Cytel

STATISTICAL SOFTWARE & SERVICES

The New Role of Drug Supply Planning in Adaptive Trials

Nitin R. Patel,

Chairman and C.T.O.

Cytel Inc.

Acknowledgements

My colleagues at Cytel

Suresh Ankolekar

Pralay Senchaudhuri

Judith Quinlan

Outline

- How are adaptive trials different?
- Adaptive Phase 2 trials
- Case study of an Adaptive Ph 2a trial
  - Combined trial: Proof of Concept + Dose Ranging
  - Advantage of Adaptive Bayesian design over 2 standard trials
  - Drug supply planning for Bayesian design
  - Drug supply planning for simpler Drop Arms Adaptive Design
- Conclusions

What's different about adaptive designs?

- Standard clinical trial designs have fixed sample sizes and results are observed only after trials are complete.
- Adaptive clinical trials employ predefined processes ("adaptive by design") to use data not available at the start of the trial to dynamically improve the statistical performance of the trial

Regulatory Perspective

- FDA guidance document expected to be released in a few months.
- EMEA has already released reflection paper.
- Use of adaptive designs for learning stage (Phase 1 and 2 trials) is encouraged.
- For confirmatory trials (Phase 3) need to provide sound rationale for adaptive approach and rigorous demonstration of integrity and statistical validity.

Common Adaptive Designs

- Dynamically change randomization ratios
  - to achieve balance in base-line prognostic factors
  - to assign fewer subjects to doses that are too low or too high
- Drop ineffective treatment arms after interim analysis
- Stop early for futility or when efficacy has been adequately demonstrated
- Increase sample size if observed variance is larger or effect size is smaller than expected
- Combine trials e.g. Ph2b+3, Ph2 PoC+Dose finding

Potential Benefits of Adaptive Trials

- Shorten trial duration and reduce costs
  - End trials early for efficacy, futility or safety
  - Combine two trials into one integrated trial (eliminate "white space", fewer subjects required)
- Improve chances of success
  - Increase the sample size based on interim estimates
  - Change randomization ratios dynamically to increase learning
- Ethically Superior
  - Fewer patients on ineffective doses, quicker identification of efficacious drugs

Gaining these benefits requires...

- Significant changes in the traditional process for design and implementation of clinical trials

- More up front time and effort for design,

  e.g. cannot use formulas to calculate sample size, computer simulation needed to find an effective design, need for software tools

- More co-ordination and detailed planning,

  e.g. randomization and drug supply

Case study of an adaptive trial

- Ph 2 trials for a new drug:
  - Ph 2a Proof-of-Concept
  - Ph 2a Dose-ranging

  } *combine into one adaptive trial*

  - Ph 2b Dose selection

design with better information

Standard Phase 2a Trials

- Proof of Concept trial
  - 2 parallel treatments (highest dose vs placebo)
  - Double blind, randomized equally to each treatment.
- Dose-ranging trial
  - Double blind with equal randomization to each dose and placebo
  - No model for dose-response

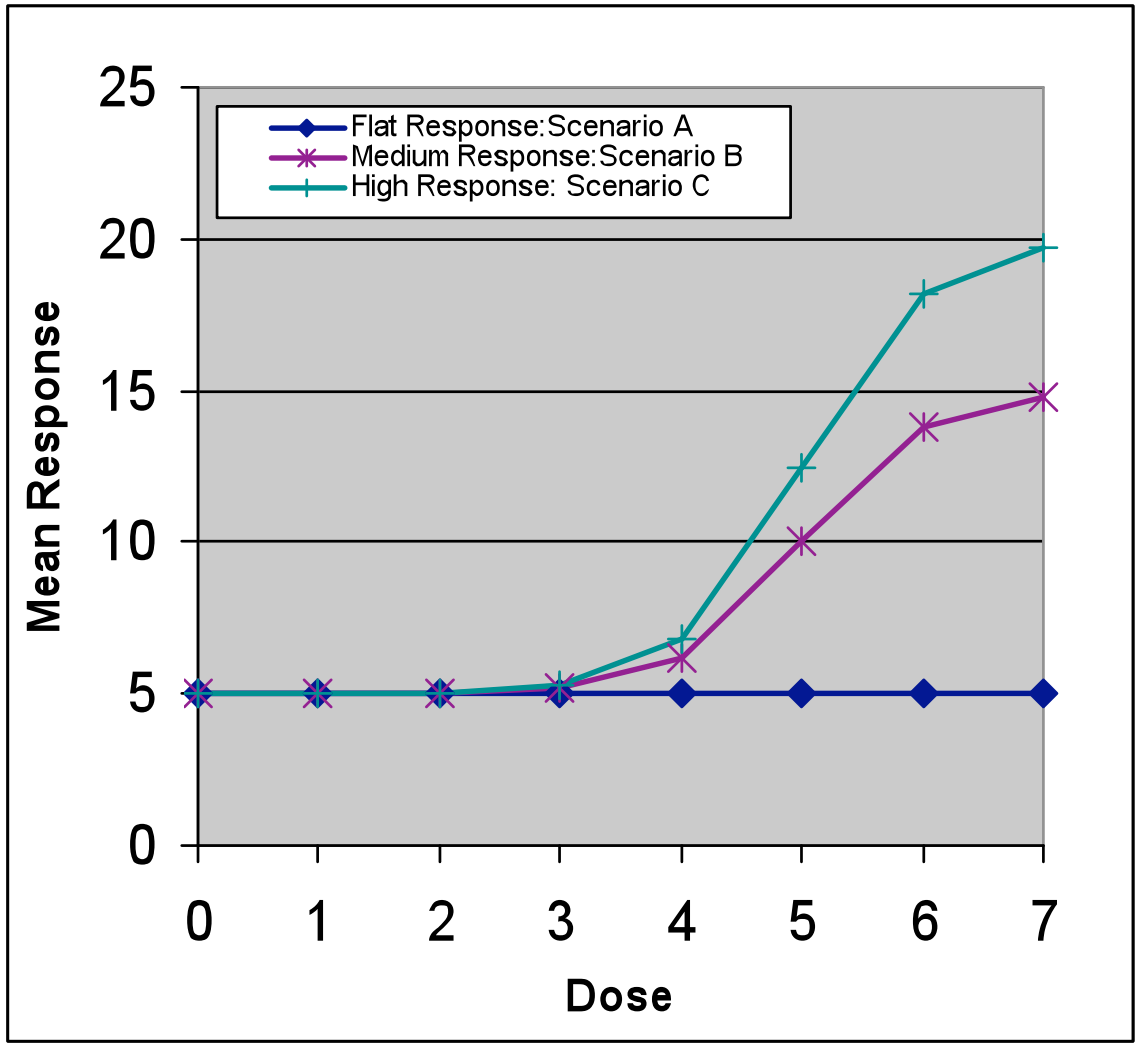
Adaptive Design Case

- Placebo controlled, double blinded trial
- Sample size = 120 (40 placebo, 80 drug).
- Cohort size = 12 (4 placebo, 8 drug)
- Seven doses of drug: 1, 2, 3, 4, 5, 6, 7 units.
- Primary endpoint assumed to be Normally distributed with standard deviation = 9.

Adaptive Bayesian Design

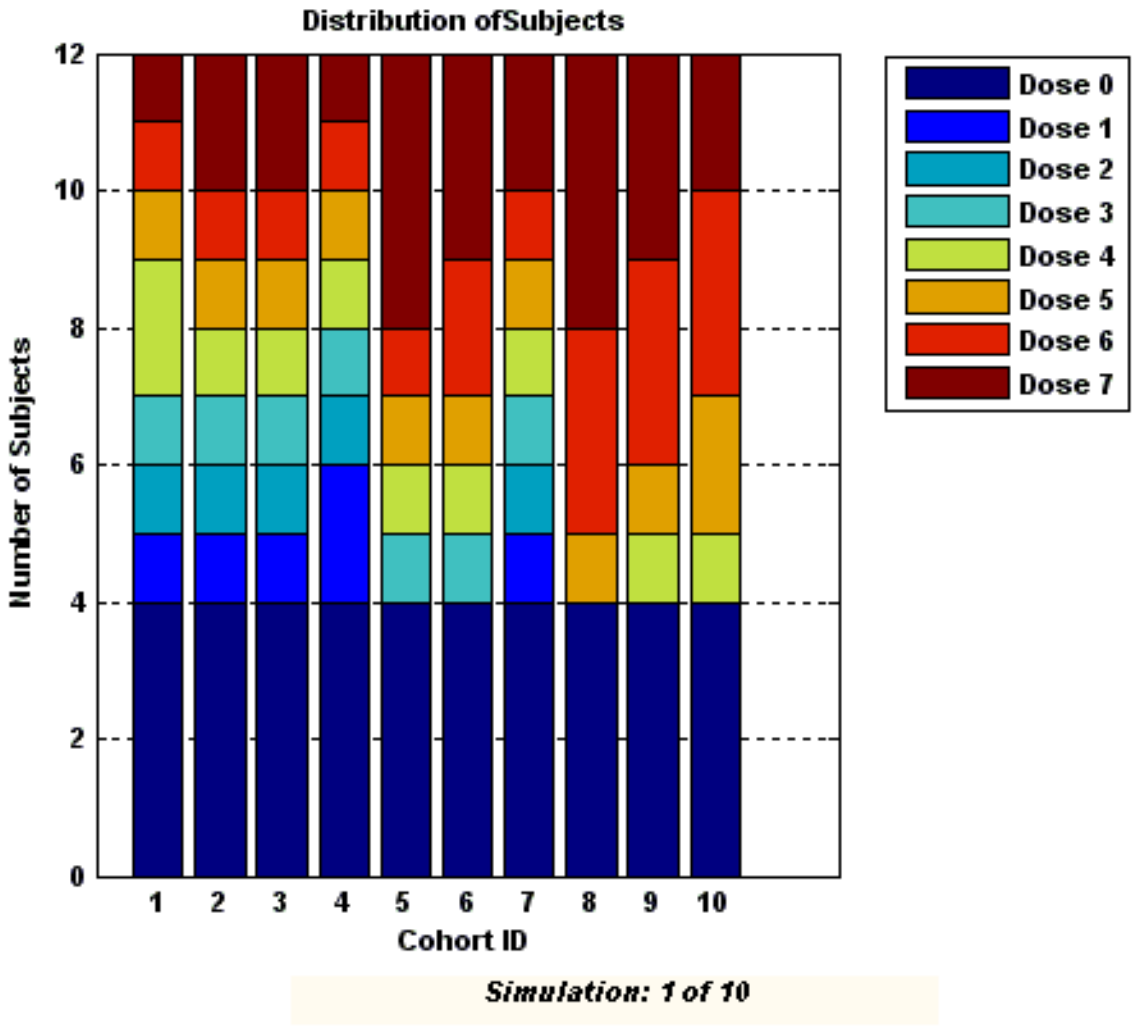
- First cohort of 12 subjects randomized to doses in equal proportions.
- Each subsequent cohort of 12 subjects is assigned doses by applying a pre-defined method to data on responses available.
- Method for dose assignment chosen to efficiently meet specific study objectives for likely dose response relationships (scenarios)
- Simulations used to investigate operational characteristics

Likely Dose Response Scenarios

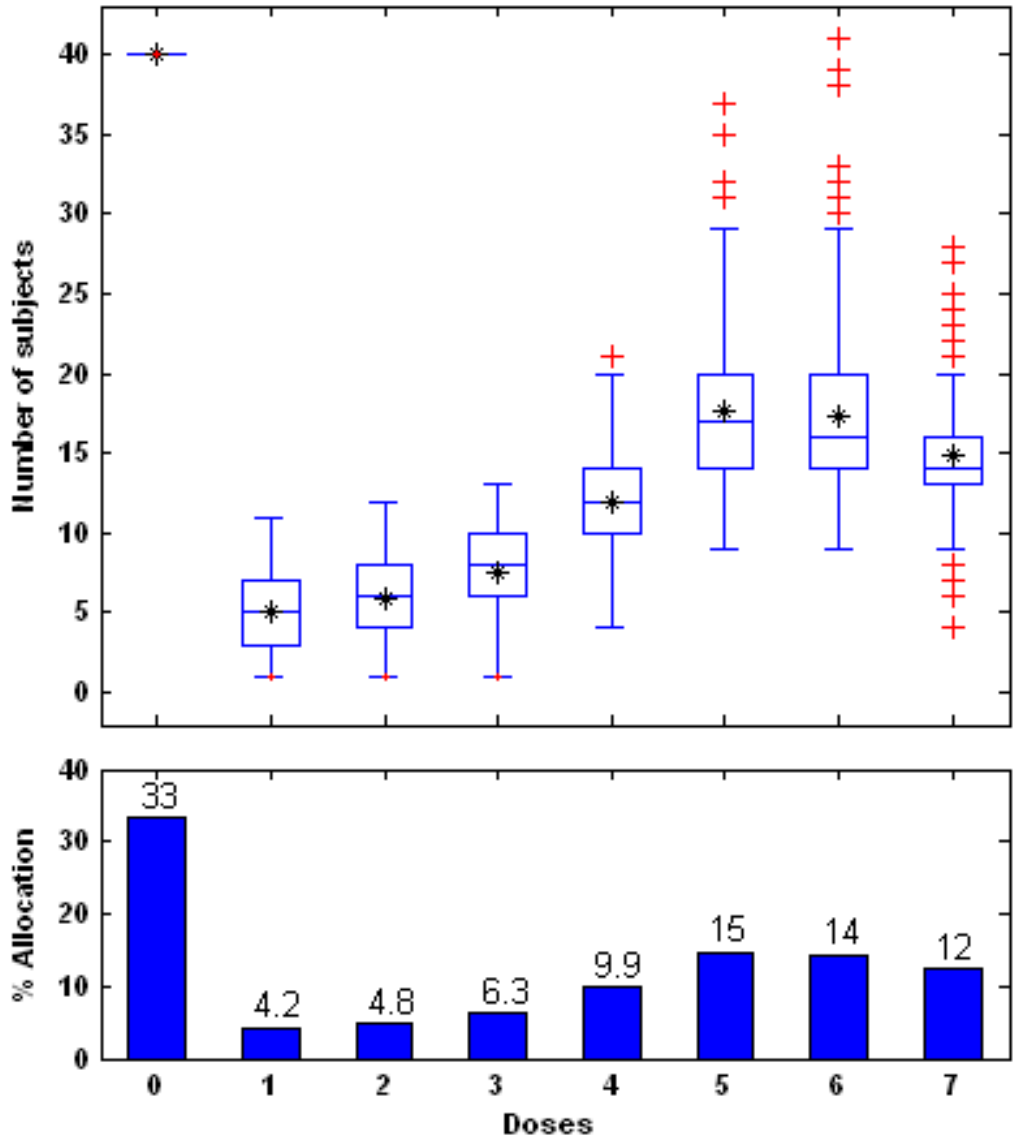


Cytel
STATISTICAL SOFTWARE & SERVICES

Adaptive dose-allocations by Cohort



500 simulated trials (Scenario C)



Criteria for Comparing Adaptive to Standard designs

- Proof-of-Concept:

  Power

- Dose-ranging:

  Efficiency in response estimation at each dose (using mean squared error metric)

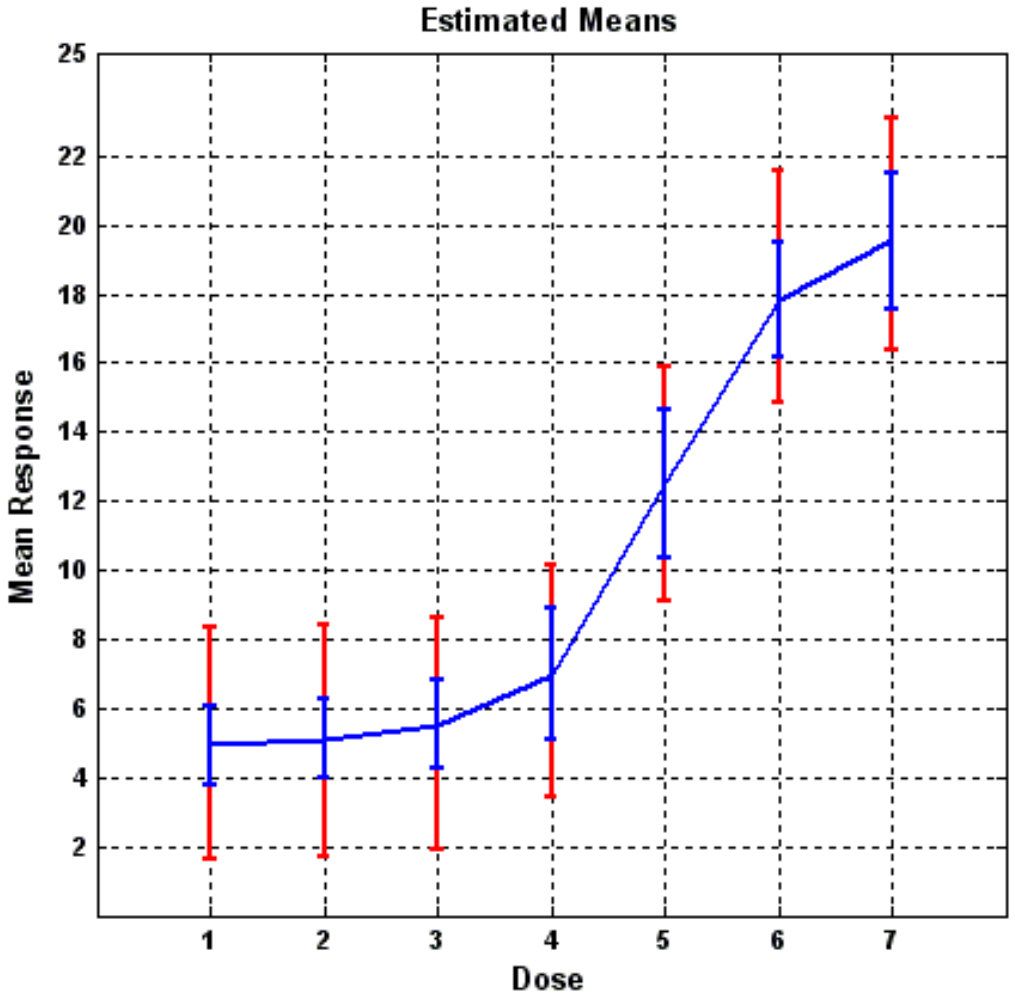
Scenario C

- Proof-of-Concept
  - Power of standard design = 0.99
  - Power of adaptive design > 0.99

- Response Estimation
  - Adaptive Bayesian Design is more efficient by more than a factor of 2 compared to standard design for all doses

(1000 simulations used for calculations)

Estimate of Dose Response Curve



Cytel
STATISTICAL SOFTWARE & SERVICES

All scenarios: Proof-of-Concept

Scenario	Power of Standard POC design (sample size = 30) %	Power of Bayesian Adaptive Combination Design %
C	99	100
B	35	99
A	5	5

All scenarios: Dose Response Estimation

Adaptive design is twice as efficient as the standard design in dose response estimation

at each dose for Scenarios B and C

(Dose response is irrelevant for Scenario A)

(1000 simulations used for calculations)

Implementation of Adaptive Design

- On-call person (unblinded statistician) to generate doses to be assigned dynamically
- Rapid transfer of needed data (email, IVRS).
- Both functions could be automated
- Drug supply is challenging because of dynamically changing randomization ratios

Estimating drug requirement

- For fixed equal allocation:
  - Requires 40 placebo kits, 80 kits for the doses. A kit is a single pack of 0,1,2,3,4,5,6 or 7 unit tablets
  - Total # kits = number of subjects = 120
- For adaptive design:
  - We know 40 kits of placebo are required and also that for the first cohort we need 2 kits of dose 4 and 1 kit for doses 1, 2, 3, 5, 6, 7.
  - We do not know how subjects in the 9 remaining cohorts will be assigned doses by the adaptive allocation process. A safe approach is to provide :

    9 cohorts x 8 subjects/cohort = 72 kits for each dose.

    Total #kits = 40+2+1x6+72x7 = 552
- Overage for adaptive design = (552 − 120)/120 = 360% (does not include allowance for buffers at sites and depot)

Modeling drug requirement

- The safe approach is very conservative. It seems very unlikely that the adaptive allocation will assign *all* subjects in cohorts 2 to 10 to a single dose

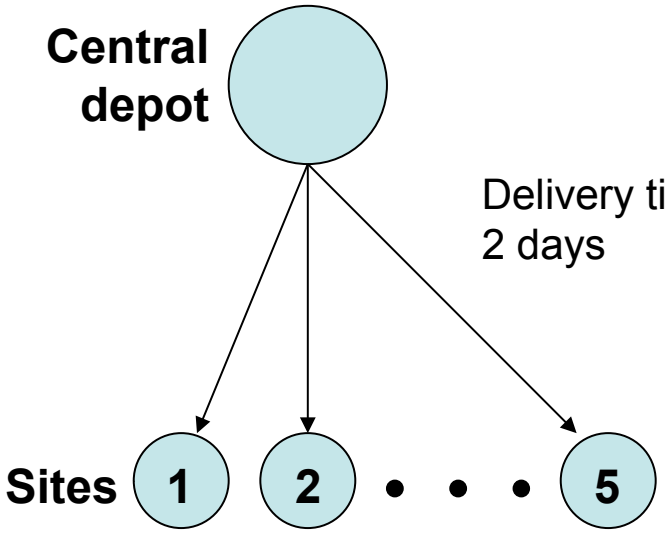
- If we consider specifics of the adaptive design and likely scenarios considered in the design we can strike a better balance between risk of randomization failure (risk of stock-out) and overage.

Combining design simulation with drug supply simulation

- The statistical design simulation tool was extended to simulate the drug supply chain to enable optimization of drug supply for the set of likely scenarios.
- Supply chain inputs that describe subject accrual rates at centers, drug requirements of the treatments and supply chain parameters were used to simulate
  - stocking and replenishment process at depots and centers (floor/ceiling system for replenishment).
  - enrolment randomness over time at each site
- Five hundred simulations were generated for each scenario

Supply Chain / Pack Types

Supply Chain



Recruitment: Random average rate=1 patients/wk

Site activation: All at start of trial

Medication Supplies

Pack Types:
- Placebo, 1, 2, 3, 4, 5, 6, 7 units

Dispensing:
- On randomization (1 pack)

Packaging Campaign:
- Single (all packs produced up-front)

IVRS Trial Supply Management:
- Trigger (Floor) & Re-supply level (Ceiling)
- Joint replenishment

Inventory Control

- The ‘trigger/resupply’ or ‘floor/ceiling’ system of inventory control with joint replenishment is very commonly used with IVRS at centers and depots.
- The system works as follows:
  - Initially a specific amount of stock is sent to each site.
  - Each day the IVRS compares the inventory position (= stock on hand + on order – back-orders) for each type of pack at each center with the trigger (or floor) level.
    - If the inventory position is greater no order is placed.
    - If it is equal or lower, an order is placed for the pack type. The size of the order is the difference between the resupply level (or ceiling) and the inventory position for that pack type. In addition, for all other packs an order is placed for an amount equal to the difference between ceiling and the inventory position.

Standard Design
Site level randomization (block size =8)

	# Packs Dispensed	Max # Packs Shipped	# Packs Campaign	Overage	Average # Consignments	Maximum # Consignments	Stock-out Probability (Estimate)
Any scenario	**120**	**193**	**256**	**113%**	**29**	36	**< 0.002**

500 Simulations: no stock out observed

Site look-ahead parameters (subjects):

Initial = 16, Floor = 2, Ceiling = 16

Trial randomization period average = 24 weeks, max=37, min =14

Number of consignments approx. 1/ week

Cytel
STATISTICAL SOFTWARE & SERVICES

Adaptive Design: Scenario C

	Placebo	D1	D2	D3	D4	D5	D6	D7
Ceiling	6	3	3	3	3	5	5	5
Floor	3	1	1	1	1	2	3	3

	# Packs Dispensed	Max # Packs Shipped	# Packs Campaign	Overage	Average # Consignments	Maximum # Consignments	Stock-out Probability (Estimate)
Scenario C	120	279	345	188%	25	30	< 0.002

Overage is 188% compared to 113% for standard design

Combining Scenarios

- Method 1:
  - Use supply strategy that works no matter which scenario is the true scenario
- Method 2:
  - Bayesian approach to combine scenarios using prior probability of each scenario

- We will use Method 1 (more conservative)

Adaptive Design: All Scenarios

	Placebo	D1	D2	D3	D4	D5	D6	D7
Ceiling	5	4	3	3	3	4	3	5
Floor	3	2	1	1	1	2	1	3

	# Packs Dispensed	Max # Packs Shipped	# Packs Campaign	Overage	Average # Consignments	Max # Consignments	Stock-out Probability (Estimate)
Scenarios ABC	120	265	351	193%	32	39	< 0.002

Overage is 193% compared to 113% for standard design

Multiple packs per kit

Suppose that treatment kits with 3 packs/kit were made up from combinations of 0, 1, and 3 unit packs as shown below.

Packs / Kit	Pack Types	Dose							
		Pb	1unit	2units	3units	4units	5units	6units	7units
3	0 unit packs	3	2	1	2	1	0	1	0
	1 unit packs	0	1	2	0	1	2	0	1
	3 unit packs	0	0	0	1	1	1	2	2

Adaptive Design: All scenarios

	Placebo	1	3
Ceiling	26	15	18
Floor	16	4	8
Campaign	318	157	188
Dispensed Max/av	215(189)	99(79)	117(92)

	# Packs Dispensed	Max # Packs Shipped	# Packs Campaign	Overage	Average # Consignments	Maximum # Consignments	Stock-out Probability (Estimate)
All Scenarios	360	625	663	84%	20.3	23	< 0.002

Overage is 84% compared to 193% for adaptive and 113% for standard design with 8 pack types

Cytel
STATISTICAL SOFTWARE & SERVICES

Another adaptive design
Dropping arms

- Medication using 3 packs/kit was considered less desirable than 1 pack/kit for compliance and dispensing errors
- Implementing Bayesian randomization is complex and expensive, and cannot be done as quickly and easily as list based randomization which is more easily tested and validated
- Dropping arms design simplifies randomization by switching between lists validated before trial begins
- Dropping arms design makes fewer assumptions about dose response relationship than Bayesian design

Drop Arms Design (One interim analysis)

- Stage 1: Randomize 60 subjects to placebo and doses 1,… 7 using permuted block of size 8 as with standard design
- Interim analysis of responses to drop all but one dose judged to be closest to target. Randomization is suspended during 3 week analysis period
- Stage 2: Randomize 60 subjects to placebo and remaining dose using permuted block of size 4
- Randomization for both sets of 60 subjects will be done at site level unlike Bayesian Design which requires study level randomization. This can lead to reduced overage

Comparison of Adaptive Designs

- Drop Arms Design has smaller power than Bayesian design. Scenario C 93% compared to 100%; scenario B 94% compared to 99%
- Bayesian Design is better at estimating dose response relationship
- Designs are similar in effectiveness in selecting clinically significant dose.
- Drop Arms Design randomizes more subjects near target dose.
- Drop Arms Design is simpler to understand intuitively.
- Drop Arms Design takes longer because it introduces a delay between stage 1 and stage 2 for interim analysis to select dose to carry forward

Drop Arms Design: All Scenarios
Site level randomization (block sizes =8,4)

	# Packs Dispensed	Max # Packs Shipped	# Packs Campaigns	Overage	Average # Consignments	Maximum # Consignments	Stock-out Probability (Estimate)
Scenarios ABC	120	234	276	130%	31	59	< 0.002

Two Campaigns: Second campaign was for dose selected at interim analysis and placebo

Trial duration average = 24 wks random+3 wk interim + 3 wk second campaign = 30 wks

Site Look-ahead settings: Initial =(18,10) Floor = (3,3) Ceiling = (18,10)

And the winner is…

- Standard design was ruled out due to poor statistical performance.
- Adaptive Bayesian design gave the best statistical performance but had acceptable overage only with 3 packs/treatment and was complex to implement
- Adaptive Drop Arms design was chosen
  - statistical performance substantially better than standard design
  - simple to implement
  - lower overage than the Bayesian design
  - moderate increase in overage compared to standard design

Conclusions

- Simple approaches to planning drug supply for adaptive trials can lead to large overages for multicenter trials
- Software tools that combine simulation of adaptive designs with simulation of the drug supply system can substantially reduce overage
- Drug supply planning for adaptive trials needs to be closely coordinated with statistical design to strike the best balance between statistical efficiency and drug supply feasibility.

Implementing adaptive designs is not a relay race…

For adaptive trials, design and implementation are critically interdependent

…it's a game of basketball

Cytel
STATISTICAL SOFTWARE & SERVICES

Thank you!

nitin@cytel.com