# Population design evaluation and optimization using PFIM 3.2: application on pharmacokinetic/pharmacodynamic warfarin

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## Context

- **Nonlinear mixed effect modeling or population analysis**
  - pharmacokinetic (PK) /pharmacodynamic (PD) data
- **Population analyses often based on limited sampling strategy**
  - ethical and / or financial reasons
- **Methodology developed to ensure informative population design**
  - based on the Fisher information matrix ($M_F$)
  - expression of $M_F$ using a first order Taylor expansion of the model [1]
- **Implementation in a R function PFIM [2]**
  - R function for population design evaluation and optimization
- **Extension of this methodology for multiple response models [3]**
  - for models with parameters quantifying influence of discrete covariates [4]
  - for models including within-subject variability [5]

⟶ **Implementation in a new version PFIM 3.2 (released in January 2010)**

## Objective

- **To illustrate the use of PFIM 3.2 using an example on the PK and the PD of warfarin, an oral anticoagulant [6, 7]**

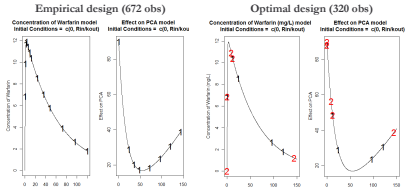
## Joint PK/PD model of warfarin

- **PK: total racemic warfarin plasma concentration**
  - single oral dose of 100 mg
  - one compartment model, first order absorption and elimination
  - exponential modeling of the random effects
- **PD: effect on prothrombin complex activity (PCA)**
  - turnover model with inhibition of the input
  - exponential modeling of the random effects

## PK/PD design on Warfarin

- **Evaluation of the empirical design**
  - one group of 32 subjects
  - 13 sampling times for PK and 7 sampling times for PD
- **Design optimization with the Federov-Wynn algorithm**
  - 32 subjects with only 5 sampling times per subject
    - ➢ common to both responses
  - sampling times from empirical design (PK + PD)

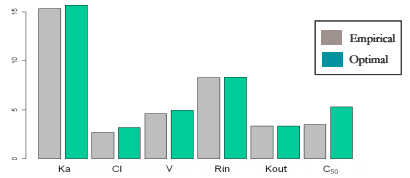
Figure 1. Empirical design versus optimal design




One group of 32 subjects — Two groups of 27 and 5 subjects

→ **2.1 less samples with optimal design than empirical design**

Figure 2. Comparison of predicted RSE for fixed effects (%)




→ **Relative standard errors (RSE) in the same range for the fixed effects**

## Pharmacogenetic on warfarin PK

- **Single nucleotide polymorphism (SNP) CYP2C9**
  - SNP on the gene of a cytochrome involved in the warfarin metabolism
  - influence of the genetic covariate on the clearance
    - clearance decrease of 50% for subjects with a mutant genotype
- **Evaluation of the optimized PK/PD design with the effect of the genetic covariate on clearance**
  - predicted power of the comparison Wald test (type I error=5%)
  - number of subjects needed (given power=90%)

Table 1. Covariate effect parameters

| Covariate | Parameter Associated | Categories | Proportions of subjects in each category (%) | β |
|---|---|---|---|---|
| CYP2C9 | CL | Wild genotype (ref) | 60 | log(0.5)=-0.69 or log(0.8)=-0.22 |
| | | Mutant genotypes | 40 | |

Figure 3 . PK/PD design evaluation output for β = log(0.5) = -0.69

```
Covariate model :

        NB: Covariates are additive on log parameters

                  Covariate 1 : CYP ( Cl )
   Categories References Proportions
(1)          W          *        0.6
(2)          M                   0.4
```

**Covariate model**

**(W=wild, M=mutant)**

```
************************* EXPECTED STANDARD ERRORS ************************

------------------------ Fixed Effects Parameters ------------------------

                  Beta    StdError       RSE
ka           1.6000000 0.2507164801 15.669780 %
V            8.0000000 0.2546378301  3.182973 %
Cl           0.1300000 0.0081193891  6.245684 %
Rin          5.4000000 0.4500934671  8.335064 %
kout         0.0600000 0.0019995041  3.332506 %
C50          1.2000000 0.0594430911  4.953591 %
beta_Cl_CYP_M -0.6931472 0.1019246011 14.704612 %
```

**Standard error and RSE of the genetic covariate effect on clearance**

```
***************************** COMPARISON TEST ******************************

                  Beta          95 % CI    exp(Beta)        95 % CI
beta_Cl_CYP_M -0.6931472 [-0.893;-0.493]          0.5 [0.409;0.611]
```

**95% confidence interval of the covariate effect**

```
Type I error = 0.05

          Expected_power Number_subjects_needed (for a given power=0.9)
beta_Cl_CYP_M      0.999999                              7.270317
```

**Expected power and number of subjects needed for the comparison Wald test**

Table 2. Results on genetic covariate effect

| β | SE (RSE %) | 95% CI(β) | exp(β) | 95% CI(exp(β)) | Expected power | Number of subjects needed |
|---|---|---|---|---|---|---|
| -0.69 | 0.10 (15) | [-0.89; -0.49] | 0.50 | [0.41; 0.61] | 1 | 8 |
| -0.22 | 0.10 (43) | [-0.41; -0.03] | 0.80 | [0.66; 0.97] | 0.63 | 64 |

→ **Increase of the number of subjects needed when the effect on the clearance decreases**

## Two-way crossover PK study on warfarin

- **Planification of a new study to assess the absence of interaction of drug X on warfarin ka**
  - two-period, two-sequence balanced crossover trial
  - inter-occasion variability on ka: $\gamma^2_{ka}$=0.3 (CV=55%)
  - expected effect of the co-medication on ka: β=log(1)=0
- **Evaluation of the empirical PK design**
  - 32 subjects
  - sampling times
    - 0.5, 1, 2, 3, 6, 9, 12, 24, 36, 48, 72, 96 and 120 hours
- **Predicted power of the bioequivalence Wald test (type I error=5%)**
- **Number of subjects needed (given power=90%)**

Figure 4. Empirical design evaluation output

```
Covariate model :

        NB: Covariates are additive on log parameters

        Covariates changing with occasion

                  Covariate 1 : Comed ( ka )
   Categories References
(1)          W          *
(2)          X

   Sequences Proportions
(1)       W X       0.5
(2)       X W       0.5
```

**Covariate model**

**(W=warfarin, X=warfarin+drug X)**

```
************************* EXPECTED STANDARD ERRORS ************************

------------------------ Fixed Effects Parameters ------------------------

                  Beta    StdError       RSE
ka           1.60 0.2889600018 18.060001 %
V            8.00 0.2087831088  2.609789 %
Cl           0.13 0.0005823788  4.479837 %
beta_ka_Comed_X 0.00 0.1448829223       Inf %
------------------------ Variance of Inter-Subject Random Effects ------------
   Omega    StdError       RSE
ka  0.70 0.2216835522 31.66907 %
V   0.02 0.0054482122 27.24106 %
Cl  0.06 0.0160606907 26.77818 %
------------------------ Variance of Inter-Occasion Random Effects -----------
   Gamma    StdError       RSE
ka   0.3 0.0713900404 23.79668 %
```

**Standard error and RSE of the co-medication covariate effect on ka**

**Standard error and RSE of the inter-occasion variability**

```
***************************** EQUIVALENCE TEST *****************************

                  Beta          90 % CI    exp(beta)        90 % CI
beta_ka_Comed_X     0 [-0.238;0.238]          1 [0.788;1.269]

Type I error = 0.05
Equivalence interval = [log(0.8),log(1.25)]

          Expected_power Number_subjects_needed (for a given power=0.9)
beta_ka_Comed_X      0.4583113                              115.5273
```

**90% confidence interval of the covariate effect**

**Expected power and number of subjects needed for the bioequivalence Wald test**

→ **To achieve a power of 90%, 116 subjects with the same sampling design would be needed to perform the bioequivalence test**

## Conclusion

- Illustration of the choice of the design and the number of subjects needed to achieve a given power of the Wald test of discrete covariate for complex PK/PD model
- Great potential of PFIM 3.2 to optimize parallel or crossover designs and to control expected power of a Wald test for comparison or bioequivalence
- PFIM 3.2 freely available at www.pfim.biostat.fr

## Reference

[1] Mentré F, Mallet A, Baccar D. *Biometrika*. 1997..
[2] Retout S, Mentré F. *Journal of Biopharmaceutical Statistics*, 2003.
[3] Bazzoli C, Retout S and Mentré F. *Statistics in Medicine*. 2009.
[4] Retout S, Comets E, Samson A, Mentré F. *Statistics in Medicine*. 2007.
[5] Nguyen TT, Bazzoli C and Mentré F. *American Conference on Pharmacometrics*. 2009 (Poster).
[6] O'Reilly RA, Aggeler PM. *Circulation*. 1968.
[7] O'Reilly RA, Aggeler PM, Leong LS. *The Journal of Clinical Investigation*. 1963.