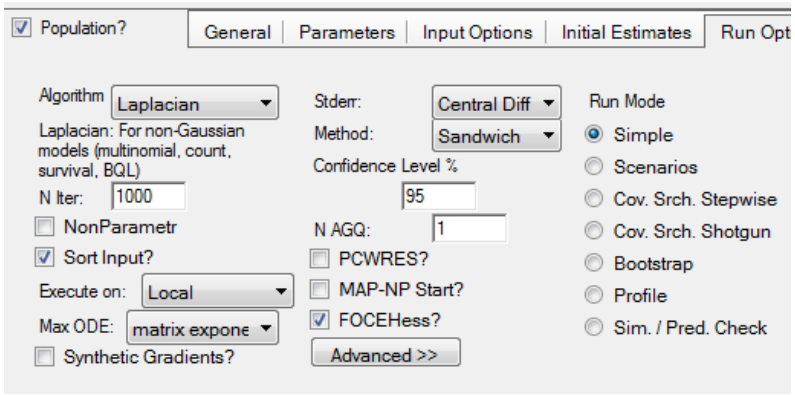
```
;fixed effects
$THETA
(0,0.01, 1) ; 1 Hazard
(0,10, 100) ; 2 D50 value
(0,1) ; 3 DUM
;random effect
$OMEGA 0 FIX ; 1 ETA_DUM

;method
$ESTIMATION SIG=3 SIGL=9
MAXEVAL=9990 METHOD=COND
LAPLACE LIKE PRINT=1
$COV MATRIX=R PRINT=E
$TABLE ID TIME EVENT
```

## NLME

```
# fixed effects
fixef(tvhaz = c(, 0.01, ))
fixef(tvD50 = c(, 20, ))


# random effect
ranef(diag(nD50, nhaz) = c(0.1, 0.1))
```




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# Demo


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# Summary

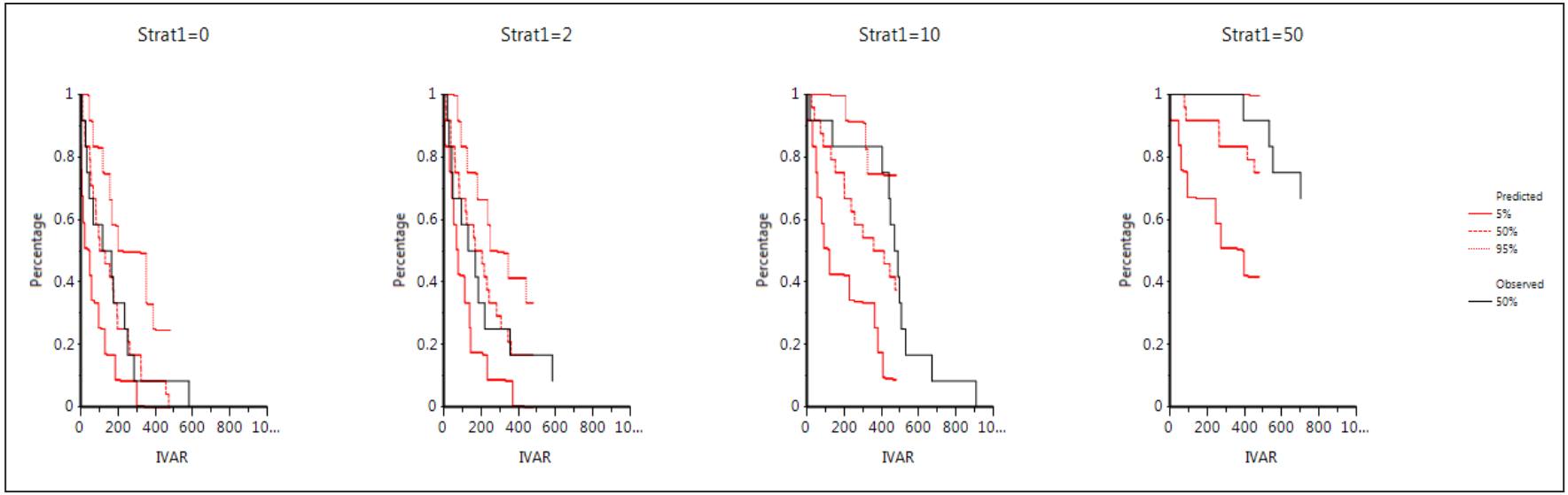
## NLME Results

| Parameter | Estimate | Stderr | CV% |
|---|---|---|---|
| tvD50 | 4.6278 | 2.87 | 62.1 |
| tvhaz | 0.0059 | 0.00 | 28.5 |

## NONMEM Results

| Method | _1_Hazard | _2_D50_value |
|---|---|---|
| Laplacian Conditional Estimation | 0.0060 | 9.24 |

## Kaplan Meier Plot




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# Questions?



# Certara University

- Link:
  - https://www.certarauniversity.com/lms
- Advanced PKPD courses:




## (302-CL) Advanced Categorical and Time-to-Event Population Modeling using Phoenix NLME

$1,495 (Academia $748)

### Course Description




This course is designed to explore advanced techniques in pharmacokinetic and pharmacodynamics modelling and simulation using categorical, count and time-to-event data. Detailed discussion of Pharsight Modeling Language (PML) covers how the Phoenix NLME engine functions and in depth lectures on the statistical theory underlying analysis of categorical, count and time-to-event data provide the necessary background to allow for complex model development. Hands-on examples from current literature to provide a complete training experience. Topics include approaches to handling data below the limit of quantitation limit, longitudinal frequency data, repeated measures time-to-event pharmacodynamics responses, drop out models, categorical pharmacodynamics endpoints, and translating models between NONMEM and Phoenix NLME.

The fee is in US dollars and includes training materials, tea, coffee and lunch. All travel, accommodation and evening meal expenses are the responsibility of the attendee. Contact info@certarauniversity.com for academic discount

All attendees are required to provide their own laptop for use during the course. Please bring a computer mouse.

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# Coming up…




NONMEM-NLME Comparisons
PD count analysis
December 13, 2018 | 10am EST
*Presenter: Bernd Wendt*

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