Management of dropout during Exercise Tolerance Test

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Introduction

- Exercise Tolerance Tests (ETT) are used to assess the effect of heart rate (HR) lowering agents during effort.
- Usually, for safety and ethical reasons, each subject can stop the exercise at his own convenience.
- Therefore, missing data due to dropout can be generated, especially when high values of heart rate are reached. This may lead to a possible misinterpretation in model evaluation.

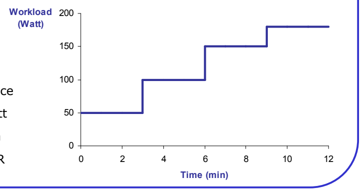
Purpose

-To illustrate that simple model evaluation can be misleading when missing at random dropout occurs

-To propose two approaches that take into account dropout in order to correctly evaluate the model.

Material

- Study design
  - 12 Healthy Volunteers
  - 1 ETT Baseline per subject (i.e before drug administration)
  - Steps of Workload (Watt): 0, 50, 100, 150, 180
  - HR measurements every minute during ETT + 1 HR at rest (supine position)
- Missing data
  - Each Subject can stop ETT at his own convenience
  - 6 HV out of 12 stopped before reaching 180 Watt
  - 10 HV out of 12 stopped before reaching 12 min
  - Missing data seem to be linked to the level of HR reached : no value over 160 bpm.
- ETT used in this study:
  - –Bicycle
  - –Increase of effort intensity every 3 min



Model without considering Dropout

PD Model (HR as a function of workload)

Different structural models have been tested (linear, Emax) using NONMEM V.The best one was a linear model.

HR=Baseline.Shift+Slope.WKLD+ε

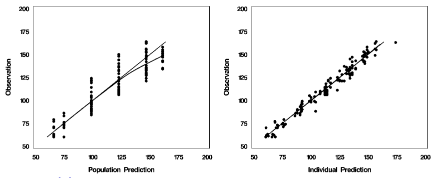
with :

- Baseline=θ_1.exp(η_1) : HR at rest (in bpm)
- Slope=θ_2.exp(η_2) : Increase of HR during ETT
- Shift=θ_3 : Shift supine/sitting position
- WKLD : Workload (in watt)
- ε : Additive Residual Error

Parameters results

	Estimate	CV (%)
Baseline	74.7	3.2
Slope	0.48	4.6
Shift	0.88	3.4
Var(η_1)	0.0069	51.4
Var(η_2)	0.0207	29.6
Cov(η_1,η_2)	0.0103	31.4
Var(ε)	28.2	14.1

Goodness of fit Plots

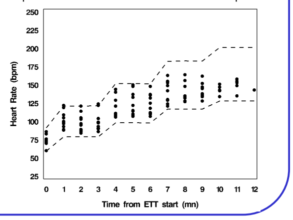


Problem

Trends in Population GOF and VPC

Visual Predictive Check

Represents the observations (dots) and the 90% prediction interval of 1000 simulated replicates



Different types of missing data (Little and Rubin, 2002)

Missing Completely At Random (MCAR):
The probability of missing is independent of observed values (no repercussion on VPC or GOF)

Missing At Random (MAR):
Missing data can be predicted based on the observed values

Missing Not At Random (MNAR):
Missing data can be predicted based both on observed and unobserved values

Considering Dropout: Approach 1

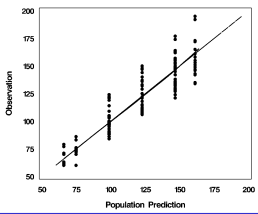
Method

Assumption: MAR dropout

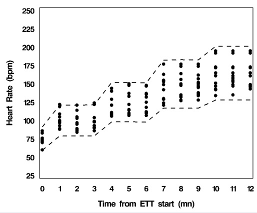
➡ Imputation of missing data using individual parameter estimates obtained from the PD model built on available observations

Results

Goodness of fit Plot



Visual Predictive Check



No longer trends in Pop GOF and VPC in our study

Support the assumption of MAR dropout

About this approach

- Appropriate in case of MAR dropout
- Easy to use
- No need to build a dropout model

Considering Dropout: Approach 2

Method

Assumption: MNAR dropout

➡ Considering dropout can have an impact on the PD model

➡ Development of a dropout model by estimating the probability of dropout at each workload.

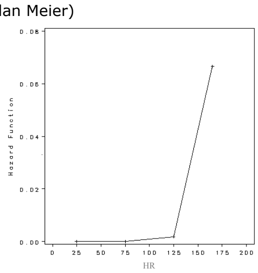
➡ With a joint estimation of the parameters of the PD model and of the dropout model.

Remark

➡ Should present no differences in the PD model in case of MCAR and MAR data

Descriptive hazard (from our study)

Estimated hazard function for dropout (Kaplan Meier)



Results

Dropout model

Considering the constraint that risk of dropout at the beginning of ETT is null, the dropout model was estimated as follow:

HAZARD=exp(Slope_H.(**HR**- Int_H))-1
IF (**HAZARD**.LE.0) **HAZARD**=0
with

Slope_H=θ_4

Int_H=θ_5

PD model

Different structural models have been tested considering dropout (linear, Emax).
The best one was still the linear model.

Parameters results

	Estimate	CV (%)
Baseline	74.4	3.1
Slope	0.48	4.7
Shift	0.88	3.4
Slope_H	0.004	66.6
Int_H	150	2.7
Var(η_1)	0.0068	50.1
Var(η_2)	0.0192	32.6
Cov(η_1,η_2)	0.0094	34.9
Var(ε)	28.2	7.1

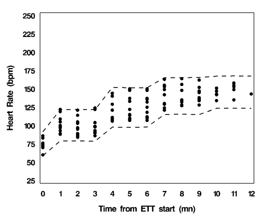
NONMEM Control file (adapted from NHG Holford)

```
$CONTR DATA=(DVID)
$SUBROUTINE ADVAN6 TOL=6
CCONTR=../CCONTR.FOR
CONTR=../CONTR.FOR
$MODEL
  COMP (CUMHAZ)
  COMP (HZLAST,INITIALOFF)
$PK
     INIV=1
     IF(TEX.EQ.0) INIV=THETA(3)
     BASE=THETA(1)*INIV*EXP(ETA(1))
     SLOPE=THETA(2)*EXP(ETA(2))
$DES
     EFFWKL=WKLSL*T
     HRP=BASE+EFFWKL
     HAZ=EXP(THETA(4)*(HRP- THETA(5)))-1
     IF (HAZ.LE.0) HAZ=0
     DADT(1)=HAZ
     DADT(2)=HAZ
$ERROR
     CMHZ=A(1); cum haz from begin to t
     HZLA=A(2); cum haz from tlast obs till t
     IF (HZLA.LE.0) HZLA=1.0D-5
     IF (CMHZ.LE.0) CMHZ=1.0D-6

     QPD=0
     NDO=0
     DO=0
     IF (DVID.EQ.2) QPD=1
     IF (DVID.EQ.3.AND.DV.EQ.0) NDO=1
     IF (DVID.EQ.3.AND.DV.EQ.1) DO=1

     IPRED=BASE+WKLSL*WKLD
     Y1=BASE+WKLSL*WKLD+THETA(6)*EPS(1)
     Y2=EXP(-CMHZ)
     Y3=EXP(-(CMHZ-HZLA))*(1-EXP(-HZLA))
     Y=Y1*QPD+Y2*NDO+Y3*DO
$EST METHOD=CONDITIONAL LAPLACE
```

Visual Predictive Check



About this approach

General approach particularly appropriate in case of MNAR dropout

Here, the dropout is MAR: no impact on the PD model and parameter estimates.

Discussion and conclusion

Impact of dropout:

- Model evaluation can be misleading when dropout occurs
- Different types of missing data -> Different approaches
- If MAR: approach 1 much easier (no dropout model needed)

In our study:

- No impact of dropout model estimation on the PD model : MAR dropout
- Model without treatment well evaluated. Will allow a better characterisation of PD model with treatment effect

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