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Adaptive Dose Finding in Early Phase Clinical Trials Incorporating Pharmacokinetic Information

M. I. ALAM, B. BOGACKA AND D. S. COAD

School of Mathematical Sciences
Queen Mary, University of London

Interest has grown in recent years in the development of dose finding methods incorporating both toxicity and efficacy as endpoints, as the dose of a new drug is acceptable only if it is safe and efficacious. This talk introduces one such new statistical method for phase I-II trials which additionally incorporates pharmacokinetic (PK) information in the dose escalation. The aim is to develop an efficient dose finding method that exposes not too many patients to either sub-therapeutic or toxic doses and recommends the best dose for further studies in phase III.

Following the assignment of a current best dose to a cohort of patients, the concentration of a drug in the blood is measured at the D-optimal time points. The dose-response outcomes are also observed for each patient. Based on the updated information, a new dose for the next cohort is selected so that the estimated probability of efficacy is maximum, subject to the condition that the estimated probability of toxicity is not more than a pre-specified level. Another condition for the dose selection is related to the total concentration of the drug in the body so that the curative purpose is likely to be achieved. This is expressed by the area under the concentration curve over time. The trial is stopped when the same dose is repeated for r cohorts or when it reaches the maximum number of m cohorts, whichever comes first. At the end, a complete analysis of the data is carried out and a dose is chosen to be recommended for further studies in phase III. The method is illustrated with an example of a one-compartment PK model with bolus input and first-order elimination. The parameters of the model are assumed to be random to account for the inter-patient variability. As the dose-response outcomes, we consider a trinomial response: neutral, efficacious or toxic, for each patient. The continuation ratio model is employed for modelling the dose-response data with uniform priors for the parameters. Thus we implement a Bayesian adaptive procedure.

The purpose of this study is to investigate the gain in efficiency of using PK measures in the dose escalation. Simulation results show that the method is capable of identifying the optimal dose accurately without exposing too many patients to toxic doses and therefore can be used as a reliable dose finding procedure.

Influence of Study Design and Associated Shrinkage on Power of the Tests Used for Covariate Detection in Population Pharmacokinetics

F. COMBES[1,2,3], S. RETOUT[2,3], N. FREY[2] AND F. MENTRÉ[1]

[1] INSERM, UMR 738, Univ Paris Diderot, Sorbonne Paris cit'e, Paris, France
[2] Pharma Research and Early Development, Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland
[3] Institut Roche de Recherche et Médecine Translationnelle, Boulogne-Billancourt, France

Objectives: In 2009, Savic et al [1] showed that high shrinkage caused by poorly informative study designs can hide or induce correlation between estimated individual parameters (EBE) and covariates. That work did not explore the impact on the power of tests used for covariate detection. The present work investigates the impact of various designs, along with the associated shrinkages, on the power to detect the effect of a continuous covariate of i) the correlation test (CT) based on EBEs, ii) the likelihood ratio test (LRT).

Methods: A one compartment pharmacokinetic (PK) model with oral first-order absorption and a weight (WT) effect on volume (coded with a power function) was used for simulation. To obtain various levels of shrinkage, different values of random effect variability (20 and 50%), of proportional residual error (30 and 40%), of β (0, 0.2, 0.5 and 1), as well as different number of PK samples per subject (2, 3 or 5), were combined. Each combination was simulated 1000 times with 500 subjects. Predicted shrinkage was computed using the approximation of the Bayesian information Matrix [2-3]. NONMEM 7.2 [4] with algorithms FOCEI and SAEM (followed by IMP for likelihood computation) was used to perform parameter estimation [5]. The type 1 error and the power of LRT and CT (from EBEs after each estimation) were computed as well as the observed shrinkage.

Results: The observed shrinkages were similar with both algorithms and were in agreement with the predicted shrinkages. As expected, the power of LRT and CT for detecting the WT effect decreased with the informativeness of the study design and its associated shrinkage. However, two unexpected outcomes were found: 1) analysis of the EBEs by CT had the same power as the LRT even in case of a sparse PK sampling and high shrinkage; 2) population parameters estimated by SAEM were less biased and less spread than with FOCEI even in case of a rich PK sampling.

Conclusion: As expected, informativeness of study design influenced the power of tests used for covariate detection. CT based on EBEs, even with a sparse PK sampling, was as powerful as LRT to detect covariate influence. These results need to be confirmed by varying model complexity, covariate effects and design. SAEM was a more accurate and precise algorithm than FOCEI to estimate population parameter even with rich PK sampling and a simple model.

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Adaptive Population Enrichment Design in Confirmatory Clinical Trials

V. DRAGALIN

Innovation Center
Aptiv Solutions
Durham, NC

There is a growing interest among regulators and sponsors in using precision medicine approaches that allow for targeted patients to receive maximum benefit from the correct dose of a specific drug. Population enrichment designs offer a specific adaptive trial methodology to study the effect of experimental treatments in various sub-populations of patients under investigation. Instead of limiting the enrollment only to the enriched population, these designs enable the data-driven selection of one or more pre-specified subpopulations at an interim analysis and the confirmatory proof of efficacy in the selected subset at the end of the trial. In this presentation, the general methodology and designing issues when planning such a design will be described and illustrated using ADDPLAN PE.

Designing a Pilot Study Using Adaptive DP Optimality

A. GULATI AND S. DUFFULL

School of Pharmacy
University of Otago
Dunedin, New Zealand.

The development timeline for a diagnostic test involves a number of steps including establishing proof-of-mechanism of the test, proof-of-concept of the test, followed by a rigorous human development stage. The proof of concept stage is designed to address the critical "go"/"no go" decision, i.e., whether the diagnostic test is worthy of further development or should be stopped for futility. The experimental conditions that underpin the proof-of-concept are critical to provide a high probability of making an appropriate decision. We are developing a clotting time test to guide choice of dose and dosing regimens for patients. There are two factors that need to be controlled for the proof-of-concept study. A pilot study (with 6 patients) was considered to explore these factors to determine a range of values to take forward for the proof-of-concept. Resources were constrained and a full factorial design was not possible. We aimed to conduct a pilot study to determine the optimal and the range of values of two factors for taking forward into a proof-of-concept study.

A nonlinear parametric function was developed to describe the response surface over the factors of interest. A continual reassessment method was used to estimate the parameters using a D-optimal design criterion. In order to provide a reasonable probability of observing a success of the test a P-optimal design criterion was incorporated using a loss function to describe the hybrid DP-optimality. The performance of the adaptive DP-optimal design will be discussed both in terms of theoretical performance as well as the outcomes from the pilot study.

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Platform for adaptive optimal design of nonlinear mixed effect models

A. C. HOOKER[1] AND J. G. COEN VAN HASSELT[2]

[1] Department of Pharmaceutical Biosciences, Uppsala University
P.O. Box 591, SE-751 24 Uppsala, Sweden
[2] Department of Clinical Pharmacology, Netherlands Cancer Institute
Amsterdam, Netherlands

Recent years have seen an increasing interest in adaptive trial design methodologies. With the growing use of nonlinear mixed effect (NLME) models to support clinical development, adaptive optimal design (AOD) approaches have also become increasingly relevant. A recent survey has found that for 10 European pharmaceutical companies the importance of AOD for NLMEM was ranked, on average, 4 on a scale of 5 [1]. Previous work has demonstrated the usefulness of AOD in PET occupancy studies [2], bridging studies [3], and population PK in children [4]. The methodology generally requires population optimization of an initial cohort of patients using a population model, analysis of that data using estimation software, updating of the prior information used for optimization and then optimization of a new cohort of patients. This process is repeated until a stopping criterion is met. Thus, for each step of an AOD, both optimization and estimation is needed, plus additional components. For evaluation and optimization of this process, multiple simulations of an AOD is needed. A general algorithm for implementing AOD methodology was created using the optimal design software package PopED [5,6] which links to NONMEM [7] and Perl speaks NONMEM [8] for the estimation steps. The AOD platform has a modular setup, so that each portion of the AOD can be substituted for alternative strategies, and a generalized and flexible design, allowing modifications for specific study design characteristics. The developed platform will be available as freeware when released. The implementation has been used to explore an example of a PK bridging study in children using allometric scaling and a simplified maturation model on clearance [9]. Various AOD strategies are explored with various levels of initial model misspecification. We show that in many cases AOD can improve parameter precision and accommodate for initial model misspecification compared to standard optimal design techniques. However, if no adaptation is needed or if the adaptation process is not carefully chosen a decrease in parameter precision or even parameter bias can be introduced, demonstrating the need for prior investigation, through simulation, of the AOD process. Acknowledgement: This work was supported in by the DDMoRe (www.ddmore.eu) project.

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Bayes Risk as an Alternative to Fisher Information in Determining Experiment Designs for Nonparametric Models

D.S. BAYARD AND R. JELLIFFE

Scientific Consultants
Laboratory of Applied Pharmacokinetics
Children's Hospital of Los Angeles
Los Angeles, California

This paper presents an experiment design approach for nonparametric models where the Bayesian prior is specified as a finite discrete probability distribution. Multiple model priors of this type are generated routinely by nonparametric population modeling programs such as NPML, NPEM and NPAG. Because of the discrete prior, the underlying multiple model estimation process can be interpreted as a classification problem. As a classification problem, estimator performance is most directly scored in terms of how well it minimizes the Bayes risk, which is defined as the probability that a maximum a-posteriori (MAP) estimator will misclassify a subject. Minimizing the Bayes risk as an experiment design criteria provides an interesting alternative to using D-optimality, or other standard criteria based on the asymptotic Fisher Information matrix. Unfortunately, evaluating Bayes risk is computationally unwieldy for many problems of practical interest. However, a theoretical upper bound on the Bayes risk has recently appeared in the literature, c.f. [1]. The upper bound is useful because it can be computed analytically without requiring numerical integration or Monte Carlo analysis. Because of its clear computational advantages, this paper proposes experiment designs for nonparametric models based on minimizing the Bayes risk upper bound. Using a simple example, certain advantages are demonstrated relative to the ED, EID, and API Fisher-based information measures from the literature. It is then shown how the Bayes risk overbound can be applied to the problem of optimal experiment design in a pharmacokinetic application.

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Influence of the Ratio of the Sample Sizes Between the Two Stages of an Adaptive Design: Application for a Population Pharmacokinetic Study in Children

C. DUMONT[(1,2)], M. CHENEL[(2)], F. MENTRÉ[(1)]

[(1)] UMR 738, INSERM, University Paris Diderot, Paris, France
[(2)] Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Suresnes, France

Objectives: Nonlinear mixed-effect models are used to analyse pharmacokinetic (PK) data during drug development, notably in pediatric studies [1,2]. To optimise their design, adaptive designs [3], among which two-stage designs, allow to provide flexibility and could be more efficient than fully adaptive design [4]. We investigated, with a simulation approach, the impact of a two-stage design on the precision of parameter estimation, by varying sample size ratio of each stage, when the "true" and the a priori PK parameters are different.

Methods: A two-stage design for a population PK study proceeds as follows. At the 1st stage, from a model and a priori population parameters Ψ_0, data for N_1 children are collected based on design ξ_1, optimised with Ψ_0. The same design is assumed for all children. At the 2nd stage, ξ_2 for the remaining N_2 children is optimised using a combined information matrix with the estimated Ψ_1 after 1st stage. At the end, Ψ_2 parameters are estimated using data of $N = N_1 + N_2$ children. We evaluated this approach and the influence of the ratio between N_1 and N_2 by a clinical trial simulation in R. The PK model was a 2-compartment model with 1st-order absorption. Optimal one- and two-stage designs were derived using PFIM [5], assuming $N = 60$ children with the same design (5 sampling times) at each stage. We assumed different "true" $\Psi^\star$ and a priori Ψ_0 parameters. From Ψ_0, we optimised ξ_1. From 10 simulated data sets, 10 vectors Ψ_1 were estimated with SAEMIX [6]. ξ_2 was then optimised for each Ψ_1. 10 simulations were performed with each of the 10 ξ_2 designs. We obtained 100 data sets. Relative root mean square errors (RRMSE) for the 100 estimated Ψ_2 were compared for the extremum designs 60-0 (ξ_1) and 0-60 ($\xi^\star$, optimal design), and two-stage designs: 50-10 (ξ_{50-10}), 30-30 (ξ_{30-30}), 10-50 (ξ_{10-50}). The standardized RRMSE was calculated for each parameter and each design as the RRMSE divided by the RRMSE of $\xi^\star$. For each design, mean standardized RRMSE was then computed.

Results: The mean standardized RRMSE equalled 2.48 for ξ_1 optimised with the wrong Ψ_0. The mean standardized RRMSE of the two-stage designs were very close to the one for $\xi^\star$, and equalled 1.15, 1.06, 1.07 for ξ_{50-10}, ξ_{30-30} and ξ_{10-50}, respectively.

Conclusions: The two-stage designs allowed to compensate from the unsatisfactory result obtained for ξ_1. When the size of the 1st cohort was small, the result was slightly worse. The design with $N_1 = N_2$ appears to be a good compromise.

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Improving Cognitive Testing with IRT and Optimal Design

S. UECKERT

Pharmacometrics Research Group
Department of Pharmaceutical Biosciences
Uppsala University, Sweden

In many complex neurologic disorders, such as Alzheimer's disease or Parkinson's disease, diagnosis and monitoring of patients depends on cognitive tests that rate a subject's ability to perform certain tasks. For these diseases, the potential to identify patients or to detect drug effects is tightly coupled to the sensitivity of the assessment. Despite the high importance of a sensitive assessment, the most frequently used cognitive tests are historically developed heuristics rather than explicitly optimized test suits. Item response theory together with optimal design methodology provides a framework that can (i) quantify the sensitivity of different test items, (ii) choose the optimal set of tests for a certain patient population and (iii) adaptively assess a subject's cognitive capability. This presentation illustrates the implementation of items (i)-(iii) using the example of the ADAS-cog test in Alzheimer's disease.

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Integrability and Bayesian D-optimality

T. WAITE

Mathematical Sciences
University of Southampton

One trend in recent years has been towards the application of more complex, typically nonlinear, empirical and mechanistic models to the analysis of experimental data. Examples include mixed-effects nonlinear compartmental models in the population approach to pharmacokinetics, and generalized linear models in industrial experiments, sometimes including random effects to model variation between blocks. These models have in common the property that the performance of any proposed design, for instance under D-optimality, may depend on the unknown values of the model parameters. Several methods have been proposed to derive designs which are reasonably efficient under a range of plausible values for the parameters, such as maximin and (pseudo-)Bayesian approaches. The latter requires specification of a prior distribution on the likely values of the parameters, but does not necessarily assume that a fully Bayesian analysis will be conducted.

We consider the construction of designs when the prior distribution is such that any fixed design is potentially uninformative; that is, the information matrix may have determinant arbitrarily close to zero. It is shown that the most popular formulation of the Bayesian D-optimality criterion experiences difficulties with integrability in a wider range of scenarios than has previously been made explicit. We give a simple example where it can be shown analytically that the usual mean-log-determinant objective function is degenerate, in the sense that it fails to discriminate between any finitely-supported designs. The example is of an exponential regression model, with a prior distribution of bounded support. This can be viewed as a very simple compartmental model with no random effects, and so integrability may be of concern also in Bayesian design for population pharmacokinetics. We consider two potential solutions to this issue. Firstly, it is demonstrated that the objective function may be non-degenerate for designs defined through a probability density function. Secondly, alternative optimality criteria are proposed which are better-behaved.

Bayesian inference and design space identification for nonlinear chemical kinetics

D. WOODS

Mathematical Sciences
University of Southampton

In the pharmaceutical industry, a regulatory requirement for a new active pharmaceutical ingredient (API) is the identification of a multivariate design space; that is, a subregion of the experimental space defined by the combinations of the controllable variables such that there is acceptable confidence of the API meeting some pre-defined purity specifications.

The use of chemical kinetics models, derived from systems of differential equations, can provide an efficient and effective method of modelling yields and impurities from a reaction but statistical inference is complicated by the nonlinear nature of the model and, in many cases, by the fact that the differential equations may not have an analytically tractable solution. We present ongoing work for Bayesian inference for such models, borrowing ideas from the field of calibration of expensive computer models. We demonstrate how the use of cheap, statistical, approximations to the intractable solution of the differential equations can make Markov Chain Monte Carlo computationally feasible. The methodology is demonstrated using a data set from GlaxoSmithKline for which we develop a multivariate design space for three responses. Some areas for future work will also be identified.

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