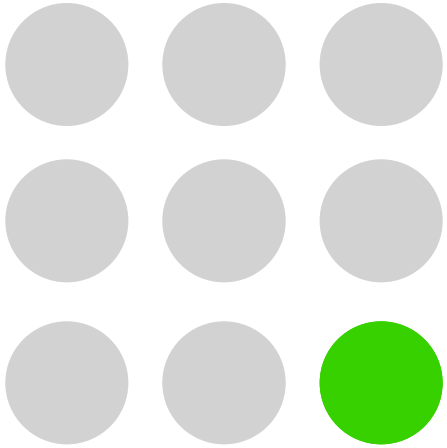
Modeling and Simulation to Improve Supply Management in Clinical Trials

A Presentation of Medidata Solutions and Cytel

23 February 2012



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Featured Presenters

Glen de Vries
President and Co-Founder, Medidata Solutions Worldwide
Glen de Vries is a Medidata founder and the original architect of the Rave® electronic data capture and clinical data management system. Glen continues to drive Medidata's technology vision and helping forge a new eClinical reality for the biopharma industry.

Nitin Patel, Ph.D.
CTO and Co-Founder, Cytel Inc.
Dr. Patel is a renowned expert in developing computational tools based-on cutting edge statistical and predictive methods. He is Cytel's Principal Investigator for an FDA clinical trial software CRADA (Collaborative Research And Development Agreement). Nitin's simulation and randomization breakthrough research is helping sponsor companies conduct even the most complex adaptive trials more routinely.

Erik Thorne
Director, Business Consulting, **Medidata Solutions Worldwide**
Erik has been a lead consultant in helping clients understand the application and potential of using Balance and electronic data capture in improving clinical trial randomization and supply management.

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Agenda

- Glen de Vries
  - A Future State for Randomization and Trial Supply Management (RTSM)
- Dr. Nitin Patel
  - Modeling and Simulation for Improving Clinical Supply
- Erik Thorne
  - Implementing the Simulation Results in Medidata's Balance
- Questions and Answers

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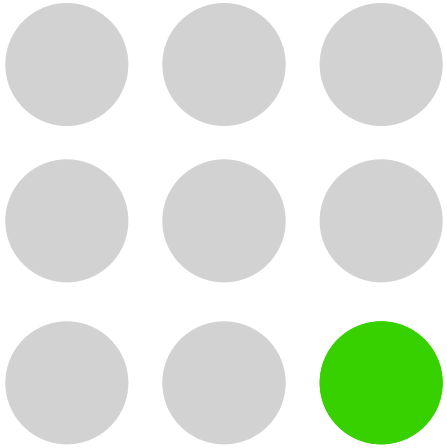
A Future State for Randomization and Trial Supply Management

Glen de Vries



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The Current State

There is tremendous strategic value in new approaches to Randomization and Trial Supply Management (RTSM)

- Critical to the clinical development process
- High cost component of a development program
- Mired in legacy processes & technologies
  - Expensive
  - Labor-intensive
  - Marginally integrated into e-Clinical infrastructure
- A high risk potential in study execution
- A high benefit potential if you can "get it right"

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The Future of RTSM

- Challenge current status quo
- Reduce
  - Costs
  - Timelines
  - Risks
- Leverage
  - Modern software
  - Less labor intensive processes (e.g. configuration vs. customization)
  - Fully integrated solutions
- Think differently about simulation and execution

These are the ideas behind Medidata Balance;
You will see them employed today!

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Today's Presentation

Dr. Nitin Patel

Chief Technology Officer, Chairman, and co-founder of Cytel

- Leverage modern modeling and simulation
- Solutions to clinical supply chain issues

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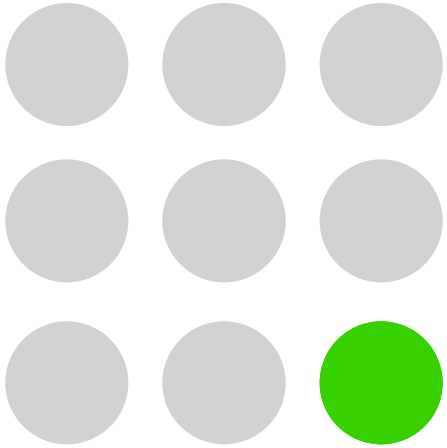
Modeling and Simulation for Improving Clinical Supply

Nitin Patel, PhD



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Simulation tools for planning drug supply in clinical trials

Nitin R. Patel
Chairman and CTO
Cytel Inc.

Outline

- Why simulate drug supply?
- How enrollment and the supply chain are simulated
- Example illustrating core capabilities of CytelDSim
- Adaptive Designs

Drug supply planning for clinical trials

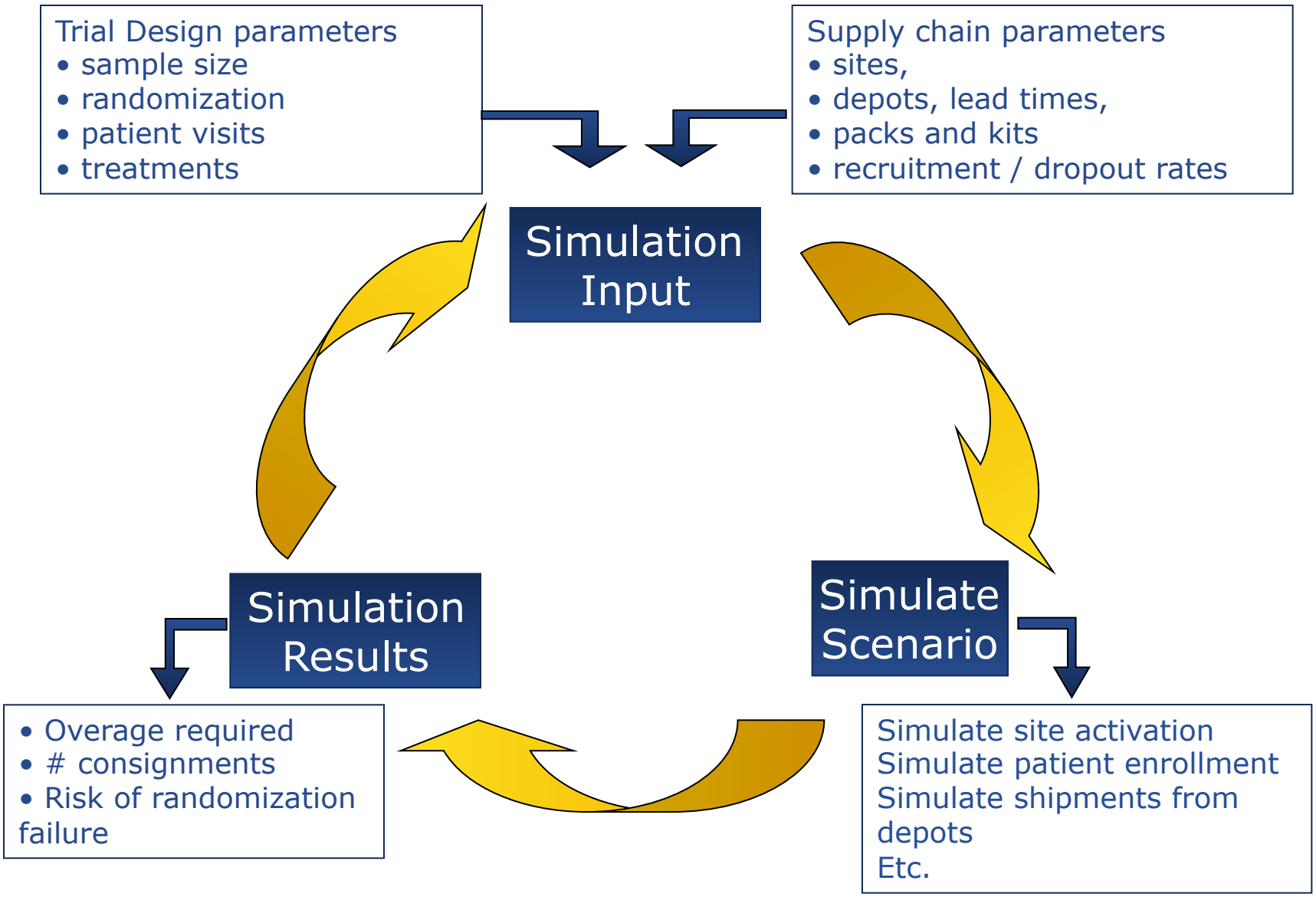
Typical questions that arise are difficult to answer:

- How much drug do we need for the trial?
- How much more needed if open more sites?

Traditional approaches to estimating drug requirement

- Use historical overages and experience with similar trials
- Use spreadsheet calculations based on averages.
- **Disadvantages :**
  - No quantitative assessment of risk of stock-out (failed randomization)
  - Not easily defensible, reliability depends on intuition
  - No systematic way to answer “what-if questions” that help to optimize drug supply (e.g. effect of multi-pack kits, effect of reducing delivery time)

Simulation Approach



Simulating uncertainty in enrollment

- We simulate the arrival of subjects for randomization using a Poisson model
- Several papers show that the Poisson model is an effective way to model the randomness inherent in patient enrollment in clinical trials.
- Analysis at Cytel of recruitment data from a sample of 39 completed Phase 2 and Phase 3 trials at a major pharmaco supports use of the Poisson model

Simulating the supply chain

- The ‘trigger/resupply’ or ‘floor/ceiling’ system is very commonly used with IRT to place orders at sites to replenish stock.
- When the stock of a pack falls to the trigger level (or below) an order up to the resupply level is placed for the pack. In addition, an amount is ordered for other packs to bring their stocks up to their resupply levels.
- These levels have to be carefully chosen to balance overage against the risk of stockout.
- CytelDSim automatically sets trigger and resupply levels to have no stockout in any of the simulated trials.
  - Users can choose trigger and resupply levels instead of these automatic settings

Example: Phase 2 dose-finding trial

- Placebo controlled, double blinded trial
  - Sample size = 472, enrollment stops when 472 subjects have been randomized
  - Four treatments pbo and 20,40,60 mg doses
  - Randomization using permuted block of size 4, balanced design (equal probability for all arms)
  - Treatment time: 6 weeks, dosage: once/day
- Base Case
  - Single dispensing visit
  - Single pack/ patient kit (4 pack types: pbo, 20, 40, 60mg tablets in bottles)
  - Single campaign

Supply chain data

- 3 countries (USA, UK, Canada), One depot in each country,
  25 sites (13, 8, 4),
  accruing at average rate of (0.6, 0.5, 0.25) subjects/week
- Variation in enrollment rates across sites within a country ranges from 50% to 150% of country average
- Site initiation times from start (first to last site):
  US (0 to 8 wks), UK (4 to 9 wks), Canada (9 to14 wks)
- Lead time for shipping consignments from depot to site 5 days
- Number of consignments/week reasonable from operational point of view: 3 consignments/wk (total across all 3 depots)

Simulating the example trial

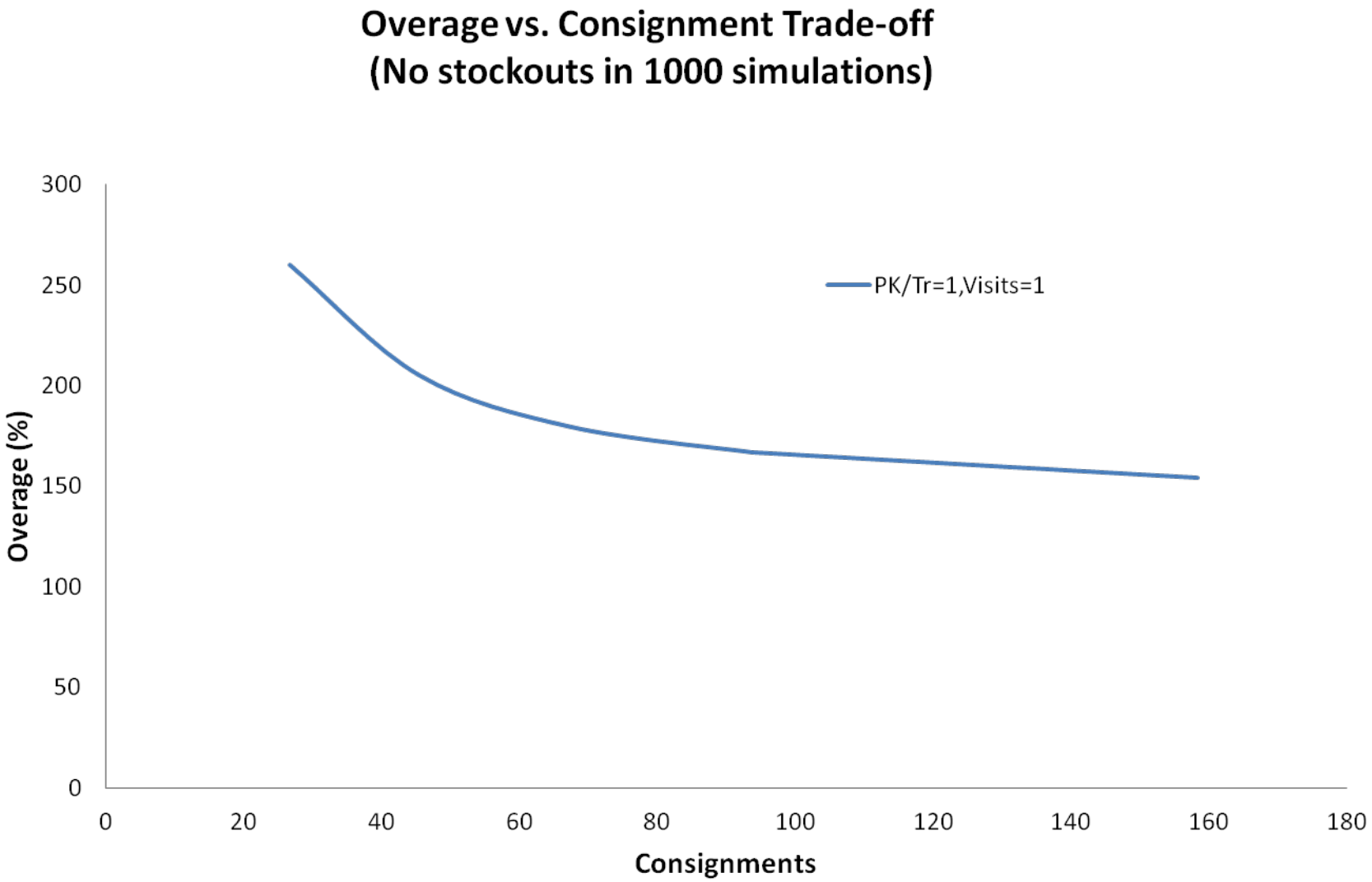
- There were no stockouts in 1000 simulated trials using a single campaign of 1200 packs
- CytelDSim automatic settings :

Levels (packs)	US	UK	Canada
Trigger	3	3	2
Resupply	5	5	4

- Overage was 154%
- Average # of resupply consignments=133 (3.0/wk)

Results from 1000 simulated trials

	Mean	StdDev	Min	Median	Max
Patients Randomized	472	0	472	472	472
Start to LPLV(Wks)	44	2.8	37	44	56
Packs dispensed to subjects	472	0	472	472	472
Packs shipped from depot	920	5.6	905	920	938
Overage shipped(%)	95%	1.2	91.7	94.9	98.7
Packs packed	1200	0	1200	1200	1200
Overage packed(%)	**154%**	0	154	154	154
Consignments	**133**	3.7	121	133	**144**
Packs per consignment	5.8	0.12	5.4	5.8	6.3
% Runs with at least 1 stockout	0	0	0	0	0


Overage vs. Consignment Trade-off
(No stockouts in 1000 simulations)
Overage (%)
300
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180
Consignments
PK/Tr=1,Visits=1

Base Case and What-if Questions

- We will use the above settings of levels and other variables of the example as a base case that will serve as a benchmark to evaluate the effects of modifications to various parameters.

- Let us illustrate how simulation can be used to optimize drug supply by providing answers to typical what-if questions.

1. Overnight delivery

- How much do we save if it is possible to use express delivery to deliver consignments overnight (next day morning)?
- CytelDSim automatic settings for 1000 simulations with no stockout:

Levels (Packs)	US	UK	Canada
Trigger	1	1	1
Resupply	3	3	3

- Overage 116% (compared to 154% for 5 days lead time)
- Average # of resupply consignments = 134 (3.0/wk)

2. Multiple dispensing visits

- Suppose protocol requires that subjects make a visit 3 weeks after the randomization visit
- Instead of dispensing a single kit for the 6 weeks treatment, we dispense a kit for 3 weeks treatment at the randomization visit. We provide a second pack for 3 weeks treatment on the visit that follows the randomization visit
- Simulating 1000 trials shows overage is reduced to 110% (from 154%) with no stockout

3. Multiple packs/kit

- What if we manufacture only placebo, 20mg, and 40mg tablets and have patients take 2 tablets for a dose in the combinations shown below :

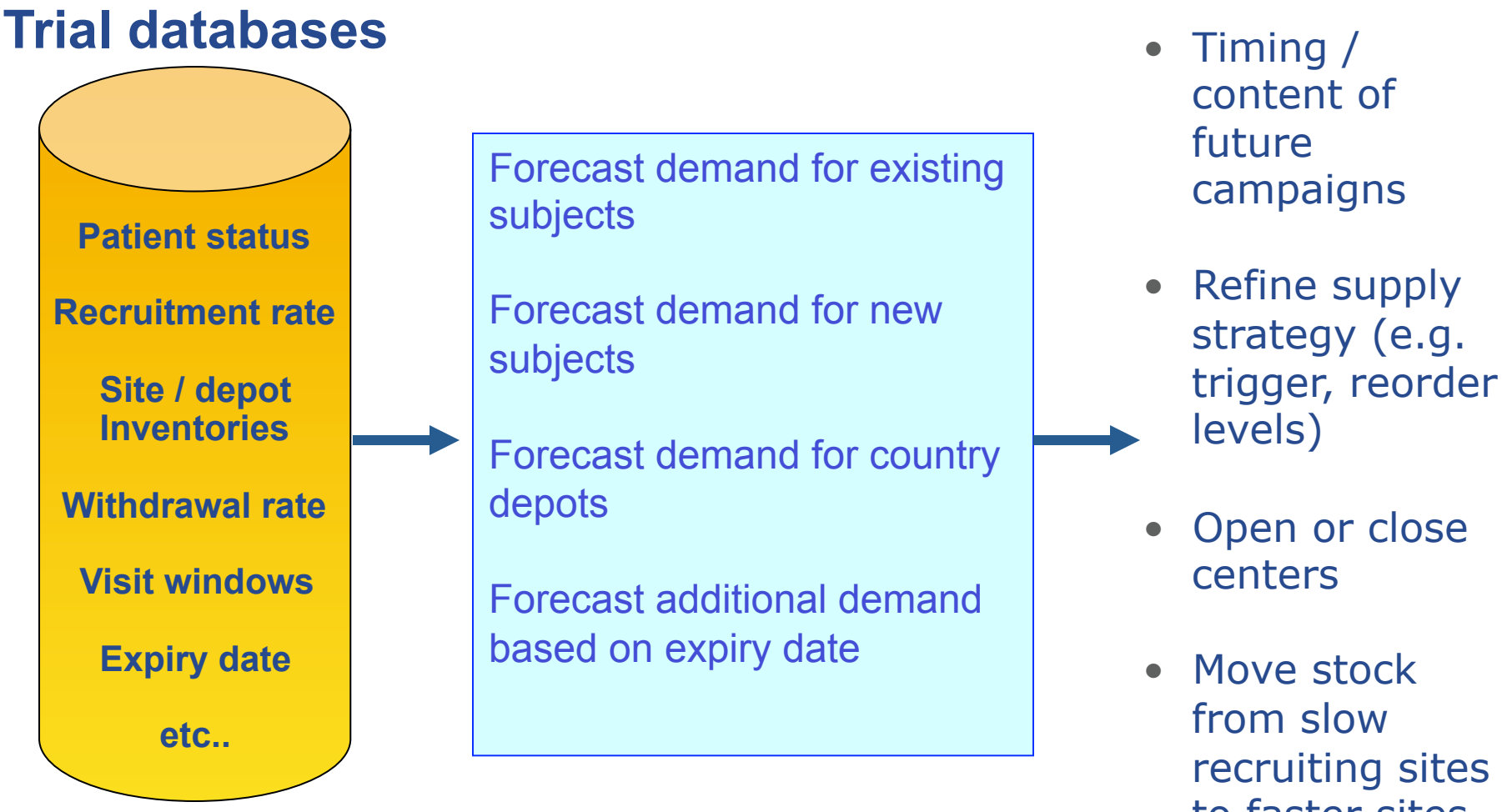
	Kits (treatments)			
Pack types	Pbo	20	40	60
Pbo	2	1	1	
20mg		1		1
40mg			1	1

- Simulating 1000 trials shows that the overage will come down substantially from 154% to 97% with no stockout

4. Overnight delivery
+ Multiple dispensing visits
+ Multiple packs/kit

- What if we combine overnight delivery, two dispensing visits and two packs/kit?
- Simulating 1000 trials shows that the overage will come down greatly from 154% to 63% with no stockout.

Mid-Study Re-simulation



Drug supply for adaptive trials

- In traditional clinical trial designs results are observed only after trials are complete.
- Adaptive clinical trials use accumulating data during the trial to improve statistical efficiency.
- Adaptations introduce uncertainty in planning drug supply. Typically overages will increase.
- Statisticians commonly use simulation tools for designing adaptive trials. At Cytel, we use our trial design simulation tools in tandem with CytelDSim to plan drug supply for adaptive trials.

Summary

- Simple approaches to planning drug supply for trials can lead to large overages or risks of missed randomizations for multicenter trials
- Software tools like CytelDSim that simulate the drug supply system can substantially reduce overage and quantify risk of stockout at the planning stage
- These tools can be used to make mid-course corrections as trial progresses
- These tools also enable evaluation of trade-offs between statistical efficacy and drug supply performance of a trial

References

1. Anisimov VV and Federov VV: *Modelling, prediction and adaptive adjustment of recruitment in multicentre trials,* Stats. in Med. 2007, v 26 pp 4958-4975

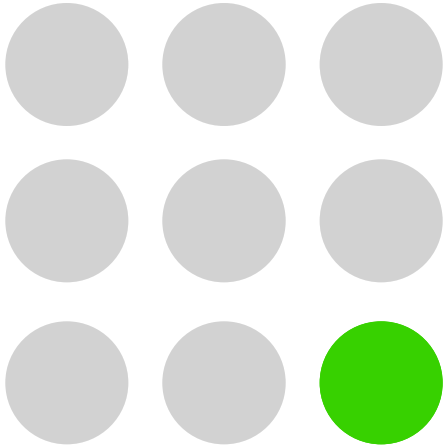
2. Jones B and Patel N: *Software and Simulation Tool for Modelling and Predicting Multicenter Recruitment,* Presentation at annual DIA Euro Meeting, Vienna, 2007

3. Nicholls G, Patel N, and Byrom B: *Simulation as a critical tool in planning adaptive clinical trials,* Applied Clinical Trials, March 2008

4. Patel N, Samanta S, Senchaudhuri P, Stocklin C: *Experience with using simulation models to plan for drug supply in adaptive trials*, Presentation Annual Joint Statistical Mtgs., Vancouver, 2010

Implementing the Simulation Plans for Supply with Medidata Balance

Erik Thorne



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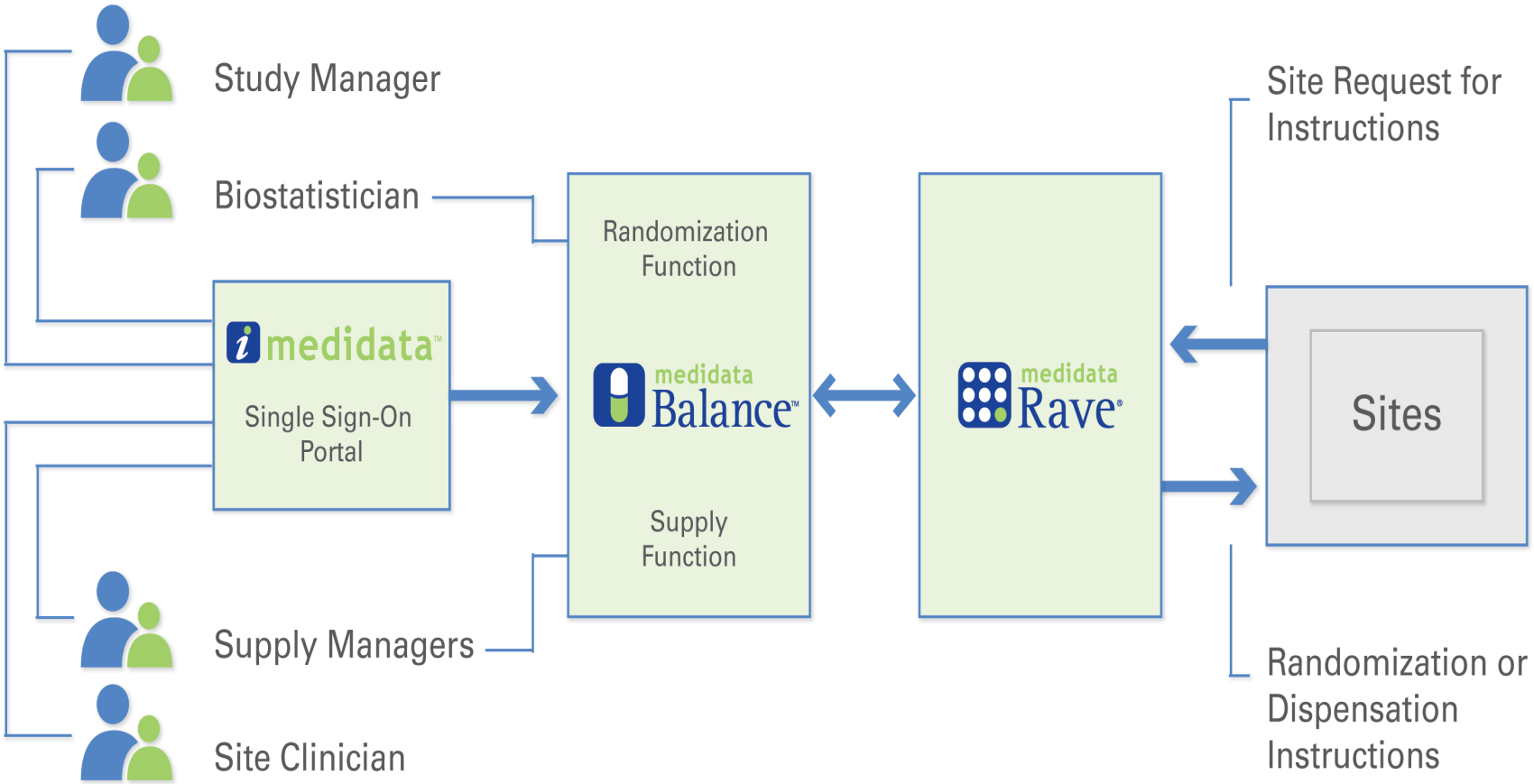
User Environment for Medidata Balance



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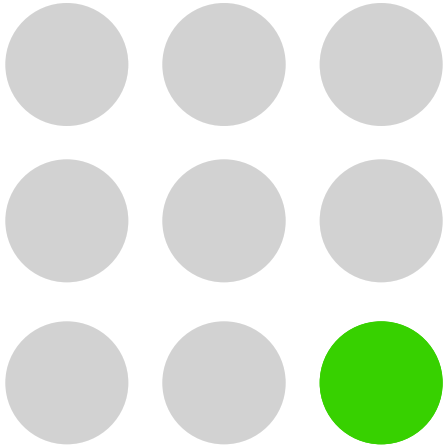
Question and Answer Session

Please enter your questions in the chat box on the left hand side of your screen.



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See us at these upcoming events:

Cytel, Inc.	Medidata Solutions Worldwide
21-Mar -- 22-Mar Philadelphia End-to-End Clinical Data Management <http://www.arena-international.com/ecdm/> Cytel expert speaker	19-21 Mar, Philadelphia, ESL 6th Forecasting and Optimizing the Clinical Supply Chain, <http://www.crownclinical.com/6th-forecasting-and-optimizing-the-clinical-supply-chain/>
21-May -- 22-May Munich European Clinical Data Forum <http://www.spgmediadesign.com/test/ecdf2012/> Cytel expert speaker	10-11 Apr, Philadelphia, CBI Risk Based Approaches to Clinical Investigation, <http://www.cbinet.com/conference/pc12029>
26-28 Mar, Copenhagen, DIA European Meeting, http://www.diahome.org/diahome/FlagshipMeetings/home.aspx?meetingid=25205 > Nitin is invited speaker	26-28 Mar, Copenhagen, DIA European Meeting, http://www.diahome.org/diahome/FlagshipMeetings/home.aspx?meetingid=25205 >
24-28 Jun, Philadelphia, DIA Annual Meeting, <http://www.diahome.org/DIAHOME/Home.aspx> Cytel expert speakers	24-28 Jun, Philadelphia, DIA Annual Meeting, http://www.diahome.org/DIAHOME/Home.aspx

Second webinar in this series: April 3, 2012, "Implementing Studies with Integrated IRT and EDC Systems", featuring Galderma Laboratories, LP

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For further information please contact:

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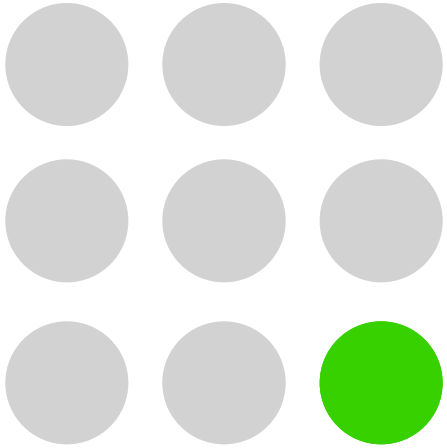
Cytel: Mike Weitz, mweitz@cytel.com

A link to a recording of the webinar will be sent to all attendees.

Your feedback is important to us. Please link to the survey following this slide.



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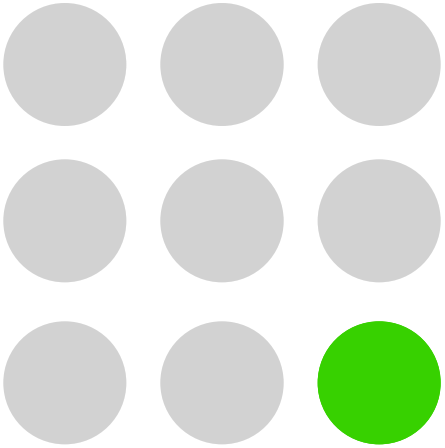
http://www.surveymonkey.com/s/566LKZN



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