

Bibliography for Computer-Assisted Trial Design

Computer Simulation in Clinical Drug Development: An Overview

Computer simulations of models of drug action have contributed to clinical drug development. Hale et al. provides an overview of the potential benefits and the available software tools.¹

- [1] Hale M, Gillespie WR, Gupta SK, Tuk B, Holford NH. Clinical trial simulation: streamlining your drug development process. *Applied Clinical Trials* 1996 Aug;5(8):35-40

Modeling Variability in Drug Response

Computer simulations relate pharmacologic and biologic variability, both within and between individuals, to clinical outcome. Quantitation of variability is a topic of broad interest. Sheiner and Ludden, and Samara and Granneman have written reviews on the subject.^{1,2}

- [1] Sheiner LB, Ludden TM. Population pharmacokinetics/dynamics. *Annu Rev Pharmacol Toxicol* 1992;32:185-209.
[2] Samara E, Granneman R. Role of population pharmacokinetics in drug development. A pharmaceutical industry perspective. *Clin Pharmacokinetics* 1997 Apr;32(4):294-312

Optimizing Trial Design

Computer simulation has been used to analyze and optimize treatment outcome for different combinations of design variables. Kodlin and Cohn developed a tumor growth model to predict the effect of several treatments on the measurement of tumor diameter.¹ Computer simulations demonstrated that considerable changes in tumor size may not be detectable in clinical trials. Elashoff et al. developed an ulcer model to describe the relationship between a duodenal ulcer treatment and ulcer recurrence.² The simulations suggested that endoscopy intervals of at most four weeks were necessary to support a claim of ulcer prevention. Schentag et al. determined the percent by which the area under the antibiotic concentration-time curve should exceed the minimum inhibitory concentration for bacterial eradication.³ Computer simulations were required to take into account variability in pharmacokinetics and in bacterial susceptibility. Wientjes et al. maximized tissue exposure to a chemotherapeutic by varying dose, residual volume, urine production, dose volume, and urine pH.⁴ Gooley et al. investigated the design of a phase I/II clinical trial in bone marrow transplantation, in which dose adjustment increased the risk of one complication while decreasing the risk of another.⁵ Rouse et al. simulated a model which predicted the effect of preventive zidovudine therapy on survival and quality of life in neonates.⁶ They concluded that zidovudine usage in asymptomatic HIV-infected pregnant women is associated with a greater number of quality-of-life years in children. The simulated relationship between dose, time, and the percentage of patients with adequate pain relief suggested that 30 mg intramuscular ketorolac was the optimal initial dose for postoperative pain relief.⁷ A model for remifentanyl anesthesia suggested that age and lean body mass are important demographic factors to consider when selecting a dosage regimen.⁸

- [1] Kodlin D, Cohn I. Simulation experiments of tumor measurement in clinical trials. *Cancer Treat Rep* 1978 Dec;62(12):2077-2083
[2] Elashoff JD, Koch GG, Chi GY. Designing a clinical trial to demonstrate prevention of ulcer recurrence: modelling simulation approaches. *Stat Med* 1988 Aug;7(8):877-888
[3] Schentag JJ, Nix DE, Adelman MH. Mathematical examination of dual individualization principles (I): Relationships between AUC above MIC and area under the inhibitory curve for cefmenoxime, ciprofloxacin, and tobramycin. *DICP* 1991 Oct;25(10):1050-1057
[4] Wientjes MG, Badalament RA, Au JL. Use of pharmacologic data and computer simulations to design an efficacy trial of intravesical mitomycin C therapy for superficial bladder cancer. *Cancer Chemother Pharmacol* 1993;32(4):255-262
[5] Gooley TA, Martin PJ, Fisher LD, Pettinger M. Simulation as a design tool for phase I/II clinical trials: an example from bone marrow transplantation. *Control Clin Trials* 1994 Dec; 15(6):450-462
[6] Rouse DJ, Owen J, Goldenberg RL, Vermund SH. Zidovudine for the prevention of vertical HIV transmission: a decision analytic approach. *J Acquir Immune Defic Syndr Hum Retrovir* 1995 Aug;9(4):401-407
[7] Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. *Clin Pharmacol Ther* 1996 Dec;60(6):619-635
[8] Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanyl. II. Model application. *Anesthesiology* 1997 Jan;86(1):24-33

Optimizing Trial Conduct

Computer simulations provide a means to investigate the impact of variability in trial execution on the results of a trial. GebSKI et al. utilized computer simulations to recommend early closure of a clinical trial of chemotherapy for breast cancer.¹ The decision was based upon interim determination of survival time distributions after entry of 243 patients in 2 years, which indicated greater power than predicted prior to starting the study. Mark and Gail investigated ordinal categorical data to determine how best to analyze missing data, when the state of being missing was not completely at random.² Albert and Demets investigated the effects of non-comparability of drug and placebo compliance on treatment efficacy in

Phase III clinical trials.³ The simulations suggested that moderate non-comparability may produce large biases in efficacy estimates.

[1] Gebski V, McNeil D, Coates A, Forbes J. Monitoring distributional assumptions and early stopping for a prospective clinical trial using Monte Carlo simulation. *Stat Med* 1987 Sep;6(6):667-678

[2] Mark SD, Gail MH. A comparison of likelihood-based and marginal estimating equation methods for analyzing repeated ordered categorical responses with missing data: application to an intervention trial of vitamin prophylaxis for oesophageal dysplasia. *Stat Med* 1994 Mar;13(5-7):479-493

[3] Albert JM, Demets DL. On a model-based approach to estimating efficacy in clinical trials. *Stat Med* 1994 Nov;13(22):2323-2335

Analyzing Model Assumptions

Computer simulations allow identification and analysis of model assumptions which are critical to trial success. Machado et al. developed a model of the treatment of HIV infection, to investigate the extent to which a surrogate endpoint can predict clinical benefit.¹ Computer simulations demonstrated substantial time savings by using the surrogate endpoint. However, estimates of clinical benefit were overestimated under conditions of delayed toxicity or when the beneficial effects were transient. Nani and Oguztoreli developed a model to describe adoptive cellular immunotherapy.² Computer simulations quantitate the contribution of critical variables, such as time delays, tumor growth parameters, and immunocyte-to-tumor cell ratio, to the therapeutic efficacy of cellular immunotherapy.

[1] Machado SG, Gail MH, Ellenberg SS. On the use of laboratory markers as surrogates for clinical endpoints in the evaluation of treatment for HIV infection. *J Acquir Immune Defic Syndr* 1990;3(11):1065-1073

[2] Nani FK, Oguztoreli MN. Modelling and simulation of Rosenberg-type adoptive cellular immunotherapy. *IMA J Math Appl Med Biol* 1994;11(2): 107-147

Comparing Trial Designs

Computer simulations provide a methodology to compare different design strategies or to validate new strategies. O'Quigley et al. proposed a new Phase I paradigm which involved determining the dose which causes a certain probability of toxicity instead of defining the entire dose-toxicity curve.¹ Piantadosi et al. recommended to incorporate AUC measurements to more rapidly achieve the target toxicity level.² Sheiner et al. compared dose ranging designs in their capability to determine the dose-response relationship.³ Girard et al. investigated the role of confounding factors such as pharmacodynamic carry-over to determine the dose-response relationship in Phase II clinical trials.⁴ Recent papers have examined the pharmacodynamic benefits of dose-controlled versus concentration-controlled trials,⁵⁻⁶ and concentration-controlled versus effect-controlled trials.⁷⁻⁸

[1] O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. *Biometrics* 1990 Mar;46(1):33-48

[2] Piantadosi S, Liu G. Improved designs for dose escalation studies using pharmacokinetic measurements. *Stat Med* 1996 Aug;15(15):1605-1618

[3] Sheiner LB, Hashimoto Y, Beal SL. A simulation study comparing designs for dose ranging. *Stat Med* 1991 Mar;10(3):303-321.

[4] Girard P, Laporte-Simitsidis S, Mismetti P, Decousus H, Biessel JP. Influence of confounding factors on designs for dose-effect relationship estimates. *Stat Med* 1995 May;14(9-10):987-1005.

[5] Sanathanan LP, Peck CC. The randomized concentration-controlled trial: an evaluation of its sample size efficiency. *Control Clin Trials* 1991 Dec;12(6):780-794

[6] Endrenyi L, Zha J. Comparative efficiencies of randomized concentration- and dose-controlled clinical trials. *Clin Pharmacol Ther* 1994 Sep;56(3):331-338

[7] Levy G, Ebling WF, Forrest A. Concentration- or effect-controlled clinical trials with sparse data. *Clin Pharmacol Ther* 1994 Jul;56(1):1-8

[8] Ebling WF, Levy G. Population pharmacodynamics: strategies for concentration- and effect-controlled clinical trials. *Ann Pharmacother* 1996 Jan;30(1):12-19

Discriminating Between Competitive Drugs

Computer simulations provide a means to identify and design the best way to discriminate between competitive drugs. Context-sensitive half-time, a pharmacokinetic concept developed with computer simulation, quantitates the contribution of distribution and elimination processes to the termination of drug effect.¹ This concept has been used to characterize and differentiate opioids being developed for anesthetic purposes.^{2,3}

[1] Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992 Mar;76(3):334-341

[2] Lemmens HJ, Dyck JB, Shafer SL, Stanski DR. Pharmacokinetic-pharmacodynamic modeling in drug development: application to the investigational opioid trefentanil. *Clin Pharmacol Ther* 1994 Sep;56(3):261-271

[3] Egan TD. Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. *Clin Pharmacokinet* 1995 Aug;29(2):80-94