Improving Study Design and Conduct Efficiency of Event-Driven Clinical Trials via Discrete Event Simulation: Application to Pediatric Oncology

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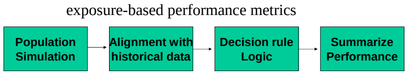
Introduction

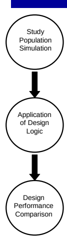
- Phase I oncology studies use a modified Fibonacci escalation with three patients per dose level and dose escalation in phase I trials guided by dose-limiting toxicity (DLT).
- Previous exploration of oncology study designs have focused on Markov processes alone (probability-based events) without consideration for time dependencies.
- Barriers to study completion include time delays associated with patient accrual and inevaluability (IE), DLT, and data submission and review.
- Discrete event simulation (DES) incorporates probability-based assignment of DLT and IE frequency and decision logic on time to event.
- Metrics for comparison of various dose escalation rules include: # subjects to complete trial, time to complete trial (define MTD), and #DLT/trial.

Objectives

1. To develop a simulation model to evaluate clinical performance metrics of event-based decision rules typically used in pediatric oncology.
2. To investigate study characteristics and features detrimental to study efficiency and propose designs which offer benefit with respect to time-based and exposure-based performance metrics



Design / Methods



- 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

Figure 1: Study level events

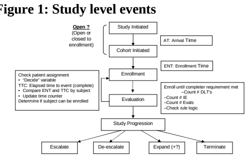


Figure 2: Patient level events

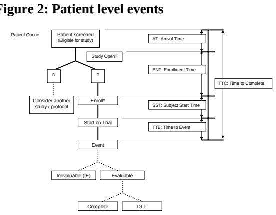
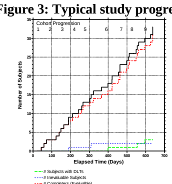


Table 1: Historical priors

NAME	AGENT	Eval Subjects	DLT/ Study	IE / Study	Cohort / Study	Study Duration (days)	Study Closure (days)	Ave time to complete Cohort (days)
0011	TMZ/CCNU	22	2	2	4	528	86	134.2
0015	Bortezomib (PS-341; Velcade®)	15	2	3	2	281	158	95.3
0016	Gefitinib (ZD1839; Iressa®)	21	2	4	4	477	347	88.6
0018	Hu14.18-IL2 Fusion Protein	28	3	1	7	563	430	59
0211	G3139(Genasense®)/Dox/CPM	29	4	5	5	606	378	106.6
0212	Depsipeptide	24	4	7	4	539	284	135.2
0214	Erlotinib (OSI-774; Tarceva®)	22	3	3	5	344	188	77.6
0215	Decitabine/Dox/CPM	11	2	2	2	220	147	94
0311	Pemetrexed(LY231514; Alimta®)	33	3	2	8	596	200	61.1
0314	Bevacizumab (Avastin®)	14	0	2	3	233	87	132.3
0316	17-AAG	17	0	5	4	427	181	116.5
0415	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

Figure 3: Typical study progression



Design / Methods

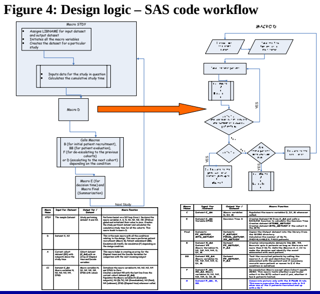
Table 2: Simulation parameter scenarios

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

Table 3: Study design operating characteristics

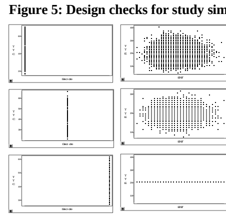
Criteria	Three-Plus-Three	Rolling Six
No. subjects at start of trial	2	2
Criteria to take third subject	< 2 DLTs	< 2 DLTs
Criteria to de-escalate dose cohort	> 2 DLTs	> 2 DLTs
Criteria to expand from 3 to 6 subjects	1/3 DLTs	1/3 DLTs only if data from all prior subjects are available before subject 4 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

Figure 4: Design logic – SAS code workflow



Results

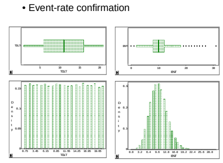
Figure 5: Design checks for study simulation

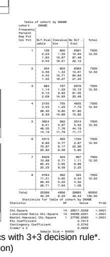


- No correlation between TTE and ENT
- No correlation between TTC and decision (event outcome)

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

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





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)

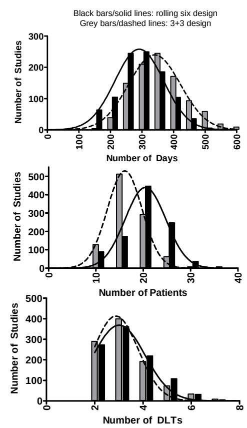
•Based model parameters used in simulation
•P(DLT)=for cohorts 0 – 7, ENT=20 days; IET=21 days ; P(IE)=0.11; TPASS = 21 days

Results

Table 4: Design evaluation simulation results

	Three-plus-three design				Rolling six design			
	Duration (days)	Subjects per trial	DLT per trial	Cohorts per trial	Duration (days)	Subjects per trial	DLT per trial	Cohorts per trial
Inter-patient arrival time*								
5 days	256±69	17±4	3±1	3±1	197±53	20±5	3±1	3±1
10 days	350±84	17±4	3±1	3±1	294±75	20±5	3±1	3±1
20 days	538±128	16±4	3±1	3±1	486±121	19±5	3±1	3±1
100 days	2178±519	16±4	3±1	3±1	2112±502	19±5	3±1	3±1
Cycle length**								
28 Days	383±94	16±4	3±1	3±1	315±82	20±5	3±1	3±1
35 Days	432±109	17±4	3±1	3±1	348±89	20±5	3±1	3±1
Increased inevaluability rate (25%)	404±107	18±4	3±1	3±1	322±81	22±5	3±1	3±1
Increased risk of DLT at starting dose***	242±59	12±3	3±1	2±1	185±39	13±2	3±1	2±1

Figure 6: Comparison of primary efficiency metrics.

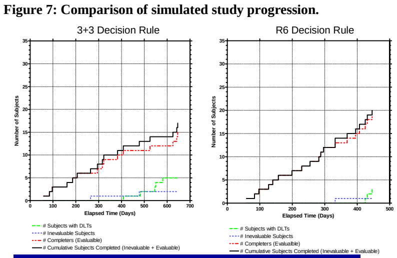


•Distribution of elapsed time to complete a given study.
•Average inter-patient arrival time of 10 days.
•On average the rolling six outperforms the 3+3 by 56 days.

•Distribution of number of patients per study
•Average inter-patient arrival time of 10 days.
•On average there are 3 more patients per study using the rolling six design.

•Distribution of number of DLTs per study.
•Average inter-patient arrival time of 10 days.
•No difference between number of DLTs between design (N = 3 patients).

Figure 7: Comparison of simulated study progression.



Discussion / Conclusions

- A DES approach to event-driven study designs allows consideration of time-based metrics as opposed to Markov-based approaches which typically focus only on event-based outcomes.
- Our SAS-based solution separates the generation of study population pools from design logic; the pediatric oncology case study agrees well with historical data.
- We anticipate using this approach to examine design dependencies for the determination of pediatric MTD and ultimately to redesign phase I conduct with the intention of reducing study duration, bringing new agents to patients faster.
- Using DES, we found that the rolling six method has the potential to significantly decrease the duration of pediatric phase 1 studies.

References

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