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SIMULATION OF CLINICAL TRIALS

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■ **Abstract** Computer simulation of clinical trials has evolved over the past two decades from a simple instructive game to ''full'' simulation models yielding pharmacologically sound, realistic trial outcomes. The need to make drug development more efficient and informative and the awareness that many industries make extensive use of simulation in product development have advanced considerably the use of simulation of clinical trials in pharmaceutical product development over the past decade. The structural and stochastic components of trial simulation models are explained as a prelude to a listing of representative simulation projects, reflecting investigative applications of statistical methods, trial design comparisons, and full simulation of new drugs being developed. Lessons learned from these projects are reviewed in the context of their current impact and potential for influencing the future of drug development.

INTRODUCTION

Computer simulation is the process of building a mathematical model that mimics a real-world situation and then using the model to conduct experiments in order to describe, explain, investigate, and predict the behavior of that situation (1). Simulation furnishes scientists with a conceptual tool for translating often-complex, real-world subject matter into a simplified form (a mathematical model), generalizing detail and exposing important assumptions. The model should capture all crucial aspects of the physical situation being described. By employing the model, simulation experiments can explore assumptions made about the model's structure and parameters. Additionally, model-based simulations may enable the investigation of actual experiment designs, which, in turn, might shed light on the model's assumptions.

The clinical trial is the preferred modern strategy for empirical evaluation of medical therapy (2). As such, it serves as a key component of the drug devel-

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opment process, when adequately designed and conducted, by providing information with which to weigh the risks and benefits of a compound. This information is used in risk management at various levels: at a regulatory level when a government agency determines, based on this information, whether or not a candidate compound may be marketed; and in a clinical setting when a physician decides whether, and if so, how a drug should be administered to a patient (2).

Clinical trial simulation is the abstraction of the clinical trial process. It is used to investigate assumptions and to influence trial design in order to maximize the amount of pertinent information gained throughout this process about the drug. Simulation is applicable to many areas of the clinical trial process. The focus here centers on the use of simulation with models based upon the dose-concentration-effect relationship (3) that reflect the disposition and effect of drugs as observed in clinical trials. In this chapter, we describe (*a*) motivations and history, (*b*) the general methodology of clinical trial simulation, including a brief description of current software available for performing such simulations, (*c*) some examples and lessons learned from using simulation in clinical trial design, and finally (*d*) our view of the current and future impact and directions for this powerful technology in drug development.

Motivations

Computer simulation has been used in the automotive and aerospace industry for over 20 years, improving the safety and durability of new products at a reduced development cost (4, 5). Similarly, the fundamental motivation for clinical trial simulation in pharmaceutical product development is to increase the efficiency of development, e.g. minimizing cost and time, while maximizing the informativeness of data generated from the trial. Clinical trial simulation aims to integrate relevant information and enable critical assessment of assumptions before resources are invested in conducting the actual clinical trial.

Before the 1990s, the drug development process, from initiation of preclinical studies through drug approval, took up to 12 years: 3.5 years for the preclinical phase; 1, 2, and 3 years, respectively, for clinical phases I, II, and III; and approximately 2.5 years for the Food and Drug Administration (FDA) review phase (6). Despite significant reductions in preclinical and regulatory review times, the clinical phase of development continues to consume up to 50% of overall drug development time. In 1997, research and development costs were estimated to be greater than $359 million US dollars (7), the majority of which was associated with the conducting of clinical trials. Nearly one third of the cost and over one half of the time (7.2 years) necessary to bring one new drug through FDA approval is spent on clinical development (8).

Why has drug development been so time-consuming and expensive? Often trials have had to be repeated because of flaws in trial design and performance that resulted in inadequate information about the safety or effectiveness of the new drug being tested (9). Identifying why a trial failed and how to prevent the failure in future trials is an additional use of clinical trial simulation. Often a

deeper understanding of drug disposition and action may be achieved during the simulation model building process, and this understanding can influence the design of subsequent trials to increase the potential for successfully achieving the scientific goals of the program.

History

The term clinical trial simulation may have been first used to describe a game entitled ''Instant Experience'' (10) during a teaching course for doctors and scientists interested in learning about practical difficulties and sources of error in clinical trial design and performance. Patient information was ''simulated'' by the game organizers, and participants were split into groups charged with designing a clinical trial to detect whether a therapeutic difference existed between two drugs, with gender as the sole prognostic factor. While developing the game rules, the organizers created a computer program to generate simulated patients for future games.

The computer program was used at other workshops (11–13), as more simulation programs began appearing to explore complex statistical aspects of clinical trial design. For example, prognostic factors influence a patient's ability to respond to treatment and often in clinical trials the number of combinations of these factors approaches the sample size. Traditional methods are inadequate for analyzing these situations, so when a new sequential treatment assignment method was developed, it was subsequently tested using simulation (14). Other aspects of trials that were explored using clinical trial simulation included sample size, influence of dropouts (15), and problems with early termination of a clinical trial (16). It was recognized that as designs were becoming more complex, traditional statistical theory was no longer valid. Simulation, however, offered the means for generating complex data sets, which included prognostic factors, for testing new analysis methods (17).

Despite new developments in statistical analysis, the underlying goal remained the same: to design a clinical trial to detect a statistically significant difference between treatments. The question being asked in the trial was simply does the drug work rather than how much does the drug work (18).

In the 1980s, clinical trial simulation entered a more informative phase, with several advances, making simulation more than only a tool for statisticians. The desktop computer was becoming more powerful and prevalent, giving researchers easy access to a tool for creating complex mathematical models reflecting fundamental pharmacological principles, e.g. pharmacokinetics and the dose-response relationship. In 1986, Tiefenbrunn et al (19) used a physiologically-based computer simulation of biochemical reactions in response to concentrations of circulating tissue-type plasminogen activator (t-PA) to prospectively characterize its pharmacodynamics, using six patients given t-PA for coronary thrombosis. The findings from this model development and simulation process permitted the prospective evaluation of dosing regimens for t-PA in clinical trials. Using this model and computer simulation studies, it was shown that the degree

of fibrinogenolysis induced by t-PA administration was almost independent of the dosing schedule (19, 20). This was an early example of applying simulation to clinical trials that yielded more than just a binary result.

In clinical pharmacology, models are created to describe data and provide a logical, biological explanation for observed drug disposition and pharmacologic effect. The early 1980s witnessed an explosion in the development of compartmental modeling analysis in clinical pharmacology (21, 22). Software (23) became available for modeling the population nature of clinical data, and literature on modeling concentration-effect (24) relationships and simultaneous pharmacokinetic and pharmacodynamic modeling (25) described how clinical pharmacology could benefit from a modeling approach. A series of papers by Sheiner & Beal (26–28) compared the population approach to traditional methods of clinical data analysis, demonstrating the limitations of traditional methods (see Table 2).

Simulation was a natural progression from the increased use of mathematical models in clinical pharmacology and has been used as an informative tool for evaluating complex clinical trial designs. One such design is the randomized concentration-controlled trial (RCCT) (29, 30). Simulation was used to investigate trial designs that efficiently provide accurate and precise estimates of pharmacokinetic parameters characterizing the dose-concentration-effect relationship in the face of high between-subject pharmacokinetic variability (see Table 4).

Prior to the early 1990s, there were no known attempts to simulate realistically an entire clinical trial based on the simultaneous integration of (*a*) a pharmacokinetic-pharmacodynamic (PKPD) drug action model, (*b*) a disease progress or placebo effect model, and (*c*) trial subject demographic covariates, between-subject variability and unexplained variability, and typical protocol deviations (e.g. dropouts, partial compliance). Simultaneously, this new and complex (''full'') level of clinical trial simulation was initiated by two groups. For purposes of teaching, the educationally sponsored (31) RIDO (RIght DOse first time) software (32) was developed. The RIDO program, which incorporated the full clinical trial simulation capability, was developed to educate pharmaceutical scientists about the basic principles of clinical pharmacology and the role of variability in understanding why clinical trials are difficult to design. A pharmaceutical developer, motivated by the FDA to evaluate the feasibility of a proposed concentration controlled trial, employed full clinical trial simulation to determine not only feasibility but also trial design features such as individualized dose adjustment procedure and sample size (56, 57) (see Table 4). The evolution of applications and software for full clinical trial simulation technology has accelerated during the past 5 years, as evinced by several key conferences and workshops (33–35) sponsored by two centers that have championed methodological advances in drug development science (31, 36).

Any software that allows for the modeling of data may be used to perform a simulation [e.g. SAS (SAS Institute, Cary, NC), NONMEM (UCSF, San Francisco, CA), Mathcad (MathSoft, Inc. Seattle, WA)], but since 1996, two innovative commercial simulation software products have provided special capabilities dedicated to simulation of clinical trials: Pharsight Trial Designer (37)

and MGA-ACSL Biomed (38). The ACSL Biomed clinical trial simulation program incorporated new routines based on a mature simulation language, advanced continuous simulation language (CACSL) (38), into existing biomedical modeling and simulation software. Use of these software packages (now both owned by Pharsight Corp.) is reflected in several recent clinical trial simulations (see Table 4). A more detailed account of the history and evolution of clinical trial simulation software in recent years is available (39).

So rapidly has this field evolved in the past few years that a draft guideline describing good practices for modeling and simulation of clinical trials in drug development has recently been published and public comment has been invited (40). Figure 1 lists the main sections and topics described in these guidelines. A key concept in these guidelines is the recommendation that clinical trial simulation be approached as an ''experiment.'' The simulation experiment should have a well-defined plan developed by those who will be directly involved in performing the simulation and applying the results of the experiment. Execution of the planned simulations will usually lead to modification of the plan as new results are made available. The simulation plan is therefore a dynamic document. To reap the full benefits of the simulation, it is essential for the plan to include a formal strategy for assessment. For consistency, the remainder of this review follows the terminology and conceptual framework recommended in the draft guideline. Readers are encouraged to study the draft guideline in conjunction with this chapter for a fuller understanding of the current state of the art of clinical trial simulation.

ANATOMY OF A CLINICAL TRIAL SIMULATION

The steps in performing any type of computer simulation are similar, with each step expected to lead to the next. Often work on a step may reveal problems with a previous step, which will then have to be revisited. This iterative process ultimately aids the trial design team in understanding underlying assumptions impacting the quality of information obtained from the trial.

Clinical Trial Simulation Questions

Clinical trial simulation has developed in the context of increased understanding of clinical pharmacology and deals with questions that are raised about how to incorporate this knowledge into the design of clinical trials. Sheiner (18) has pointed out a useful conceptual framework for the epistemology of drug development. Phase III clinical trials are usually undertaken to answer a yes/no question (''Does the drug work?'') that is approached statistically by a test of the null hypothesis. This is a confirming type of trial. Earlier in drug development, trials aim to investigate properties of the drug that may be elucidated using statistical estimation—e.g. the treatment effect size and dose-response relationship, etc. This is a learning type of trial.

1 PLANNING A SIMULATION PROJECT
- *1.1 Simulation Team*
- *1.2 Simulation Plan*
- *1.3 Overall Objectives and Specific Aims*
- *1.4 Assumptions*
- *1.5 Design of the Simulation Project*
- *1.6 Simulation Project Design*
  - 1.6.1 Experimental Design
  - 1.6.2 Replications
  - 1.6.3 Trial Design Properties
- *1.7 Models for Simulation*
  - 1.7.1 Input-Output Models
  - 1.7.2 Covariate Distribution Models
  - 1.7.3 Execution Models
  - 1.7.4 Source of Models
- *1.8 Computational Methods*
  - 1.8.1 Random Number Generation
  - 1.8.2 Simulation of Probability Densities
  - 1.8.3 Differential Equation Solvers
  - 1.8.4 Computer Requirements
- *1.9 Analyses*
- *1.10 Critical Assessment of Simulation Results*
- *1.11 Reporting*

2 EXECUTION OF THE SIMULATION PROJECT
- *2.1 Model Building*
- *2.2 Model Checking and Validation*
- *2.3 Analyses*
  - 2.3.1 Replication Analysis
  - 2.3.2 Simulation Study Analysis
- *2.4 Report Contents*

3 CRITICAL ASSESSMENT OF SIMULATION
- *3.1 Prospective Evaluation*
- *3.2 Retrospective Evaluation*
- *3.3 Cumulative Evaluation*

Figure 1 From the Table of Contents of Simulation in Drug Development: Good Practices (40).

Confirming: Power

Confirming-type trials are designed to give an answer to such simple binary or categorical questions as whether or not the drug works. If the null hypothesis is rejected, then a clear answer is obtained. If the null hypothesis is not rejected, it could be because the drug does not actually work or because the design or analysis of the trial was not sufficiently powerful. A priori power analysis seeks to protect against this kind of ''Still don't know'' answer to the ''Does the drug work?'' question. There is extensive theory and experience of evaluating the power of a

design to answer a yes/no question for many common design and analysis method combinations.

Learning: Power, Bias, and Precision

In addition to an affirmative answer to the yes/no question of whether a drug works, questions of direct interest to the patient and prescriber, such as the size of the effect or when the peak effect occurs, must also be answered. From a statistical perspective, these are estimation problems, and analyses that address these main questions of learning trials are rare. In this instance, clinical trial simulation can be a powerful tool. Responses are predicted using reasonable models of drug action and disease progress, along with stochastic elements such as patient variability and measurement error.

Modeling assumptions, trial design properties, and analysis methods can all be evaluated to understand the power of a design to answer more informative yes/no questions based on complex underlying concepts, e.g. whether an offset drug effect model can be distinguished from a slope effect model (54). Simulation can also be used to evaluate the bias and precision of the estimates of quantitative descriptors reflecting treatment effect size, time to peak effect, etc.

Simulation Model

Computer simulation requires a mathematical model that adequately reflects the actual situation being simulated. The model employed in a clinical trial simulation must, at a minimum, approximate a description of the clinical effect of a drug and, optimally, should be based upon the dose-concentration-effect relationships for the drug. The rapidly developing interest in clinical trial simulation has led to a variety of overlapping terms. The terminology used for defining a simulation model is listed in Table 1 and is further elaborated in the following sections. A simulation model is made up of three components (40): input-output model, covariate distribution model, and trial execution model.

Input-Output Model The input-output (IO) model incorporates all scientific knowledge about the disease and drug. It may include (but is not limited to) the following components:

Structural Model The structural model incorporates pharmacokinetics, pharmacodynamics, disease status and progress, and placebo responses.

Covariate Model The covariate model serves to integrate patient-specific features (covariates such as age, weight, etc) that are associated with systematic differences between individuals. Covariate models are used to predict model parameters typical of an individual with a particular combination of covariates.

TABLE 1 Terminology for models involved in clinical trial simulations

Model	Components	Partially descriptive synonyms
Input-output model	Pharmacokinetics Pharmacodynamics[a] Disease progress Placebo response Covariate model relating covariates to typical parameter values Population parameter variability that includes between- and within-subject variability Residual unexplained variability that includes measurement error and model misspecification error Pharmacoeconomics	Structural model Variance model Pharmacostatistical model Outcome model PKPD model[b] Drug intervention model
Covariate distribution model	Demographic covariates (e.g. age, weight, gender, disease severity, concurrent treatment) Distribution and covariance of demographic covariates	Population Model demographics Trial subject inclusion/exclusion criteria
Trial execution model	Nominal design (protocol) Deviations from nominal protocol	Trial design Deviation from protocol model Compliance model Subject withdrawal Missing observations Adaptive design model

[a]Pharmacodynamics includes drug effects on biomarkers, surrogate endpoints, and clinical endpoints and outcomes.
[b]PKPD, pharmacokinetics pharmacodynamics.

Pharmacoeconomic Model Project resource models, when employed, are considered part of the IO model because they predict responses (e.g. costs) as a function of the trial design and execution.

Stochastic Models The IO model includes stochastic components that include the following. (*a*) Population parameter variability comprises between-subject and within-subject variability in model parameters. In practical terms, within-subject variability is largely defined by between-occasion variability (42) but includes stochastic variation in parameters, such as clearance, that may occur within an occasion (within-occasion variability). A term often used for population

parameter variability is inter-individual variability. (b) Residual unexplained variability accounts for model misspecification and measurement error. A term often used for residual unknown variability is intra-individual variability.

Covariate Distribution Model The distribution of demographic covariates in the trial subject sample is obtained from a model for the distribution of covariates in the target trial population. Such a model reflects the expected frequency distribution of the various covariates and, more importantly, the relationships among the covariates, e.g. age and renal function are related, such that renal function typically decreases with age in an adult population. The covariate distribution model should not be confused with the covariate model used to relate covariates to IO model parameters (see above).

Trial Execution Model Although in real clinical trial practice, good faith attempts are made to perform or execute the trial according to the (nominal) trial protocol, human behavior and real-world events always intervene, and deviations or violations of the protocol are common. Thus, clinical trial simulations must recognize that the nominal trial protocol will never be executed with absolute perfection. There will be protocol deviations, e.g. subjects may withdraw, doses may not be taken as prescribed, or observations may be missing. Computer instructions that reflect both the nominal protocol and models for protocol deviations define the trial execution model.

Analysis of Simulated Data

Analysis of a Single Trial Replication Simulation may be used to define responses across subjects within a single trial. For the single clinical trial, the unit for replication is each individual in the trial. The outcome of the trial can be defined qualitatively, in terms of whether or not it supported the rejection of a statistical null hypothesis (in the case of a confirming trial), or quantitatively, when it provided estimates of the trial outcome measure effect size(s) (in a learning trial). An individual subject outcome measure might be a statistic such as the time of peak drug effect or slope of a dose-response curve.

Analysis of the Simulation Experiment Simulation may be used to define responses across trials. For the simulation experiment, the unit for replication is each clinical trial. The outcome of a simulation experiment will be based on the analysis of the outcome measures obtained from each clinical trial replication. The power of a specific clinical trial design is determined from the number of trials that reject the null hypothesis. Bias and precision of statistics such as the estimated treatment effect size, or parameters such as the maximum drug effect, are typically computed. When simulation is employed to investigate influence of various trial design features, a sensitivity analysis may be employed in a meta-analysis framework to compare power or estimation properties of the varying design factors.

CLINICAL TRIAL SIMULATION SOFTWARE

Numerous techniques are available for clinical trial simulation and most of the work reported to date has used general-purpose modeling and statistical software such as SAS. Clinical trial simulation involves several steps, each of which may be performed using different software tools.

Development of a Simulation Model

Input-Output Model PKPD model building and parameter estimation, typically using data from previous clinical trials, may be done using either individual nonlinear regression programs [e.g. WinNonlin (Pharsight, Mountain View, CA), ADAPT II (Biomedical Simulations Resource, Los Angeles, CA)] or population mixed effect modeling programs [e.g. NONMEM (23), NPML (44)].

Covariate Distribution Model We are not aware of specific software for developing a model of the distribution of covariates in a target population for a clinical trial, thus general-purpose software is employed. Large databases exist that could be used to create such a model, e.g. NHANES (45).

Trial Execution Model Models accounting for the nominal trial protocol and deviations such as subject withdrawal, variable compliance with medication, and missing observations have typically been based on ad hoc procedures within the simulation software program employed for the simulation. Software for collecting and reviewing medication compliance is available from suppliers of electronic monitoring systems (46). Attempts have been made to use such data to develop a model suitable for simulation (47).

Simulation

The same software program used for development of the IO model may be used to simulate clinical trial response data. The key element is the ability to add random (stochastic) variability to the model as residual error (measurement and model misspecification error) and IO model parameter variability. More realistic simulations will also include stochastic variation in sampling subject specific values from the covariate distribution model, and in the deviations from the nominal protocol defined by the trial execution model. Standard statistical software—e.g. SAS and S-Plus (MathSoft, Seattle, WA), or more specialized programs such as NONMEM and Pharsight Trial Designer—can accomodate all of these features. General statistical software is least convenient because all components of the simulation model must be created by the user. NONMEM has a comprehensive library of pharmacokinetic models but requires the user to create a data file to specify doses, covariates, and observation times for each subject. Dedicated commercial simulation software such as Pharsight Trial Simulator can be expected to provide more convenient trial simulations with predefined model and trial

design libraries, and for integration of all routines and procedures necessary for accomplishing the simulation.

Analysis of Simulated Data

For statistical analysis of a single simulated clinical trial, standard statistical software will most commonly be used for confirmatory-type trials but more complex model-based procedures (e.g. mixed effects nonlinear modeling with NONMEM) will be preferred for more informative learning trials (18). Commercial simulation software should allow the user to conveniently select from a variety of typical trial outcome measures (e.g. response at a specified time, peak response, area under the curve of a response) and perform standard analyses (e.g. analysis of variance). Most of the user-written software is employed to perform a set of replication level analyses and to summarize the simulation experiment results, e.g. clinical trial simulator, developed by one of us (NHG Holford).

For analysis of either a single trial replication or a simulation experiment, the distribution of individual or trial responses may be informatively displayed in graphical form, e.g. showing the scatter of responses as a function of time after the start of treatment or the distribution of outcomes from many trials. Meta-analysis of comparative power or estimation properties across varying trial design factors may be accomplished using standard analysis of variance or regression procedures.

REVIEW OF CLINICAL TRIAL SIMULATION PROJECTS

Below, we present representative examples of research projects or practical applications known to us that have used simulation in relation to clinical trial questions. Much recent work in this area has only been reported in abstract form or has been communicated primarily at conferences. Therefore, we have drawn extensively from our own experiences and describe them using the format of Holford et al (40). We acknowledge that the tables are incomplete in many places and apologize to authors whose work we may have incorrectly interpreted or of which we are unaware. We intend the tables to provide a view of what questions have been investigated and what techniques have been used. The ''Lessons Learned'' columns (Tables 2, 3, and 4) indicate what we think are key new knowledge and insights that have been derived with respect to the overall application of clinical trial simulation. Each project may have had other objectives but we have chosen not to elaborate on them.

We have identified three levels of simulation projects. The first deals with evaluations of statistical properties and analytical methods used as the basic tools of clinical trial simulation. The second entails the application of simulation to investigate the general properties of certain classes of clinical trial designs. The third deals with full clinical trial simulations applied to specific drugs and specific designs.

Investigations of Statistical Properties and Analytical Methods

Simulation has long been used by mathematical statisticians and others to investigate properties and performance of statistical and data analysis methods. Illustrative examples of such investigations applied to two widely employed PKPD model building and parameter estimation techniques can be seen in Table 2. These methodological investigations bear primarily on the properties of estimation methods that are widely used in the specific projects detailed below.

Simulations of a typical pharmacokinetic experiment, analyzed by two nonlinear regression estimation methods, enabled Peck et al (48) to describe the less biased and more precise parameter estimates derived from maximum likelihood estimation using a general parametric residual variance model (extended least squares) versus weighted least squares regression analysis. Likewise, Sheiner & Beal (28) demonstrated via simulation that estimation of population PK parameters using mixed-effects modeling enabled efficient use of sparse data compared with the two-stage weighted least squares method.

Investigations of Trial Designs

Simulation has also been used to investigate power and estimation properties of various clinical trial designs. Six illustrative examples that have utilized PKPD-type IO models in simulation models of common clinical trial designs are listed in Table 3. Simulations of competing clinical trial designs have been useful in evaluating their comparative advantages and limitations. Optimal sampling design methods, aimed at the timing of a minimum number of pharmacokinetic observations for estimation of model parameters with minimum bias and variance, were investigated by D'Argenio (49) comparing optimal designs with standard intensive sampling schemes. The investigation of randomized concentration controlled trial (RCCT) designs reported by Sanathanan & Peck (50) investigated the extent of improvement in sample size efficiency that can be gained from the RCCT design in comparison to the traditional randomized dose controlled trial design when between-subject PK variability is high. Following the theoretical investigation by simulation of escalation designs in learning type trials (51) pointed to a reevaluation of the merits of cross-over and dose-titration trials. The investigation by Holford (53) of the enrichment design used in confirmatory trials of tacrine (for Alzheimer's disease) showed that the criterion used to identify responders during a titration phase was little different from simple randomization, because of the unrecognized contribution of between-occasion variation in observing the cognitive response to treatment. The difficulties in distinguishing different drug effects on disease progression was highlighted by simulating trials of a pseudo-drug, pstat (54). This study also pointed out the value of considering monetary costs of alternative study designs. Finally, El-Tahtawy et al (55) used Monte-Carlo simulation to investigate bioequivalence trial designs applied to

TABLE 2 Simulation projects evaluating statistical and data analysis methods used in simulation of clinical trials

Statistical Property or Analytical Method	Reference	I/O Model	Covariate Distribution Model	Trial Execution Model	Simulation Experiment	Replication Analysis	Simulation Experiment Analysis	Lessons Learned
		Structural Model	**Covariate**	**Nominal Trial Design**	**Model Factors**	**Null hypothesis**	**Confirmatory Hypothesis**	
		Stochastic Component	**Data Source**	**Protocol Deviation Model**	**Design or Analysis Factors**	**Descriptive Aims**	**Learning Hypothesis**	
		Software		**Source**	**Software**	**Software**	**Software**	
		Data Source		**Software**	**Replications**			
Extended Least Squares Estimation	48	PK	None	Individual PK experiment	PPV, RUV, randomization seed	Estimation methods equally accurate and precise	Power (capacity to estimate true model parameters)	Simulation is a valuable procedure for evaluating novel nonlinear parameter estimation methods
		RUV		None	ELS vs WLS (various weights), initial PK parameter estimates	Bias and precision of estimates	Comparative bias and precision of ELS vs WLS estimates	
		LSNLR (61)		NA	LSNLR	LSNLR	Simple Statistics	
		Authors		NA	100 subjects			
Nonlinear mixed effects modeling (NONMEM)	28	PK	None	Individual PK experiment	RUV	Estimation methods equally accurate and precise	Capacity to estimate true model parameters	Simulation is a valuable procedure for evaluating novel population PK estimation methods
		PPV, RUV		None	NONMEM vs 2-stage WLS	Precision	Bias and precision of NONMEM vs 2-stage WLS estimates	
		NONMEM		NA	NONMEM	NONMEM	Simple Statistics	
		Authors		NA	50 trials			

NA: Not Applicable

TABLE 3 Simulation projects evaluating trial designs

Experimental Design Aspect	Reference	I/O Model	Covariate Model	Trial Execution Model	Simulation Experiment	Replication Analysis	Simulation Experiment Analysis	Lessons Learned
		Structural Model	Covariate	Nominal Trial Design	Model Factors	Null hypothesis	Confirmatory Hypothesis	(in all cases: simulation was a valuable procedure for evaluating competing clinical trial designs)
		Stochastic Component	Data Source	Protocol Deviation Model	Design or Analysis Factors	Descriptive Aims	Learning Hypothesis	
		Software		Software	Software	Software	Software	
		Data Source		Source	Replications			
Optimal Sampling Times	49	PK	None	Sequential population PK trial	PPV, RUV	Optimal vs. conventional sampling trials	Capacity to estimate true population parameters	"Optimal sampling and preexperiment simulation may be useful tools for designing informative pharmacokinetic experiments"
		PPV, RUV		None	Sampling times	PK estimates	Bias, precision	
		ADAPT		NA	ADAPT	ADAPT	Simple statistics	
		Author		NA	30 trials			
Randomized Concentration-Controlled Trial (RCCT) and Dose-Controlled Trial (RDCT) Designs	50	PK, PD	None	Parallel dose- & concentration response trial	PPV, RUV	Dose vs concentration control	Power	RCCT is more powerful & efficient than RDCT when PK PPV is high
		PPV, RUV		none	Concentration and dose control methods	Concentration – Effect slope estimate	Bias and precision	
		SAS		NA	SAS	SAS	SAS	
		Authors		SAS	5000 trials			
Escalation Design	51, 52	PD	None	Parallel, Crossover, Escalation	None	Treatments not different	Power	Escalation designs are valuable for learning type trials.
		PPV,RUV		None	Parallel, Crossover, Escalation	Treatment effect size	Bias	
		Author		NA	NONMEM	NONMEM	Simple statistics	
		NA		NA	50 trials			

TABLE 3 (continued) Simulation projects evaluating trial designs

Enrichment Design (Tacrine)	53	PK, PD, DP,PL	Smoker effect on drug sensitivity	Parallel, titration, enrichment	Fixed	Treatments not different	Power	Enrichment design for certain tacrine trials were flawed. Titration design is powerful. Automated procedures were required for complex simulation experiment and numerically intensive analysis
		PPV, RUV	Sponsor data	None	Number and timing of observations, Enrichment design	PK, PD, DP, PL model Parameter estimates	Bias and Precision	
		NONMEM		None	Trial Designer	NONMEM	CTS	
		Sponsor data		N/A	100trials			
Designs for Evaluating Disease Progress (Pstat)	54	PK, PD, DP,PL, PEC	None	Parallel	Offset, slope, both drug effects with linear DP model.	Drug has no effect	Power	Spread out sampling is essential to distinguish drug effects on disease progress. Cost is a major factor in evaluating designs.
		PPV, RUV		None	Number and timing of observations, dose size, number of subjects	PK, PD, DP, PL model parameter estimates	Bias and Precision Cost	
		NONMEM		NA	Trial Designer	NONMEM	CTS	
		Sponsor data		NA	100 trials			
Bioequivalence trials of highly variable drugs	55	PK	None	Crossover	Formulation release rate, RUV, parameter correlation	Power independent of RUV	Power	Served as basis for regulatory policy for bioequivalence designs
		PPV, RUV		None	Single vs multiple dose regimens	Bioequivalence		
		NA		NA	SAS	SAS	SAS	
		Authors			1000 trials			

NA: Not Applicable

highly variable drugs. These simulations were used to justify regulatory guidance documents (55; AA El-Tahtawy, personal communication).

Drug-Specific Clinical Trials

Tables 4 and 5 list characteristics of 19 recent clinical trial simulation projects involving specific drugs (some drug products are not identified to respect confidential information), nine of which were undertaken by the authors. These nine simulations, as well as the pioneer simulation of mycophenolate mofetil, are reported in greatest detail, whereas all others (Table 5) are less completely reported because of the lack of publicly available information. The entries in Tables 4 and 5 are similar, with the exception of the final right hand column, which reflects lessons learned from the author's simulation projects (Table 4) or stated goal of the other reported simulations (Table 5).

The simulation by Hale et al (56, 57) of a proposed concentration controlled trial was the first reported demonstration of the practical utility of a full clinical trial simulation that determined trial feasibility and influenced trial design features for an actual drug in development. It is important to note that this project was motivated by a specific request for the simulation by the FDA, signaling official regulatory interest and receptivity to this novel technology. Regulatory interest has persisted, as evinced not only by the FDA's acceptance of trial simulation in other regulatory submissions (see Table 4) but also Agency cosponsorship of several recent conferences and guidelines encompassing population modeling and trial simulation.

Evaluation of a new and evolving technology is essential as a guide to future directions for research, application, and evaluation. Table 4 lists several impediments for simulation, including difficulties encountered with retrospective data retrieval, nonavailability of adequate modeling databases (especially placebo and disease progress data), time pressures interfering with completeness of simulations, and useful prerequisites such as the need for input from disease experts, value of IO model features reflecting drug discontinuation and rebound effects, and value of standards for model diagnostics and model evaluation techniques. Although some of these matters have been considered in the good simulation practices guideline (40), others are philosophical and require cultural and attitudinal changes. For example, prospective integration of modeling and clinical trial simulation in a drug development program should optimally commence in the preclinical phase, leading to use of simulation in planning the first human clinical trial (58).

IMPACT AND FUTURE DIRECTIONS

Application of clinical trial simulation in contemporary drug development programs is variable and often absent or incomplete—hence, measurable impact is modest at best. Simulation of PK properties of a new drug, derived primarily from phase I normal volunteer studies, is sometimes utilized to define dosage regimens

TABLE 4 Simulation projects evaluating drug specific clinical trials

Drug	Reference	I/O Model	Covariate Distribution Model	Trial Execution Model	Simulation Experiment	Replication Analysis	Simulation Experiment Analysis	Lessons Learned
		Structural Model	**Covariate**	**Nominal Trial Design**	**Model Factors**	**Null hypothesis**	**Confirmatory Hypothesis**	
		Stochastic Component	**Data Source**	**Protocol Deviation Model**	**Design or Analysis Factors**	**Descriptive Aims**	**Learning hypothesis**	
		Software		**Software**	**Software**	**Software**	**Software**	
		Data Source		**Source**	**Replications**			
Mycophenolate Mofetil	56,57	PK, PD	None supported by data	RCCT	Fixed	Treatments not different	Power	Modeling enabled prediction of graft-rejection probability with respect to AUC, while simulation affirmed study feasibility and led to design of a successful trial
		PPV, RUV		None	Number of subjects, maximum daily dose	Treatment effect siz	Comparison with actual trial	
		SAS	1 phase 2 trial	NA	SAS	SAS	SAS	
		1 Phase 1 trial		NA	5000 trials			
Seroquel	(62) and unpublished results (CDDS, 1998)	PK, PD, PL, DP	None supported by data	Parallel	Fixed	Treatments not different Dose-response slope zero	Power	Retrospective data retrieval was difficult. Placebo prediction based on inadequate database
		PPV, RUV		Random subject dropout	Fixed	Drug and placebo effect sizes	Comparison with actual trial	
		NONMEM	1 Phase 1and 1 Phase 2 trials	ACSL Biomed	ACSL Biomed	SAS	SAS	
		1 Phase 1 and 1 Phase 2 trials		Sponsor experience	100 trials			

TABLE 4 (continued) Simulation projects evaluating drug specific clinical trials

NSAID Formulations	(63) and unpublished results) CDDS, 1999)	PK	Fed/fasted	Cross-over	Fixed	formulations not different formulations equivalent	Power	Value of diagnostics of IO model for model selection Unexplained poor prediction of effect size
		PPV, RUV		None	number of subjects, duration of sampling	Covariate and treatment effect size	Comparison with actual trial	
		NONMEM	Dog and human PK	NONMEM	NONMEM	SAS	SAS	
		Literature, in vitro study, dog and human PK		NA	100 trials			
Anticoagulant	Unpublished results (CDDS, 1999)	PK, PD, PL, DP	Disease severity	Parallel	Fixed and escalation scheme	None	NA	Time pressure interfered with completeness of M&S. Rapid and simple simulation provided decision support by sponsor and regulatory agency.
		PPV, RUV		None considered	Dose, infusion duration	Treatment effect size	Dose-response relationship	
		NONMEM	4 Phase 1and 1 Phase 2 trials	NA	ACSL-Biomed	Simple statistics	Simple statistics	
		4 Phase 1 trials		NA	10 subjects			
Antihypertensive	Unpublished results (CDDS, 1999)	PK, PD, PL, DP	Clearance–creatinine	Parallel	Fixed	Treatments not different	Power	Placebo prediction based on inadequate database IO model may have been suboptimal for lack of model for drug discontinuation & rebound effects Prospective M&S may enable avoidance of an unnecessary trial.
		PPV, RUV		Random subject dropout Noncompliance	Fixed	Drug and placebo effect size	Comparison with actual trial	
		NONMEM	2 Phase 2 trials	NONMEM	ACSL-Biomed	SAS	SAS	
		2 Phase 2 trials		Sponsor experience	100 trials			

TABLE 4 (continued) Simulation projects evaluating drug specific clinical trials

CNS drug	Unpublished results (CDDS, 1999)	PK, PD	None	Parallel	Fixed	Feasibility of sufficient exposure	Power	Simulation facilitated No Go decision of first trial in human from preclinical information.
		PPV, RUV		None considered	Dose, administration route	None	PK	
		NONMEM	4 preclinical studies	NA	Trial Designer	Simple statistics	Simple statistics	
		4 preclinical studies		NA	20 subjects			
CNS drug	Unpublished results (CDDS, 1999)	PK, PD	Baseline severity Normal	Cross over	Fixed	Formulations therapeutically equivalent	Therapeutic equivalence	Therapeutic equivalence between two formulations may be investigated via simulation with a firm understanding of PK/PD relationship
		PPV, RUV		None	Fixed	None	NA	
		NONMEM	2 Phase 2 and 1 Phase 3 trials	NA	SAS	SAS	SAS	
		2 Phase 2 and 1 Phase 3 trials		NA	18 subjects			
Anti-arthritic drug	Unpublished results (CDDS, 1999)	PK, PD, DP	Age, gender, weight, renal function Multivariate Normal	Parallel	Subject dropouts, missing observation	Treatments not different	Power	Disease expert's opinion was helpful in developing and justifying complex simulation models.
		PPV, RUV		Random subject dropout Random missing observations	Dosing schedule	PD and DP parameter estimates	Bias, precision	
		NONMEM	Disease expert	NA	Trial Designer	NONMEM	CTS	
		Literature, sponsor experience		Sponsor experience	100 trials			
Deep Brain Stimulation for Parkinson's Disease	Unpublished results (CDDS, 1999)	PD,DP	None	Incomplete crossover	None	Treatment has no effect on disease progress	Power	Longer trial duration required than originally planned
		PPV, RUV		None	Timing and number of observations	NA	NA	
		NA	NA	NA	Trial Designer	NONMEM	CTS	
		Investigator Experience		NA	100 trials			
Anti-Parkinson's Disease Drug	Work in progress (CDDS, 1999)	PD, DP	None	Parallel	Drug effect on disease progress	Treatment has no effect on disease progress	Power	Work in progress
		PPV, RUV	NA	None	Number and timing of observations	Treatment effect size	Bias and precision (Actual trial results will be compared with simulation predictions)	
		NONMEM		NA	Trial Designer	Trial Designer	CTS	
		DATATOP(64)		NA	100 trials			

TABLE 5 Simulation projects evaluating drug specific clinical trials: published reports with incomplete information

Drug	Reference	I/O Model	Cov. Dist. Model	Trial Execution Model	Simulation Experiment	Replication Analysis	Simulation Experiment Analysis	Goal
		Structural Model	Covariate	Nominal Trial Design	Model Factors	Null Hypothesis	Confirmatory Hypothesis	
		Stochastic Component	Data Source	Protocol Deviation Model	Design or Analysis Factors	Descriptive Aims	Learning Hypothesis	
		Software		Software	Software	Software	Software	
		Data Source		Source	Replications			
Treatment of Migraine	65 (abstract)	PK, PD	UA	Parallel	Absorption rate, potency	Treatments not different	Power	To evaluate design strategies and model assumptions
		UA		UA	Study duration, number of subjects, dose,	Treatment effect size	Dose-response relationship	
		NONMEM	UA	UA	Trial Designer	S-Plus	S-Plus	
		UA		UA	100 trials			
Ketorolac	66	PK, PD	None	Parallel	Fixed	None	NA	To evaluate design strategies and model assumptions
		Mixture of PPV & RUV		None	Fixed	Treatment effect size	Dose-response relationship	
		NONMEM	NA	NA	NONMEM	S-PLUS	S-PLUS	
		"several clinical trials"		NA	1000 subjects			
GW262570 Anti-diabetic Drug	67 (abstract)	PK	UA	Parallel	ED50, Emax	Treatments not different	Power	To find a study design to detect a drug effect.
		UA		UA	Dose, duration	none	NA	
		UA	UA	UA	UA	UA	UA	
		UA		UA	UA			
Docetaxel	68 (abstract)	PK, PD	Body surface area, protein binding, hepatic function	Parallel	Fixed	None	NA	To predict safety profiles.
		Median		None	Protein level	Treatment effect size	Dose-response relationship	
		SAS	180 patients	NA	ACSL Biomed	Simple statistics	Simple statistics	
		180 patients		NA	100 trials			

TABLE 5 (continued) Simulation projects evaluating drug specific clinical trials: published reports with incomplete information

Anticholinergic agent	69 (abstract)	PK, PD	UA	UA	Potency	Treatment s not different	Power	To examine the impact of trial design on the ability to characterize the dose-response relationship and demonstrate efficacy over placebo
		UA		None	Study size, dose	Treatment effect size	Dose-response relationship	
		UA	UA	NA	UA	UA	UA	
		"data and publications available at the time "		NA	UA			
GI198745 5-a-reductase	70 (abstract)	PK, PD	Dose	Parallel	Fixed	None	NA	To predict dose vs DHT reduction
		UA		None	Fixed	Treatment effect size	Dose-response relationship	
		UA	48 subjects	NA	SCI Clinical Trials Forecaster	Simple statistics	Simple plot	
		48 subjects		NA	UA			
Capecitabine Anti-cancer	43	PK, PD	UA	Parallel	Fixed	None	NA	To Predict tumor size and adverse reaction to decide dosing schedule
		UA		None	Dosing time	Treatment effect size	Dose-response relationship	
		UA	NA	NA	ACSL BioMed	Simple statistics	Simple statistics	
		UA		NA	50 subjects			
GPIIB/IIIA antagonist	71 (abstract)	PK, PD	UA	Parallel	Fixed	Treatments not different	Power	To decide if a Phase II trial could improve the success rate of a Phase III trial.
		UA		None	Dose	Treatment effect size	Dose-response relationship	
		UA	NA	NA	UA	UA	UA	
		"Phase I data" and published data		NA	500 subjects			
GM-0911	72 (abstract)	PK, PD	Baseline severity	Parallel	Formulation, tolerance	Treatments not different	Power	To predict the impact of tolerance on a new formulation in a trial
		UA		UA	UA	UA	UA	
		UA	UA	UA	UA	UA	UA	
		UA		UA	UA			

UA:Unavailable or unclear

for evaluation in phase II trials. As this procedure is often performed without taking into account between-subject variability or pharmacodynamic linkages, an opportunity is lost to influence trial design features such as dosages and dosage intervals, or ''go/no go'' decisions for direction of product development. Two important exceptions provide instructive illustrations of the power of clinical trial simulation in a drug development program.

As highlighted above, PKPD-based clinical trial simulation of the organ antirejection agent, mycophenolate mofetil, was employed to evaluate study feasibility and to influence multiple trial design features of a proposed RCCT in renal transplant patients (56). The simulation model, derived from 41 patients, employed a binary-outcome clinical response (transplant rejection, yes or no) and guided the design of a RCCT that, when completed, was adjudged to have successfully met its scientific objectives (57). In the case of the antiretroviral agent, alovudine (R Desjardins, personal communication), PKPD-based simulations of alovudine activity and toxicity, derived from two concentration controlled trials (RCCT) in HIV patients (59), provided a strong rationale to halt the further development of the drug. The 12-h area under the alovudine concentration-time curve value above which unacceptable hematologic toxicity occurred ($>$300 ng ml^{-1} h^{-1}), was less than threefold that of the area under the alovudine concentration-time curve above which a 50% or greater reduction in viral serum HIV antigen concentration (p24) was observed. When between-subject PK variability was taken into consideration, simulations predicted unacceptable toxicity in a high proportion of patients at dosages necessary to achieve antiretroviral effectiveness.

Despite the modest impact of current applications of clinical trial simulation in drug development, there is reason to expect increasing incorporation of this technology in all phases, from discovery to phase IV. Several major pharmaceutical firms are committing major resources to the establishment of intellectual and computational capabilities for prospective incorporation of modeling (41) and for clinical trial simulation in selected drug development programs.

In the near term, lessons learned from experience in recent years with clinical trial simulation (e.g. Table 4) provide direction for the next steps in the realm of research and development management and education. Thus, drug developers that plan to benefit from this technology should provide for trained personnel and resources to enable prospective integration of modeling and clinical trial simulation in drug development programs (to mitigate problems cited above with retrospective data retrieval, company cultural resistance or lack of cooperativeness, unrealistic time pressures, etc), commencing in the preclinical phase, and fully integrating the modeling and simulation approach in all subsequent clinical phases. This step alone has major implications for education and training of personnel needed for this bold evolution in drug development. Because the trained personnel needed for this approach are already scarce, consideration should be given to expansion of existing, and establishment of new, educational programs to develop the large number (hundreds) of experts in clinical trial simulation that will be needed.

Comprehensive databases and models for adequately modeling the disease progress and placebo response patterns in various diseases and treatments are

sorely needed. Equally needed is an understanding of the consequences to subjects of the interruptions and resumptions of drug regimens (60) that often occur during clinical trials, leading to loss or exaggeration of drug effects, rebound effects, tolerance, and other nonlinear deviations from simple models of drug effect. Evaluating, improving, and implementing the draft simulation good practices guidance (40) is another valuable next step in advancing the quality, utility, and confidence in this novel technology.

In the far future, we foresee a central role for clinical trial simulation in a revolutionary paradigm shift in drug development practices. Today, drug development continues its inefficient tradition of many tens to hundreds of clinical trials per new drug application, supporting a mostly empirically derived safety-and-effectiveness database—with modest or no role of trial simulations. In our vision of a very different future, clinical trial simulations will be the principle scientific activity, and actual clinical trials will be few, aimed at informing simulation models and confirming simulation predictions. The impact of clinical trial simulations in this vision of the future will go well beyond the success and efficiency of actual development activities. It will impact the selection and training of scientific personnel involved in drug development, as well as the demography of clinical trial subjects, and possibly even the economics of development—virtual clinical trials may reduce overall cost of drug development by reducing the total number of trials, especially ones that are prone to failure or that are unnecessary.

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