**BACKGROUND**

- **Dose-response studies**: Importance of identifying the right dose
  - Two main analysis approaches: multiple comparisons between doses or modelling [1]
  - Modelling: more flexible, increasingly used in drug development
  - Specific case: several doses evaluated for each patient
  - Modelling through nonlinear mixed effects models (NLMEM)

- **Importance of choice of design**
  - Trial with one dose/patient: methods to choose robust efficient design for estimating the minimum effective dose already proposed [2]
  - Trial with several doses/patient: how to choose appropriate population design?
    - (the number of patients) / (the number of doses) / which doses?
  - Impact on the study results (precision of parameter estimates, power of test, ...)

- **Design evaluation and optimisation in NLMEM**
  - Simulations: time consuming, limited number of designs evaluated
  - Population Fisher information matrix (M0)
  - M0 for NLMEM, using first order approximation of the model [3,4]
  - Implementation in R function PFIM [5,6] and in other software

**MOTIVATING EXAMPLE & OBJECTIVE**

- **Motivating example**: Dose-response trial with several doses/patient [7]
  - Emax model
  - Parameters E0 = 5, Emax = 30, D50 = 500 mg
  - Modelling through NLMEM
  - Exponential model for random effects
  - With standard deviation of inter patient variability = 0.7 for E0, Emax and 0.3 for D50
  - Additive model for random error with standard deviation of random error = 2

  **Objective**: To design this dose-response study using PFIM 3.2

1. To study the influence of design on criterion and precision of D50 estimation
2. To study the influence of covariate on D50 on design optimisation and to evaluate the power of the comparison Wald test for this covariate effect

**METHODS**

Designing with PFIM 3.2 [5]

- Computing population Fisher information matrix M0 by linearisation of the model [3,4]
- Prediction of standard errors (SE) or relative standard errors (RSE) for population parameters from the diagonal terms of M0
- Optimisation of designs with Fedorov-Wynn algorithm [8]

1. Evaluation of the influence of design on criterion and precision of D50 estimation

**RESULTS**

1. Influence of design on criterion and precision of D50 estimation

![Figure 1: Example of a dose-response trial](image)

<table>
<thead>
<tr>
<th>Design (N,n)</th>
<th>Total number of doses (n)</th>
<th>D50 (mg)</th>
<th>RSE(D50) (%)</th>
<th>Criterion</th>
<th>( \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(100,2)</td>
<td>100</td>
<td>1</td>
<td>200</td>
<td>0%</td>
<td>0.98</td>
</tr>
<tr>
<td>(100,4)</td>
<td>100</td>
<td>4</td>
<td>400</td>
<td>20%</td>
<td>0.96</td>
</tr>
<tr>
<td>(100,4)</td>
<td>100</td>
<td>4</td>
<td>400</td>
<td>20%</td>
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<td>(100,2)*</td>
<td>100</td>
<td>2</td>
<td>200</td>
<td>0%</td>
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</tr>
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<td>200</td>
<td>2</td>
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<td>20%</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**2. Influence of covariate on design optimisation and prediction of power of the comparison Wald test for this covariate effect**

![Figure 2: Relative standard errors of D50 and criteria computed by PFIM for different designs](image)

- close optimal designs with 2 doses/patient: very little difference of efficacy criterion between design (100,2) vs. (200,2)
- close optimal designs with 4 doses/patient: very little difference of efficacy criterion between design (100,4) vs. (100,4)*

![Figure 3: Power of the Wald test for D50 comparison computed by PFIM for different designs and associated criteria](image)

**CONCLUSION**

- Dose-response studies with several doses/patient can be analysed by NLMEM
- Designs of these studies can be evaluated/optimised using PFIM 3.2: useful tool for designing clinical trials, allowing users to:
  - take into account discrete covariates
  - compute power and number of subjects needed