PODE 2010

Population Optimum Design of Experiments: Workshop

Berlin – 11/12 June 2010

Program:

Friday 11.06.2010

14:15-14:30 Welcome

Session 1

14:30 - 15:00 **Approximations of the population Fisher information matrix – differences and consequences**

Joakim Nyberg, Sebastian Ueckert and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Sweden

15:00 - 15:30 **Optimization of sampling times for PK/PD models: approximation of elemental Fisher information matrix**

Valerii V. Fedorov, **Sergei L. Leonov**
GlaxoSmithKline, Collegeville, U.S.A.

15:30 - 16:00 **Application of Quasi-Newton Algorithms in Optimal Design**

Sebastian Ueckert, Joakim Nyberg and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Sweden

16:00 - 16:30 Coffee break

Session 2

16:30 - 17:00 **Optimal design and QT-prolongation detection in oncology studies**

Sylvain Fouiliard, **Marylore Chenel**
Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, France

17:00 - 17:30 **Design evaluation and optimisation in crossover pharmacokinetic studies analyzed by nonlinear mixed effects models**

Thu Thuy Nguyen, Caroline Bazzoli, France Mentré
UMR738 INSERM and University Paris Diderot, Paris, France

17:30 - 18:00 **D-optimal Adaptive Bridging Studies in Pharmacokinetics**

Lee-Kien Foo, Stephen Duffull
University of Otago, New Zealand

Saturday 12.06.2010

Session 3

09:30 - 10:00 **Design Evaluation and Optimization for models of Hepatitis C viral dynamics**
J. Guedj (1), C. Bazzoli (2), A.U. Neumann (3), **F. Mentre** (2)
(1)Los Alamos National Laboratory, New Mexico, USA; (2) INSERM, UMR 738 Paris, France; (3)Bar-Ilan University, Ramat-Gan, Israel;

10:00 - 10:30 **Noninferiority trial designs for odds ratios and risk differences**
Joan F. Hilton
University of California San Francisco

10:30 - 11:00 **Optimum designs for nonlinear mixed effects model in the presence of covariates**
Barbara Bogacka
Queen Mary, University of London, England

11:00 - 12:00 General discussion (future meetings)

PODE 2010

Population Optimum Design of Experiments: Workshop

Berlin – 11/12 June 2010

Preliminary list of participants:

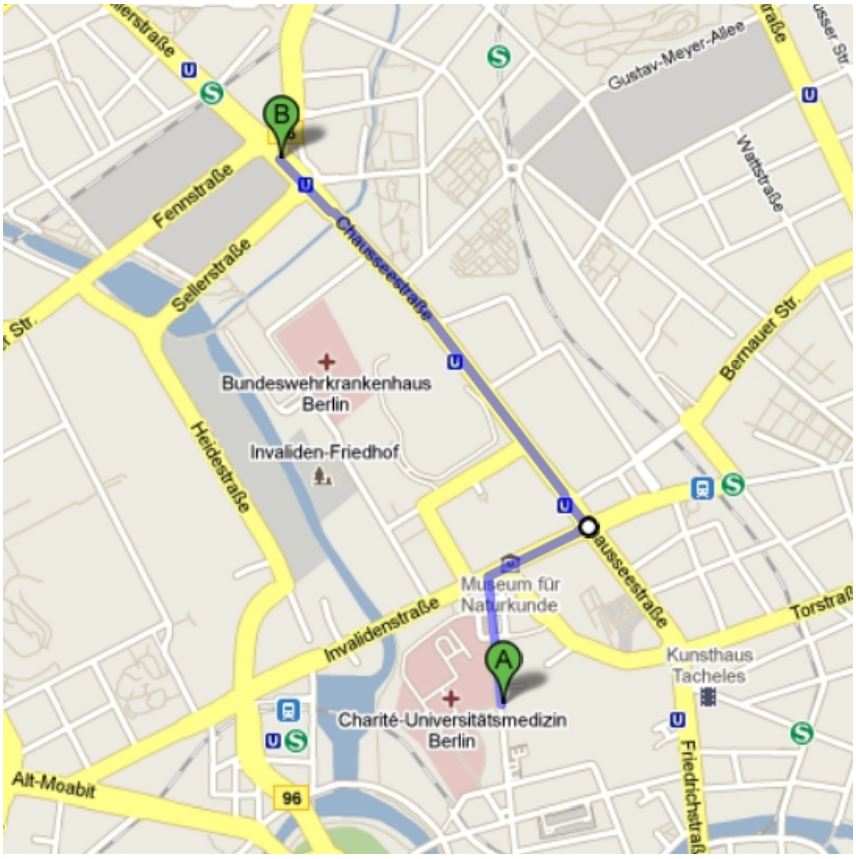
Participant	From	Presentation
Anthony Atkinson	London	-
Barbara Bogacka	London	Yes
France Mentré	Paris INSERM	Yes
Thu Thuy N'Guyen	Paris INSERM	Yes
Emmanuelle Comets	Paris INSERM	-
Anne Dubois	Paris INSERM	-
Marylore Chenel	Paris INSERM	Yes
Sylvie Retout	Basel Roche	-
Kayode Ogungbenro	Manchester	-
Valeri Fedorov	GSK	Maybe
Sergei Leonov	GSK	Yes
Stephen Duffull	Otago	-
Julia Korell	Otago	-
Lee-Kien Foo	Otago	Yes
Pavan Kumar	Otago	-
Mats Karlsson	Uppsala	-
Andrew Hooker	Uppsala	-
Sebastian Ueckert	Uppsala	Yes
Marilee Andrew	Uppsala	-
Joakim Nyberg	Uppsala	Yes
Camille Vong	Uppsala	-
Alexandre Sostelly	Uppsala/Lyon	-
Aris Dokoumetzidis	Athen	-
Katrin Roth	Berlin, Bayer-Schering	-
Thomas Schmelter	Berlin, Bayer-Schering	-
Hermann Kulmann	Berlin, Bayer-Schering	-
Robert Offinger	Passau	-
Ulrike Graßhoff	Magdeburg	-
Maryna Prus	Magdeburg	-
Tobias Mielke	Magdeburg	-
Rainer Schwabe	Magdeburg	-
Leonid Gibiansky	Quantpharm	-
Ekaterina Gibiansky	Quantpharm	-
Paolo Denti	Cape Town	-
Chao Zhang	Cape Town	-
Emmanuel Chigutsa	Cape Town	-
Joan Hilton	San Francisco	Yes
Ivelina Gueorguieva	Surrey	-
Simon Davis	Certara	-
		10 talks

PODE 2010

Population Optimum Design of Experiments: Workshop

Berlin – 11/12 June 2010

Your way to the workshop:



1. Leaving the Conference-Building of PAGE, you will have to walk along the Luisenstraße in northern direction (the direction with the building, which crosses the street), until the street ends. (400 m)

2. Turn to the right and walk along the Invalidenstraße (300 m). At the junction Invalidenstraße/Chausseestraße (there will be rails on the street), you have to turn to the left and to walk along the Chausseestraße.

3. After about 1.2 km you will see at the subway-station „Reinickendorfer Straße“ on your left hand side the buildings of Bayer-Schering, where the workshop will take place. Enter the building Müllerstraße 178 through the main entrance.

Approximations of the population Fisher information matrix – differences and consequences

Joakim Nyberg, Sebastian Ueckert and Andrew C. Hooker

Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Joakim Nyberg

Objectives: The First Order (FO) Population Fisher Information Matrix (FIM) can be approximated assuming that the variance of the model is independent of the typical values in the population model, named the Reduced FIM, or by less severe approximations assuming that there is a dependence between the variance and all parameters in the model, i.e. the Full FIM. These two different approximations and their implications have been presented previously [1]. More recently, a software comparison between population optimal design software at the Population Optimal Design of Experiments (PODE) workshop 2010 [2] resulted in an example where the Reduced FIM gave more similar results to an empirical calculation of the relative standard errors after stochastic simulations and re-estimations.

In this work we present examples where a divergence between the Full and Reduced FO approximations occur, and how to handle this with either simulation approximations or more accurate analytical approximations. We also elaborate on when to use which approximations and their implications.

References:

[1] Nyberg, J., Ringblom, J., Karlsson, M.O., Hooker, A.C. "Different approximations and methods for calculating the FIM and their consequences". PODE 2008. http://www.maths.qmul.ac.uk/~bb/PODE/PODE2008.html

[2] Mentré, F., Bazzoli, C. "Comparison of software tools for population optimal designs". PODE 2009. http://www.maths.qmul.ac.uk/~bb/PODE/PODE2009.html

Optimization of sampling times for PK/PD models: approximation of elemental Fisher information matrix

Valerii V. Fedorov, Sergei L. Leonov

GlaxoSmithKline, Collegeville, U.S.A.

Sergei Leonov

Introduction: Optimal design of population PK and PD studies has seen an increasing interest over the last decade. In 2006, an annual Population Optimum Design of Experiments (PODE) workshop was initiated on the theory of optimal experimental design for nonlinear mixed effects models and its applications in drug development; see http://www.maths.qmul.ac.uk/~bb/PODE/PODE.html. A special session was organized at PODE 2007 to present different software tools for population PK/PD optimal designs. Presentations at this session were summarized at PAGE 2007 meeting, see Mentré et al. [3]; and a discussion of software tools continued at PODE 2009.

Methods and Objectives: The key component for constructing model-based optimal designs is the Fisher information matrix of a properly defined single observational unit; see Fedorov and Hackl [1]. In the context of PK/PD studies the elemental information matrix corresponds to a sequence of sampling times for an individual subject; e.g., see Gagnon and Leonov [2], Retout and Mentré [4]. In our presentation, we focus on certain options of calculating/approximating the information matrix which include different ways of modeling population variability; different orders of approximation of the mean response; regular scale of measurements vs log-scale for PK data.

Results: We present several examples, including (a) rather simple ones, where closed-form expressions may be obtained and, therefore, the comparison of different options becomes quite transparent, and (b) more complex models which are used in practice and which require Monte Carlo simulations to validate the results.

References:

[1] Fedorov VV, Hackl P. (1997), *Model-Oriented Design of Experiments*. Springer, NY.

[2] Gagnon R, Leonov S (2005). Optimal population designs for PK models with serial sampling, *J. Biopharm. Statist.*, **15**(1), 143-163.

[3] Mentré F, Duffull S, Gueorguieva I, Hooker A, Leonov S, Ogungbenro K, Retout S (2007). Software for optimal design in population pharmacokinetics and pharmacodynamics: a comparison In: *Abstracts of the Annual Meeting of the Population Approach Group in Europe (PAGE)*. ISSN 1871-6032, http://www.page-meeting.org/?abstract=1179

[4] Retout S, Mentré F (2003). Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics, *J. Biopharm. Statist*., **13**(2), 209-227.

Application of Quasi-Newton Algorithms in Optimal Design

Sebastian Ueckert, Joakim Nyberg and Andrew C. Hooker

Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Sebastian Ueckert

Objectives: Finding the most efficient design of an experiment involves non-linear optimization problems which are in general computationally expensive. Currently a number of different algorithms such as Steepest Descent, Line Search or Simulated Annealing are employed to solve these problems. In this work the usage of quasi-Newton methods for design optimization and possible applications are presented.

Quasi-Newton methods iteratively build up and invert an approximate Hessian matrix of the objective function to find a local optimum. Here, we present the advantages of this approach (e.g. improved convergence rate compared to the Steepest Descent) and discuss possible complications (e.g. handling of design space constraints).

In addition; this work shows how the approximate Hessian matrix, obtained during the optimization, can be used to calculate local sampling windows. Furthermore, it is illustrated how the evaluation of integrals in global optimal design can be performed efficiently by combining the Laplace approximation with a quasi-Newton method.

Optimal design and QT-prolongation detection in oncology studies

Sylvain Fouiliard and Marylore Chenel

Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier,

Marylore Chenel

Objectives: QT interval prolongation is considered as a biomarker of *torsade de pointe* (TdP) in cardiac safety assessment in drug development. Thus, specific QT/QTc studies are usually performed in healthy volunteers, allowing an accurate estimation of such noisy data as QT interval length. This is however not possible in the specific context of oncology, where patients only can receive the drug.
Population approach may help the description of PKPD relationship while taking into account all sources of variability (e.g. circadian rhythm, inter-individual variability, inter-occasion variability, residual error) [1], but the clinical constraints of phase I/II studies in oncology limit electrocardiogram (ECG) schedules.
Based on both known population PK and QT circadian rhythm models, assuming the PKPD relationship and testing different effect sizes, we propose a design strategy in order to assess cardiac safety by optimizing ECG sampling times.
Our aim is to propose a cardiac safety assessment method, based on both optimal sampling design and population PKPD modelling. The ultimate goal is to estimate the power of detection of any potential effect of SX compound on QT interval length.

Methods: First, a population PK model of drug SX was developed based on both oral and IV phase I studies (45 patients). This model was used to simulate the concentration of the drug based on the administration schedule of further studies.
Secondly, a population model describing the circadian rhythm of QTc was developed using data from two former QT/QTc phase I studies including a total of 160 healthy volunteers under placebo. Both model buildings were performed using NONMEM VI with the FOCE-I method.
Based on preliminary experience in PKPD of QT length, we assume a linear relationship between drug concentration and QTc effect. A range of values of the drug effect on QTc was tested (from 5 ms to 100 ms).
At last, the ECG record times planned in the trials to come were evaluated using PopDes 3.0 design evaluation feature and were compared to the optimal ones obtained by D-optimality criteria (with Fedorov exchange optimization algorithm) [2]. Planned ECG schedules are on days 1 (predose, 1h and 4h after 1^{st} dose, 1h and 4h after 2^{nd} dose), and on days 2, 4, 14 and 22 (predose and 1h after 1^{st} dose each day). In parallel, the precision of estimation of the drug effect parameter was used in the computation of the power of detection of a significant drug effect.

Results: SX concentration-time data were fitted with a 3-compartment model with a first-order absorption. Inter-individual variability was added on clearance CL, bioavailability F,

absorption rate Ka and on inter-compartmental constants Q2 and Q3. The residual error was multiplicative. The circadian rhythm of QTc was modelled as a mesor and a sum of three cosine terms (one amplitude and one lag-time per cosine term), representing three periods of 24, 12 and 6 h, with inter-individual variability on every parameter except the second amplitude term, and an additive residual error. The drug effect is assumed to be proportional to the mesor.
The proposed design lead to a good estimation of every parameter of the model, according to the RSEs given by the population Fisher information matrix. Whatever the tested value of the drug effect, the statistical power of detection of a significant QT effect (i.e. that may cause a QT-prolongation adverse event) was found to be over 90 %. Comparison with optimal designs (under various time constraints) showed possible improvements for future studies.

Conclusions: This work proposes a modelling and simulation based strategy in order to make sure QT prolongation risk is correctly assessed in the context of clinical trials in oncology. Although the assumptions made on PKPD relationship is not negligible and will be assessed throughout further trials, the first results show a good power of detection of a QT-prolongation related adverse event with a feasible ECG recording design in oncology patients.

References:

[1] Piotrovsky, V. "Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation". AAPS J 7.3 (2005): E609-E624.

[2] Ogungbenro K, Dokoumetzidis A, Aarons L. "Application of optimal design methodologies in clinical pharmacology experiments". Pharm Stat. (2009) Jul-Sep;8(3):239-52.

Design evaluation and optimisation in crossover pharmacokinetic studies analyzed by nonlinear mixed effects models

Thu Thuy Nguyen, Caroline Bazzoli, France Mentré

UMR738 INSERM and University Paris Diderot, Paris, France

Thu Thuy Nguyen

Objectives: Nonlinear mixed effects models (NLMEM) can be used to analyze crossover pharmacokinetic (PK) bioequivalence trials. Before modelling, it is important to define an appropriate design. The main approach for design evaluation and optimisation has been for a long time based on simulations but it is a cumbersome method. An alternative approach is based on the population Fisher information matrix (MF) which expression for NLMEM [1,2] was implemented in the R function PFIM [3,4,5]. We aim to propose an extension of the evaluation of MF for NLMEM in crossover trials and to apply this extension to design a future crossover PK study of amoxicillin in piglets.

Methods: We extended MF for NLMEM with inclusion of within subject variability, in addition to between subject variability, and with discrete covariates changing between periods. We used a linearization of the model around the random effects expectation. The power of the Wald test of comparison or equivalence was computed using the predicted standard error (SE). We evaluated these developments by simulations mimicking a crossover study with two periods, where piglets received amoxicillin and placebo at period 1 then amoxicillin and a product X at period 2. The objective of the trial is to show the absence of interaction of X on the PK of amoxicillin. Simulations were performed for a rich design as well as for an optimal sparse design derived from the rich one and with different values of treatment effect on amoxicillin clearance. We then used the extension of MF to plan a future study, with similar crossover design as the simulation study, based on results of a previous study of amoxicillin in piglets.

Results: For various simulated scenario, predictions of SE and powers by MF were close to the empirical ones obtained after fitting the simulated trials with the SAEM algorithm [6,7] in MONOLIX 2.4 [8]. The optimal sparse design had similar power as the rich design. These extensions were implemented in the new version 3.2 of PFIM, available since January 2010 [5]. For the application, from the expected SE computed by PFIM 3.2 for the future study, we predicted much more needed subjects than the previous study to show the absence of interaction of X on the PK of amoxicillin with good power.

Conclusions: This extension of MF for NLMEM is relevant. PK bioequivalence trials analyzed through NLMEM allow sparse designs and can be performed in patients. PFIM can be used to efficiently design these trials.

References:

[1] Mentré, F., Mallet, A., Baccar, D. (1997) Optimal design in random effect regression models, *Biometrika*, 84(2):429-442.

[2] Bazzoli, C., Retout, S., Mentré, F. (2009) Fisher information matrix for nonlinear mixed effects multiple response models: Evaluation of the appropriateness of the first order linearization using a pharmacokinetic/pharmacodynamic model, *Statistics in Medicine*, 28:1940-1956.

[3] Retout, S., Duffull, S., Mentré, F. (2001) Development and implementation of the population Fisher information matrix for evaluation of population pharmacokinetic designs, *Computer Methods and Programs in Biomedicine*, 65:141-151.

[4] Bazzoli, C., Retout, S., Mentré, F. (2010) Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0, *Computer Methods and Programs in Biomedicine*, 98:55-65.

[5] http://www.pfim.biostat.fr/.

[6] Kuhn, E., Lavielle, M. (2005) Maximum likelihood estimation in nonlinear mixed effects model, *Computational Statistics and Data Analysis*, 49:1020-1038.

[7] Panhard, X. and Samson, A. (2009) Extension of the SAEM algorithm for non linear mixed effects models with two levels of random effects, *Biostatistics*, 10:121-135.

[8] http://www.monolix.org/

D-optimal Adaptive Bridging Studies in Pharmacokinetics

Lee-Kien Foo, Stephen Duffull

University of Otago, New Zealand

Lee Kien Foo

Background:
Bridging studies are a method for extrapolating information gathered from clinical study in an original region (prior population), e.g. an adult patient population, to a new region (target population), e.g. a paediatric patient population. Since the PK profile of the prior and target populations may be different then optimally designed studies based solely on the prior population may be suboptimal when applied to the target population. Optimal adaptive design can be used to address this issue which the design phase and estimation phase is updated in the experiment, where the parameter estimates obtained in the current iteration are used to design the experiment for the next iteration. This approach can provide reliable estimates of PK parameters under uncertainty and sampling restrictions [1]. Here we propose a new method for applying optimal adaptive design to bridging studies.

Objective:
To develop a D-optimal adaptive bridging study (D-optimal ABS) that has general applicability to pharmacokinetics.

Methods:
Our proposed D-optimal ABS starts with collecting sample data from all prior population patients enrolled following an initial (arbitrary) study design. Patients of the target population will be divided into B batches. The prior population sample data will be modelled and the estimated parameter values from the best model used to locate a D-optimal sampling schedule (D1) that will be applied to the first batch target population patients. The first batch of target population patients will be enrolled and data collected according to D1 will be pooled with a reduced data set arising from the prior population, where the prior population data is reduced by an amount proportional to the size of the batch of the target population. The pooled data will be modelled and the D-optimal design (D2) is located for the new model. Subsequently a second batch of target population patients is enrolled and data collected according to D2. The iterative process of estimation and design was repeated until all batches of the target population patients have been enrolled. The size of batches will also be considered for optimization.

Simulation Study:
The D-optimal ABS was designed and assessed using simulations under two different scenarios. In scenario 1, the PK profile of prior and target populations are similar where the design optimized based on prior population PK profile is a good but not optimal design for target population. In scenario 2, the PK profile of the prior and target populations are different

and a design optimized based on prior population PK profile will perform poorly for the target population. The simulations are carried out in MATLAB and NONMEM, called from MATLAB, is used for estimation. For each scenario, 100 adaptive bridging studies were simulated. The relative percentage difference of the estimated parameter values from the empirical (true) parameter values were used to assess performance of the adaptive bridging study.

Scenario 1: *{adult to paediatric}*
In this scenario the D-optimal ABS is for an adult (prior) to paediatric (target) patients for a small molecule drug. The drug is taken orally and assumed to follow a Bateman PK model. Two hundred adult patients and twenty five paediatric patients were simulated and the paediatric patients were divided into five enrolment batches with five patients in each batch. The nominal parameter mean of adult patients were CL = $4Lh^{-1}$, V = 20L, Ka = $1h^{-1}$ and dose = 100 mg. The nominal parameter mean of CL and V for paediatric patients are scaled allometrically to CL = $1.56Lh^{-1}$, V = 5.71L. Ka is assumed to be the same as adult patients and dose = 29 mg. The variance of the log-normal between subject variability was 0.1 for both populations. A combined residual error model was assumed. The two hundred adult patients each provided 6 blood samples following an arbitrary sampling schedule.

Scenario 2: *{normal weight to obese adult}*
In this scenario, the D-optimal ABS is for a normal weight (prior) to obese (target) adult patients for a large molecule drug which is given subcutaneously. We assumed the disposition phase to follow a 1-compartment model. In both populations the absorption profile followed a transit compartment model, with the obese patients having significantly greater mean transit time. The populations consisted of 60 normal weight and 60 obese adult patients. The obese patients were divided into five batches with twelve patients in each batch. The nominal parameter mean of normal weight patients were CL = $4Lh^{-1}$, V = 20L, MTT (mean transit time) = 3h, N (number of transit compartment) = 2 and dose = 100mg. The nominal parameter mean of obese patients were CL = $5.2Lh^{-1}$, V = 30L, MTT = 20h, N = 20 and same dose is given. The variance of the log-normal between subject variability for CL, V and MTT are assumed to be the same for both populations with value 0.2. We assumed there is no between subject variability for N in both populations. A combined residual error model was assumed. The 60 normal weight patients each provided 8 blood samples following a D-optimal sampling schedule.

Results and Discussion:
Scenario 1:
Two hundred adult patients with 6 samples per patient provided precise parameter estimates for the adult population. The adaptive design with fixed reduction rate of adult patient data (20% per iteration) provided precise parameter estimates for the paediatric population at the 5th (final) iteration. Results from scenario 1 showed that D-optimal ABS was not inferior compared to the study design optimized on prior population used directly in the target population.

Scenario 2:
Sixty normal weight adult patients with 8 D-optimal samples per patient provided precise parameter estimates for the normal weight adult population. The D-optimal ABS with fixed reduction rate of normal weight adult patient data (20% per iteration) provided acceptable parameter estimates for the obese adult population at the 5th (final) iteration. In this setting a D-optimal ABS design performed better than when a D-optimal design from the prior population was applied to the target population.

Conclusions:
Optimal adaptive designs for bridging studies are a potentially useful method for learning about new populations. The proposed design method for bridging studies provided reasonable parameter estimates for the target population even when the PK profile of the prior and target populations were widely divergent.

References:
[1] Boulanger B, Jullion A, Jaeger J, Lovern M and Otoul C. Developtment of a Bayesian Adaptive Sampling Time Strategy for PK studies with constrained number of samples to ensure accurate estimates. PAGE 17 (2008) Abstr 1310 (http://www.page-meeting.org/?abstract=1310)

Design Evaluation and Optimization for models of Hepatitis C viral dynamics

J. Guedj (1), C. Bazzoli (2), A.U. Neumann (3), F. Mentre (2)

(1)Los Alamos National Laboratory, New Mexico, USA ;(2) INSERM, UMR 738, 146 rue Henri Huchard 75018 Paris, France ; (3)Bar-Ilan University, Ramat-Gan, Israel;

France Mentré

Objectives: The Neumann's model of viral dynamics is the standard explanation for the biphasic decline of Hepatitis C virus (HCV) during frequent administration of Interferon (IFN) and has brought important insights for understanding HCV pathogenesis [1]. This model can be extended to account for pharmacokinetics variation, when drug is administered on a weekly basis [2]. Since this model is based on a complex system of non-linear Ordinary Differential Equations (ODE), the parameter estimation is challenging and requires a rich data set if individual estimation is performed. By borrowing strength from the between-patients variability, nonlinear mixed effect models (NLMEM) allow sparser design within each patient to analyze the observations of the whole sample. Yet, the accuracy of the viral parameters that can be expected using NLMEM has not been investigated so far.

Methods: : In the context of non-linear dynamics without a closed-form solution, the computation of the exact FIM in NLMEM involves heavy computation [3]. Here we use an approximation of the FIM based on the first-order linearization around the mode of the random effects that allows to avoid most of the computation burden [4,5].
We show that this approximation, implemented in the software PFIM, provides a good estimation of the FIM. We compare the ability of different popular designs in HCV clinical trials to estimate the parameters of viral dynamics. Furthermore, we propose different optimal designs according to the maximal number of sampling measurements that is allowed for each patient. We show how an appropriate choice for the sampling measurements can dramatically improve the identifiability of the most critical viral parameters for the prediction of the treatment outcome.

Conclusions: The results can be used for both clinical and methodological purposes.

References:

[1] Neumann et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 1998; 282:103–107.

[2] Talal et al. Pharmacodynamics of PEG-IFN Differentiate HIV/HCV Coinfected Sustained Virological Responders From Nonresponders. Hepatology 2006; 43:943–953.

[3] Guedj et al. Practical Identifiability of HIV Dynamics Models. Bulletin of Mathematical Biology 2007; 69(8):2493–2513.

[4] Mentre et al. Optimal design in random-effects regression models. Biometrika 1997; 84:429–442.

[5] Bazzoli et al. Fisher information matrix for nonlinear mixed effects multiple response models: evaluation and comparison by simulation to results from FO, FOCE and SAEM algorithms. Statistics in Medicine 2009; 28(14):1940–1956

Noninferiority trial designs for odds ratios and risk differences

Joan F. Hilton

University of California San Francisco

Objectives: This study presents constrained maximum likelihood derivations of the design parameters of noninferiority trials for binary outcomes with the margin defined on the odds ratio (ψ) or risk difference (δ) scale. The derivations show that, for trials in which the group-specific response rates are equal under the point-alternative hypothesis, the common response rate π^N, is a fixed design parameter whose value lies between the control and experimental rates hypothesized at the point-null, $\{\pi_C, \pi_E\}$. We show that setting π^N equal to the value of π_C that holds under H_0 underestimates the overall sample size requirement. Given $\{\pi_C, \psi\}$or $\{\pi_C, \delta\}$ and the type I and II error rates, our algorithm finds clinically meaningful design values of π^N, and the corresponding minimum asymptotic sample size, $N = n_E + n_C$, and optimal allocation ratio, $\gamma = n_E / n_C$. We find that optimal allocations are increasingly imbalanced as ψ increases, with $\gamma_\psi < 1$ and $\gamma_\delta \approx 1/\gamma_\psi$, and that ranges of allocation ratios map to the minimum sample size. The latter characteristic allows trialists to consider trade-offs between optimal allocation at a smaller N and a preferred allocation at a larger N. For designs with relatively large margins (e.g., $\psi > 2.5$), trial results that are presented on both scales will differ in power, with more power lost if the study is designed on the risk difference scale and reported on the odds ratio scale than vice versa.

Key Words: active-controlled trial, allocation ratio, ancillary parameter