Optimizing Event-driven Clinical Trial Efficiency with Discrete Event Simulation:

Case Study - Pediatric Oncology

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19th ACCP Frontiers Symposium: *"Innovative Approach for Early Drug Development*

Disease Models and Novel Trial Design"

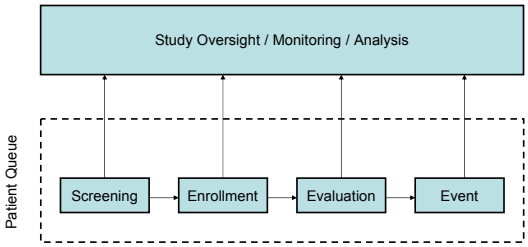
Outline

- Event-driven clinical trials
- Discrete-event simulation
- M&S Requirements and Approach
- Case study:
  - Simulating and comparing phase I, pediatric oncology designs
- Conclusions and Future Applications

Event-driven Clinical Trials

- Requirements based on the occurrence or frequency of pre-defined events
- Less dependent on achieving pre-specified sample size
  - Traditional sample size criteria often employed to assess the number of events required to fulfill hypothesis testing approach.

Event-driven Clinical Trials



Event-driven Clinical Trials

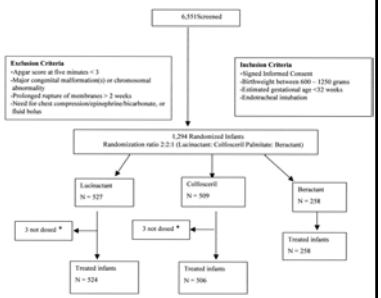
Design / Examples	Endpoints	Analysis
Randomized, parallel, active-control • OPTIMAAL Trial • BEAUTIFUL Trial • pancreatic cancer; best supportive care vs glufosfamide	Mortality Composite score[c] Survival	RR[a]; ITT[b] RR; ITT RR; EFS[d]
Psychopharmacology, double-blind, placebo controlled fMRI	Reaction time (w/ or w/o imaging)	General, linear model, random-effects analysis
Double-blind, randomized, placebo-control trial •Darifenacin in OAB patients	Warning time[e]	Wilcoxon rank sum; ITT

[a]RR = Response rate
[b]ITT = Intention to treat
[c]Mortality + hospital admission
[d]EFS = Event free survival
[e]Time from first sensation of urgency to voiding

Event-driven Clinical Trials

"Therefore, the study was powered to test differences between these 2 products. The hypothesis being tested was that "X" would be superior to "Y". A reference arm "Z" was of secondary interest. To keep the **trial** at a workable size, a 2:2:1 randomization scheme was used. The **trial** was designed to be **event-driven**, and the expected frequency of events was based on the observations reported in an earlier **trial** comparing "X" and "Z". Accordingly, we anticipated that the frequency of RDS would be 40% for X but only 30% for Y and the frequency of death related to RDS up to 14 days would be 7.5% for X but only 3.5% for Y. On the basis of these assumptions, the **trial** would continue until 420 infants had developed RDS and 66 infants had died from RDS-related causes. This number of events would provide 94% power to detect the prespecified difference between X and Y for the occurrence of RDS at 24 hours and 83% power for the occurrence of death related to RDS by 14 days."

Enrollment flow diagram



Moya, F. R. et al. Pediatrics 2005;115:1018-1029

Event-driven Clinical Trials

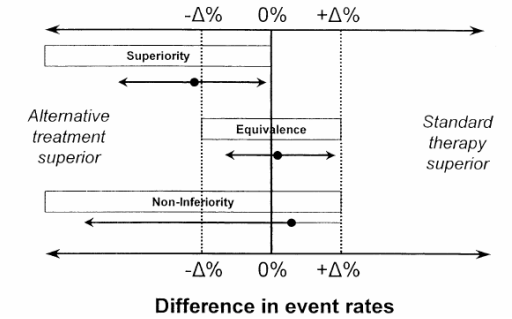
What Drives Study Efficiency?

- Time to enroll patients
- Patient evaluability / replacement
- Time to event(s)
- Waiting / decision / administrative time

Ultimately effects “n”

Event-driven Clinical Trials

Sample size consideration



Simulating Time Events

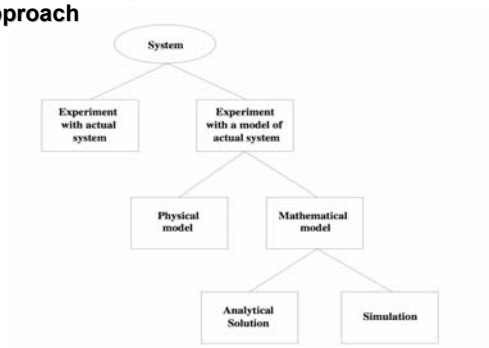
Advantages

- Ability to compress time, expand time
- Ability to control sources of variation
- Avoids errors in measurement
- Ability to stop and review
- Ability to restore *system state*
- Facilitates *replication*
- Modeler can control level of detail

**Discrete-Event Simulation: Modeling, Programming, and Analysis* by G. Fishman, 2001, pp. 26-27

Simulating Time Events

Approach



Simulation, Modeling & Analysis (3/e) by Law and Kelton, 2000, p. 4, Figure 1.1

Discrete Event Simulation

- What is discrete event simulation?
  - Modeling, simulating, and analyzing systems
  - Computational and mathematical techniques
- **Model**: construct a conceptual framework that describes a system
- **Simulate**: perform experiments using computer implementation of the model
- **Analyze**: draw conclusions from output that assist in decision making process
- We will first focus on the *model*

Discrete Event Simulation

- Deterministic or Stochastic
  - Does the model contain stochastic components?
  - Randomness is easy to add to a DES
- Static or Dynamic
  - Is time a significant variable?
- Continuous or Discrete
  - Does the system state evolve continuously or only at discrete points in time?
  - Continuous: classical mechanics
  - Discrete: queuing, inventory, machine shop models

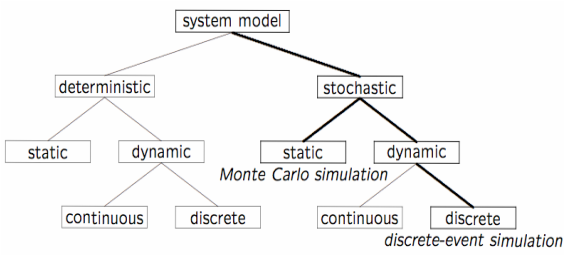
Discrete Event Simulation
Definitions

- Discrete-Event Simulation Model
  - *Stochastic*: some variables are random
  - *Dynamic*: time progression is important
  - *Discrete-Event*: significant changes occur at discrete time instances

vs

- Monte Carlo Simulation Model
  - *Stochastic*
  - *Static:* time evolution is not important

Discrete Event Simulation
Model Taxonomy



Discrete Event Simulation
Components

- *Activities* where things happen to entities during some time (which may be governed by a probability distribution)
- *Queues* where entities wait an undetermined time
- *Entities* that wait in queues or get acted on in activities
  - Entities can have attributes like kind, weight, due date, priority

Discrete Event Simulation

Clinical Trial Simulation – Simple Construct

- Patient arrivals, enrollment and evaluation, arrival queueing
- Single site for incoming patients

- IAT = Inter-arrival time (stochastic or constant)
- IET = In-evaluability time (stochastic or constant)
- EVT = Event time (stochastic)

State:

- Now: current simulation time
- Available: number of patients waiting to be enrolled
- Enrolled: number of patients enrolled
- Complete: number of patients evaluated (passed or reached endpoint)
- Open: Boolean, true if study open to enrollment

Events:

- Pass: Patient completes evaluation without endpoint
- IE: Patient is in-evaluable
- Endpoint: Patient achieves endpoint

Discrete Event Simulation

Clinical Trial Simulation – Study level events

Patient arrives at site. If the study is open (and patient is available), they will be enrolled. Otherwise, the patient is skipped (enters another study).

- IAT = Inter-arrival time
- IET = In-evaluability time
- EVT = Event time
- Now: current simulation time
- Available: number of patients waiting to be enrolled
- Enrolled: number of patients enrolled
- Complete: number of patients evaluated (passed or reached endpoint)
- Open: Boolean, true if study open to enrollment

```
Arrival Event:
Available := Available+1;
If (Open)
    Open:=TRUE;
    Schedule patient enrollment_i @ Now + IAT;
```

Discrete Event Simulation

Clinical Trial Simulation – Patient level events

A patient enters the trial and gets evaluated

```
Patient Enrolled:
Available:=Available - 1;
Enrolled:=Enrolled+1;
If (Open:=TRUE) andif (Available>0)
   Schedule patient enrollment_{i+1} @ Now + IAT;
Else
    . . . criteria for halt or delay;
```

Discrete Event Simulation

Clinical Trial Simulation – Patient level events

A patient reaches endpoint.

Endpoint Event:

Complete := Complete + 1;

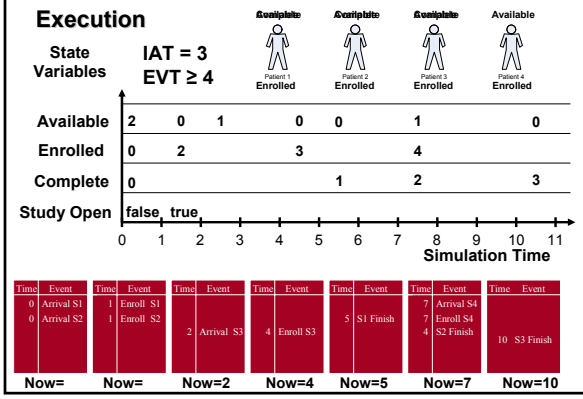
Patient event @ Now + IAT + EVT;

. . . . Determine if endpoint reached → count

. . . . Determine if and how study proceeds

Discrete Event Simulation

Execution



Discrete Event Simulation

Execution

- Time
  - Important to distinguish among simulation time, wallclock time, and time in the physical system
  - Paced execution (e.g., immersive virtual environments) vs. unpaced execution (e.g., simulations to analyze systems)
- DES computation: sequence of event computations
  - Modify state variables
  - Schedule new events
- DES System = model + simulation executive

Discrete Event Simulation
Execution

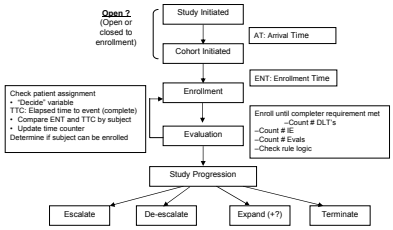
- Data structures
  - Pending event list to hold unprocessed events
  - State variables
  - Simulation time clock variable
- Program (Code)
  - Main event processing loop
  - Event procedures
  - Events processed in time stamp order

Discrete Event Simulation
Reality

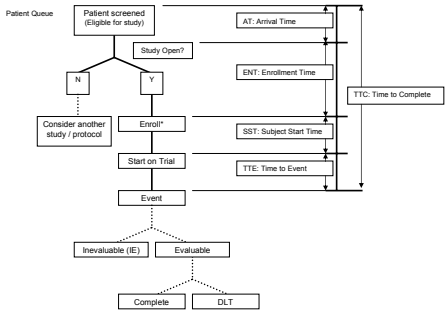
Case Study:
Pediatric Phase I Oncology Trials

- Decompose study and patient-level time-based events to explore time to event and time to complete
- Evaluate simulation models with respect to historical COG data
- Compare design efficiency for 3+3 versus Rolling 6 decision logic

Study-level Events



Patient-level Events



Historical Priors

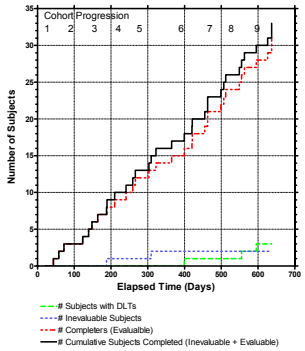
12 COG Trials

NAME	AGENT	Evaluable Subjects	DLT per Study	IE per Study	Cohorts per Study	Study Duration (days)	Administrative Time/Study Closure (days)	Time to Complete Cohort, Mean (days)
ADVL0011	TMZ/CCNU	22	2	2	4	528	86	134.2
ADVL0015	Bortezomib (PS-341; Velcade®)	15	2	3	2	281	158	95.3
ADVL0016	Gefitinib (ZD1839; Iressa®)	21	2	4	4	477	347	88.6
ADVL0018	Hu14.18-IL2 Fusion Protein	28	3	1	7	563	430	59
ADVL0211	G3139(Genesense®)/Dox/CPM	29	4	5	5	606	378	106.6
ADVL0212	Depsipeptide	24	4	7	4	539	284	135.2
ADVL0214	Erlotinib (OSI-774; Tarceva®)	22	3	3	5	344	188	77.6
ADVL0215	Decitabine/Dox/CPM	11	2	2	2	220	147	94
ADVL0311	Pemetrexed(LY231514; Alimta®)	33	3	2	8	596	200	61.1
ADVL0314	Bevacizumab (Avastin®)	14	0	2	3	233	87	132.3
ADVL0316	17-AAG	17	0	5	4	427	181	116.5
ADVL0415	Oxaliplatin/Irinotecan	13	5	1	3	289	178	52
	Median	21.5	2.5	3	4	452	184.5	77
	Range	11-33	0-5	1-7	2-8	220-606	86-430	33-274

Historical Priors

Study Progression

Representative study progression from COG phase I study (ADVL0311)



Simulating Study Design Entities

Distributional Assumptions

Parameter and Definition	Distribution and Assumptions	Simulation Scenarios
ENT, Enrollment Time: Days between subject arrival or start of cohort for first subject* of cohort	Poisson, Mean = 20	Mean Varied: 5, 20, 30, 40, 50, 100, 200 days; variance 1 – 3X
SST, Subject Start Time: Days between enrollment and start of evaluation	Normal, Mean = 2	Mean varied: 2, 5, 10 days
TDLT, Time to DLT: Days between start of evaluation and the occurrence of DLT	Uniform; Mean = 20 Poisson, Mean = 10, 15, 18, 20 days	Uniform (Mean 20) Poisson (Mean 10, 15, 18 and 20 days)
IET, Inevaluability Time: Days between start of evaluation and designation of patient as inevaluable	Normal, Mean = 21	Mean varied: 10, 15, 21 days
P(DLT), Probability of DLT: Cohorts (0 to 7)	.02 .05 .1 .3 .50 .75 .9 .95	Cohort start position varied 0, 1, or 2
P(IE), Probability of Inevaluability: Probability that a subject is inevaluable	Independent of dose cohort	0.11, 0.25, 0.05
TPASS, Time to evaluability (Pass): Days between start of evaluation and designation of patient as evaluable†	Constant, study constraint (typically 21 or 28 days)	21, 28, 35 days
TTC, Time to complete: Sum of ENT, SST and TTE‡	Normal	N/A

* Can also reflect time between cohort being open to enrollment and actual arrival (enrollment) if study is suspended mid-cohort.
† Assumes evaluable without DLT
‡TTE (time to event) refers to the time in days that it takes for a subject to be designated as evaluable due to DLT (TDLT), evaluable without DLT as a completer (TPASS) or inevaluable (IET)

Study Design Comparison

Conventional 3+3 vs "Rolling 6" Design

Criteria	Three-Plus-Three	Rolling Six
No. subjects at start of trial	2	2
Criteria to take third subject	< 2 DLTs	< 2 DLTs
Criteria to de escalate dose cohort	> 2 DLTs	> 2 DLTs
Criteria to expand from 3 to 6 subjects	1/3 DLTs	1/3 DLTs only if data from all prior subjects are available before subject 4 enrolls; otherwise continue to enroll patients 4, 5 and/or 6 until 1/N DLTs, then enroll to 6
Criteria to escalate dose cohort	0/3 DLTs, or 1/6 after expansion	0/3 DLTs, or 1/6 after expansion OR 0/5, 0/6 DLTs if no expansion
Suspension of trial	After 3rd patient	After 6th patient
Maximal tolerated dose	≤ 1/6 DLTs after de escalation	≤ 1/6 DLTs after de escalation

DES Application

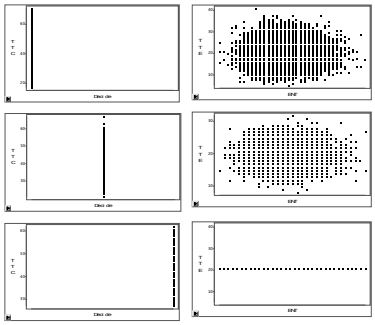
- Simulate “N” Trials
- Within each trial, populate “X” cohorts
- Within each cohort, simulate “i” subjects for possible study enrollment
- For each subject, simulate requisite event probabilities and time to event based on random sample from target distributions
- Determine actual event outcomes based on comparison of time to event metrics (first event to occur is event of record)

- Enrollment status assessed based on study being “open”
- Decision criteria assessed and counted
- Enrollment procedure (# of subjects available for enrollment) assessed and modified based on decision criteria
- Cohort progression based on decision criteria (event counting) for cohort and/or study being met
- “Waiting time” added at various event milestones
- Time to complete metrics (subjects, cohort, study) assessed

- Compare design proposals via event and time based metrics
- Chart / project study progression metrics

Design Checks

Study Simulation



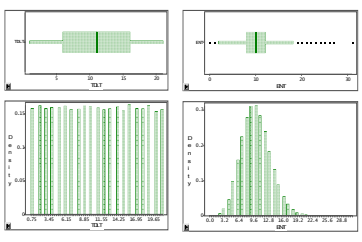
- No correlation between TTE and ENT
- No correlation between TTC and decision (event outcome)

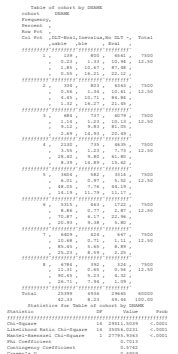
Decide = 1 (DLT); Decide = 2 (IE); Decide = 3 (Pass)

Design Checks

Study Simulation

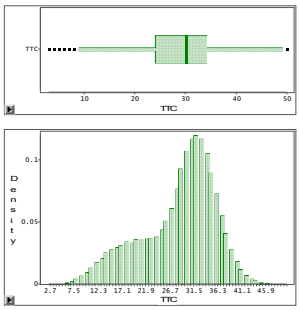
- Verification of distributional requirements
- By cohort composition
- Event-rate confirmation





Design Checks
Study Simulation

- The composite time scale
- TTC = ENT + SST + TTE



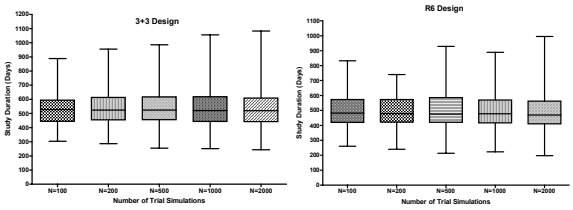
Design Checks
Effect of Simulation Sample Size

Impact of sample size on DES study efficiency metrics with 3+3 decision rule*. Values reported as arithmetic mean (standard deviation)

Simulated Trials (#)	Study Duration (Days)	Subjects/study (# subjects)	DLT/study (# subjects)	IE/study (# subjects)	MTD Cohort (Cohort #)
100	528.0 (115.8)	16.1 (3.2)	3.14 (1.04)	1.48 (1.18)	2.23 (0.76)
200	538.0 (114.5)	16.4 (3.2)	3.11 (1.08)	1.39 (1.22)	2.17 (0.76)
500	543.7 (131.9)	16.4 (3.7)	3.08 (1.03)	1.58 (1.36)	2.23 (0.86)
1000	537.7 (128.5)	16.3 (3.6)	3.09 (1.05)	1.48 (1.29)	2.15 (0.81)
2000	530.6 (124.4)	16.3 (3.6)	3.10 (1.10)	1.46 (1.28)	2.14 (0.85)

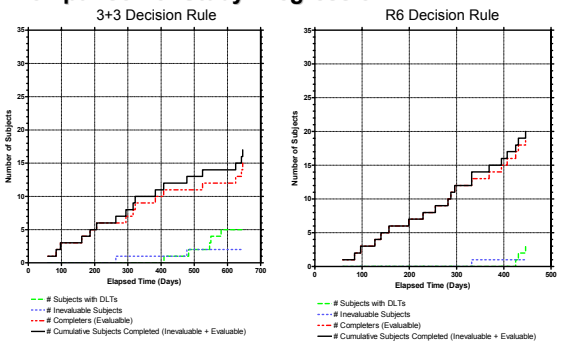
* Based model parameters used in simulation; P(DLT) = for cohorts 0 – 7, ENT = 20 days; IET = ; P(IE) = 0.11; TPASS = 21 days

Design Checks
Effect of Simulation Sample Size



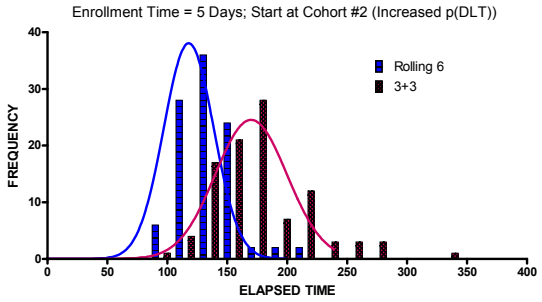
Post Processing

Comparison of Study Progression



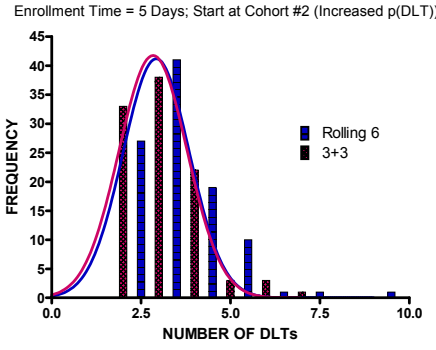
Post Processing

Comparison of "Time to Complete"



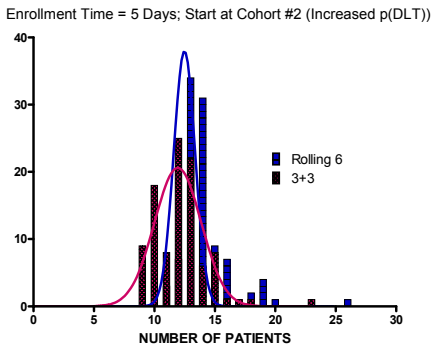
Post Processing

Comparison of Number of DLTs / study



Post Processing

Comparison of Number of Patients / study



Conclusions

- DES can be used to . . .
  - Capture time-based study events
  - Evaluate time-based outcome metrics
  - Compare design constructs
  - Evaluate decision rule logic

Acknowledgements

Jeffrey M Skolnik, MD

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Discrete Event Simulation

Examples

Category	Examples
Pharmacoeconomics	• Economic evaluation of tumor necrosis factor inhibitors for rheumatoid arthritis (Kamal, 2006) • Long-term costs and effects of new interventions in schizophrenia (Heeg, 2005) • Improving resource allocation / reducing the health burden related to schizophrenia (Haycox, 2005) • Cost analysis of a hospital-at-home service compared with conventional inpatient care (Campbell, 2001)
Clinical Risk Factors	• Impact of CV risk factor reduction on transplant outcome (McLean, 2005) • Impact of HIV on increasing the probability and the expected severity of tuberculosis outbreaks (Porco, 2001) • Vaccine efficacy for susceptibility and infectiousness as prognostic factors for vaccine trials in HIV (Longini, 1999)
Disease Progression	• Methodological benefit of DES in depicting disease evolution of major depression (Le Lay, 2006) • Breast cancer incidence and mortality in the U.S. population from 1975 to 2000 (Fryback, 2006) • Patient progression following coronary event, through treatment pathways and subsequent events (Cooper, 2002 and Babad, 2002) • Modeling of the AIDS pandemic - discrete-event simulation relating contact rate heterogeneity to the rate of HIV spread (Leslie, 1990)
Hospital Operations Research	• Biology of end-stage liver disease and the health care organization of transplantation in the US (Shechter, 2005) • Impact of surgical sequencing on post anesthesia care unit staffing (Marcon, 2005) • Cancellation of electively scheduled cases on the day of surgery (Dexter, 2005) • Performance of hospital accident and emergency department (Codrington-Virtue, 2005) • Staffing for entry screening, triage, medical evaluation, and drug dispensing stations in a hypothetical antibiotic distribution center operating in disease prevalence bioterrorism response scenarios (Hupert, 2002)
Pharmacodynamics / Transduction Modeling	• CD4+ memory T cell generation to track individual lymphocytes over time (Zand, 2004) • Lymphocyte-mediated destruction of malignant lymphoid cells circulating through tissue compartments of immune syngeneic C58 mice (Look, 1981)