Drug Supply Modelling Software

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Abstract

The Supply Modelling tool predicts the drug supply needed to cover patient demand during a clinical study. The GSK Research Statistics Unit, in collaboration with the GSK Global Supplies Operations group, developed a statistical approach controlling the risk of running out of stock for a patient. The tool's wide use by clinical teams has enabled significant cost benefits in GSK R&D.

Our software tool designed as an R package allows for

- central and centre-stratified randomization,
- equal or different treatment proportions within the randomization block,
- and other factors.

Our user interface for the *Study Manager* was built by embedding the R package into the Excel environment with RExcel.

Background: Drug Development Process

Several strongly interconnected stages

- Statistical study design
  models, sample size, randomization scheme
- Patient recruitment modelling
  countries, centres, recruitment duration
- Drug supply planning
  randomization scheme, study design, doses, costs,…
- Manufacturing models
  recruitment → supply prediction → manufacturing process

Background: Supply Chain Process

- Multicentre study:
  - Patients are recruited at different centres
  - After screening process — randomized to different arms
- Scenario (typical for a large study)
  - One (or two) central and several regional depots
  - Each depot — several local centres
  - Delivery time to regional depots — a few weeks/months
  - Delivery time to local site — a few days
- Supply strategy
  - Initial shipment to regional depots
  - Later on — with some frequency or on demand
- Clinical trial supply stage is very costly
- Goals:
  - Minimize risk of stock out for a patient
  - Reduce Overage (amount of unused drug)

Background: Current Situation

Recent (~3–4 years ago) practice in GSK: statistical methods were not used. A centrally randomized study might have been planned with high supply overage.

Correct planning techniques should account for:

- various uncertainties in input information
- recruitment and randomization can be viewed as stochastic processes
- variation in recruitment and randomized patients across centres/depots

Monte Carlo simulation is very computer intensive and may lead to:

large computational time,
multivariate optimality problems,
Low precision or large computation times to compute small critical probabilities.

With the new technology described here, supply overage has been reduced (often to less than 100%) with a cost savings to GSK of over £50 million per year.

Risk Approach in Supply Modelling

- The approach uses the notion of risk (probability in a single study) that the assigned drug may not be available to a small number of patients. The approach is based on the developed technique for modelling
  - patient recruitment
  - randomization process

- Risk 5% means that in a study:
  - ✓ with probability 95% all randomized patients will get the correct treatment assignments,
  - ✓ with probability 5% the treatment may not be available for one or more patient s.

Recruitment Planning

The Drug Supply stage is very costly (comprising over 2/3 of drug development costs) and substantially affected by the recruitment process.

It is imperative to develop statistical modelling approaches that can

- account for uncertainties,
- can provide accurate prediction of the number of recruited patients in depots/sites for different time periods and on different arms
- predict critical supply levels needed to satisfy patient demand
- and avoid extra supply overages

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Modelling Patient Recruitment

RSU developed statistical methodology *(Anisimov, Fedorov, 2005–2007)* and an innovative predictive patient recruitment modelling tool:

- Accounts for randomness in recruitment over time, variability in different sites, site initiation delays
- Computes mean and predictive intervals for the predicted number of recruited patients over time, and for total recruitment time
- Data-driven, uses estimation, Bayesian adjustment, prediction
- All computations are based on closed-form analytic expressions, so no Monte Carlo simulation is necessary.

Additional features:

- Evaluating minimal number of sites, adaptive adjustment, predicting performance of sites/countries

R Package for Recruitment Planning (1)

In our R package, we use a Poisson–gamma recruitment model, where the patients arrive at centres according to a Poisson process with rates λ_i which are assumed to be independent gamma-distributed random variables.

Motivation for Poisson-Gamma (negative binomial) model

- Centers are sampled from a “Gamma” population,
  i.e. rates are Gamma distributed.
- There exists a prior information described by mean α/β
  and variance α/β^2
- The use of the Gamma mixing is one of the simplest and elegant ways to model over-dispersion

R Package for Recruitment Planning (2)

We use a Block permuted randomization scheme where patients are allocated to treatments according to randomly permuted blocks of a fixed size:

For two treatments (A and B),
with blocks of size 4,
and equal proportions within block (2:2),
there are 6 possibilities for different permuted blocks:

(A,A,B,B) (A,B,A,B) (A,B,B,A) (B,A,A,B) (B,A,B,A) (B,B,A,A)

Impact on Drug Supply Planning

- Patient recruitment modelling is the basis for:
  - Predictive intervals for the number of patients recruited in sites/depots in any time interval
  - Calculating the probability of a given number of critical events: several pts registered within a short time (shorter than delivery time to site), empty sites, …

- Further development stage (for supply modelling):
  - Evaluate impact of randomization
  - Predicting the number of patients randomized to different treatment arms in centres/depots for different randomization schemes

    Anisimov (2007, 2009, 2010)
  - Evaluating probabilities of stock out

Randomization Impact

Randomization strategy essentially influences drug supply overage.

- Unstratified randomization
  - Patients are allocated to treatments according to randomly permuted blocks *without* regard to clinical centre

- Centre-stratified randomization
  - Separate randomization lists by randomly permuted blocks *in each* centre

- **Unstratified randomization is more expensive than Centre-stratified randomization as it leads to extra supply overages** (20-50% extra depending on scenario).

- With unstratified randomization, it is possible for one centre to have all patients on the same treatment. Since it could be any treatment, we would need enough supplies to cover worst case scenarios.

Effect on GSK's R&D

- Use of the team's innovative risk-based prediction tool have saved the company over £50 million per year.
- Members of GSK's R&D Supply Chain Team have won the European Supply Chain Excellence Award for Innovation (Nov. 2009). http://www.supplychainexcellenceawards.com/Innovation.aspx

RExcel (1)

- Excel is the most prevalent software used for data storage and interpretation.
- RExcel (Baier and Neuwirth, 2007) integrates the powerful statistical and graphical functions in R into the Excel user interface.
- Data can be exchanged between Excel and R. The user can use R functions in Excel cell formulas, effectively controlling R calculations from Excel's automatic recalculation mechanism.

RExcel (2)

- It is easy to construct a stand-alone RExcel workbook which hides R almost completely from the user and uses Excel as the main interface to R.

Our end users are familiar with supply issues, but not with recruitment modelling. Therefore we designed a user-friendly Excel interface to be used by the study manager.

RExcel Interface to the Modelling Package

- **Input (main variables):**
  - # of patients (range)
  - Sizes of regions (# of centres or range)
  - # of treatments
  - # of regional depots
  - # of dispenses
  - Risk level
  - Expected study duration
  - Randomization type
  - No-preloading or preloading

  (typical scenarios are built jointly with CTS & GSO Teams)

- **Output:**
  - Supply Overages
  - Total number of treatment packs needed at different stages

Overage Worksheet (1)

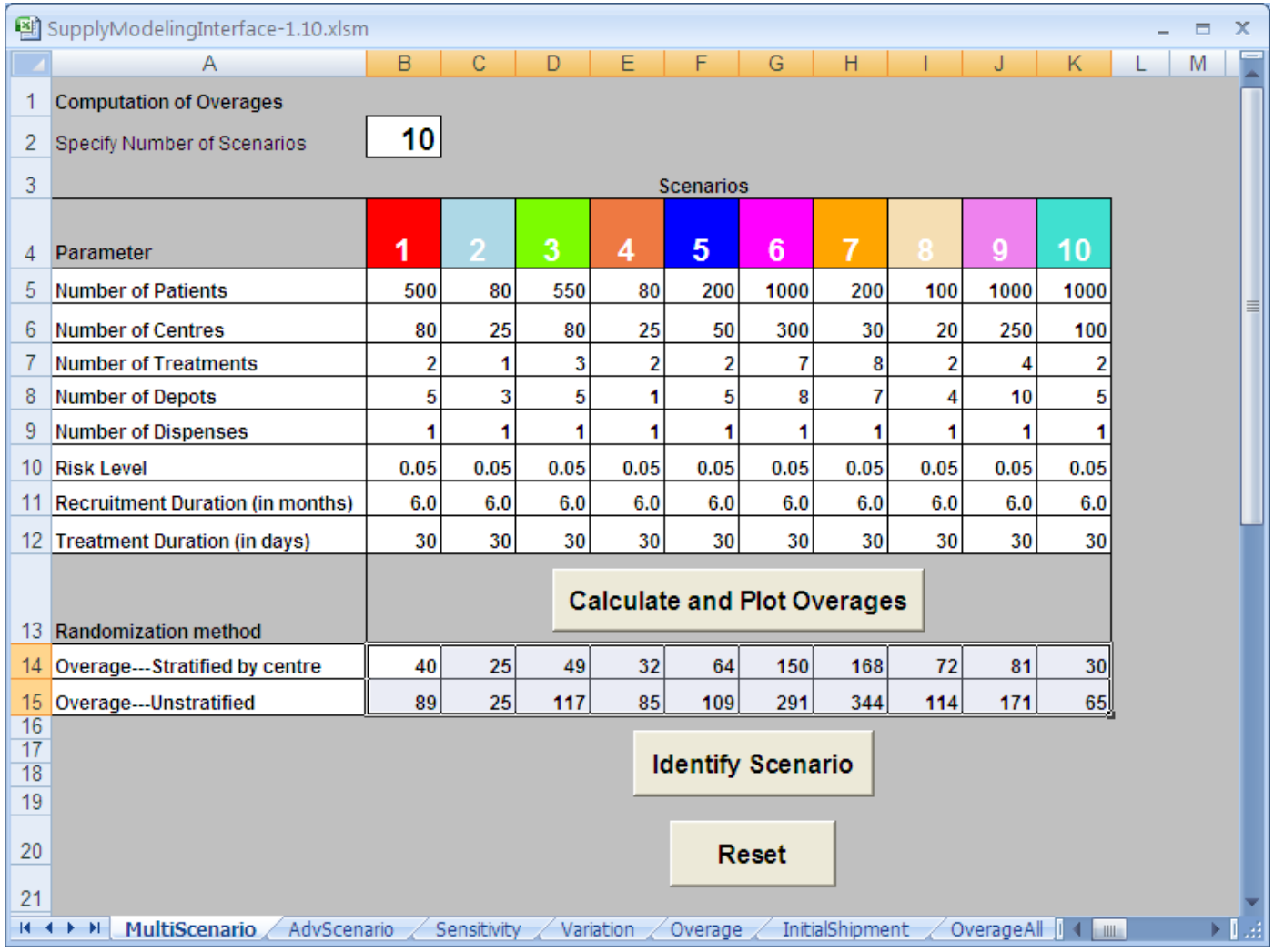
	Parameter	Value
5	Number of Patients	500
6	Number of Centres	80
7	Number of Treatments	2
8	Number of Depots	5
9	Number of Dispenses	1
10	Risk Level	0.050
11	Recruitment Duration (in months)	6.000
12	Treatment Duration (in days)	30

	Randomization method	Overage	Overage (preloading)	Total # of packs for each treatment
14	Stratified by centre	40	**	700
15	Unstratified	89	94	946

Overage Worksheet (2)

- The basic Overage worksheet uses the main input variables for a single scenario
- The Overage worksheet displays information about anticipated overages and total number of packs for each treatment
- The Overage worksheet can calculate overages with or without preloading (shipments of drugs prior to enrolment of any patients) of sites
- The other worksheets in this workbook assume no preloading

Multiple Scenario Worksheet (1)


SupplyModelingInterface-1.10.xlsm

Computation of Overages

Specify Number of Scenarios: 10

	Scenarios									
Parameter	1	2	3	4	5	6	7	8	9	10
Number of Patients	500	80	550	80	200	1000	200	100	1000	1000
Number of Centres	80	25	80	25	50	300	30	20	250	100
Number of Treatments	2	1	3	2	2	7	8	2	4	2
Number of Depots	5	3	5	1	5	8	7	4	10	5
Number of Dispenses	1	1	1	1	1	1	1	1	1	1
Risk Level	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Recruitment Duration (in months)	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Treatment Duration (in days)	30	30	30	30	30	30	30	30	30	30
Randomization method	Calculate and Plot Overages									
Overage---Stratified by centre	40	25	49	32	64	150	168	72	81	30
Overage---Unstratified	89	25	117	85	109	291	344	114	171	65

Identify Scenario

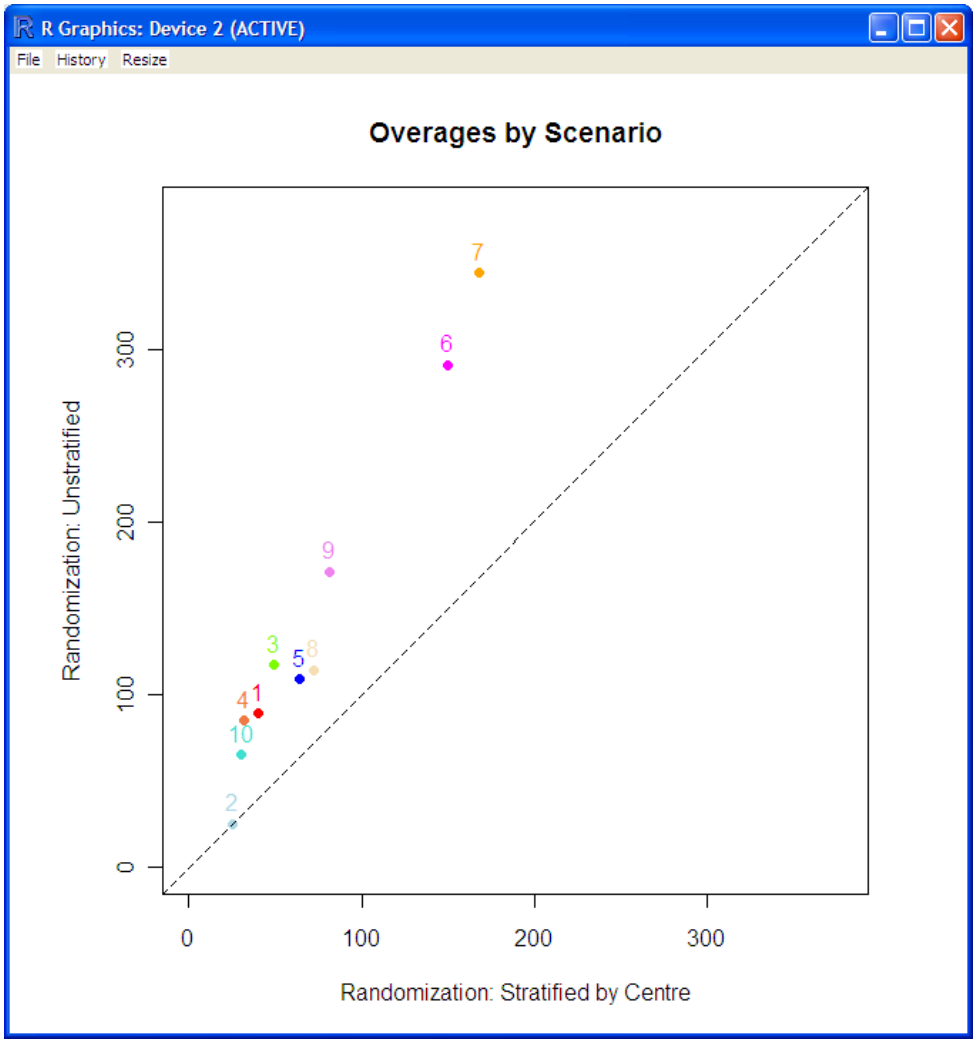
Reset

MultiScenario | AdvScenario | Sensitivity | Variation | Overage | InitialShipment | OverageAll

Multiple Scenario Worksheet (2)

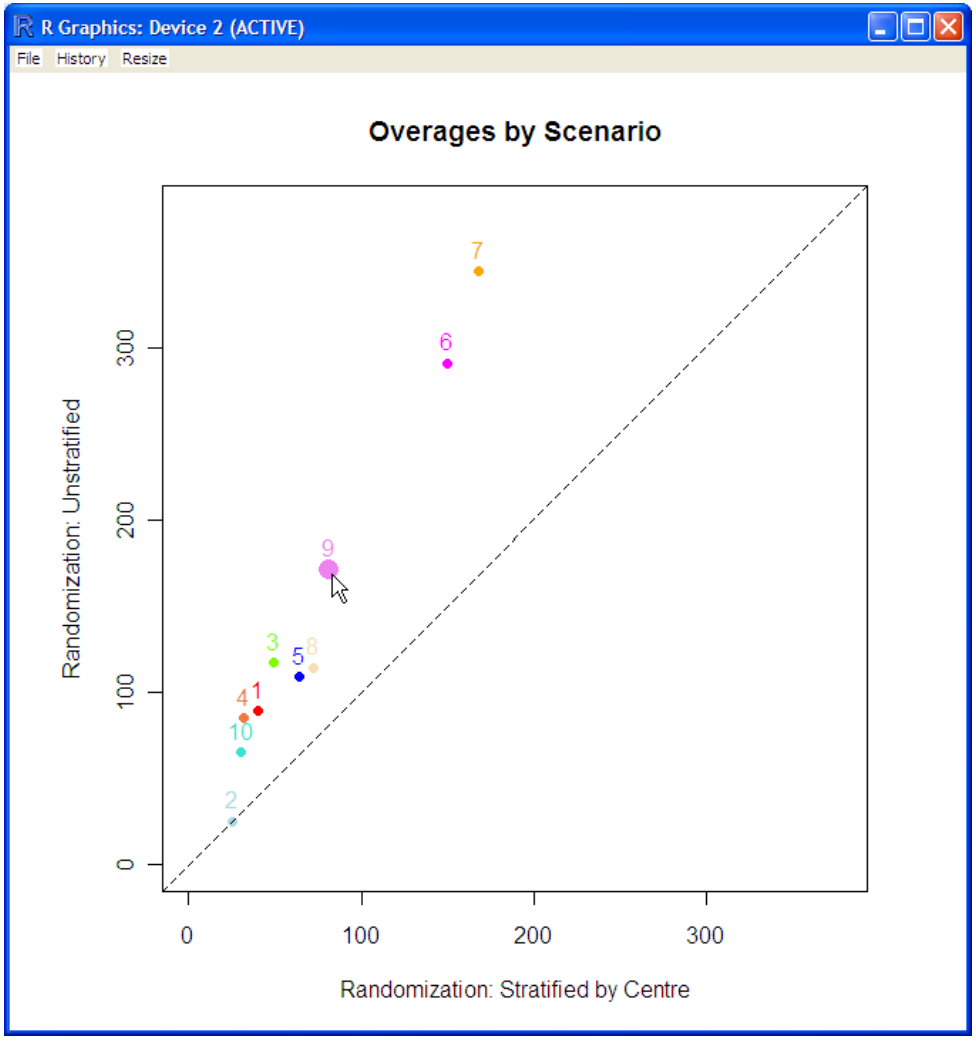
- Initial Entry into the workbook. Several scenarios may be specified.
- Initially, each scenario is assigned default values of the secondary parameters associated with the individual treatments and depots.
- The worksheet calculates overages under two randomization schemes and plots the overages for each scenario and for each randomization scheme.

Plot of Overages

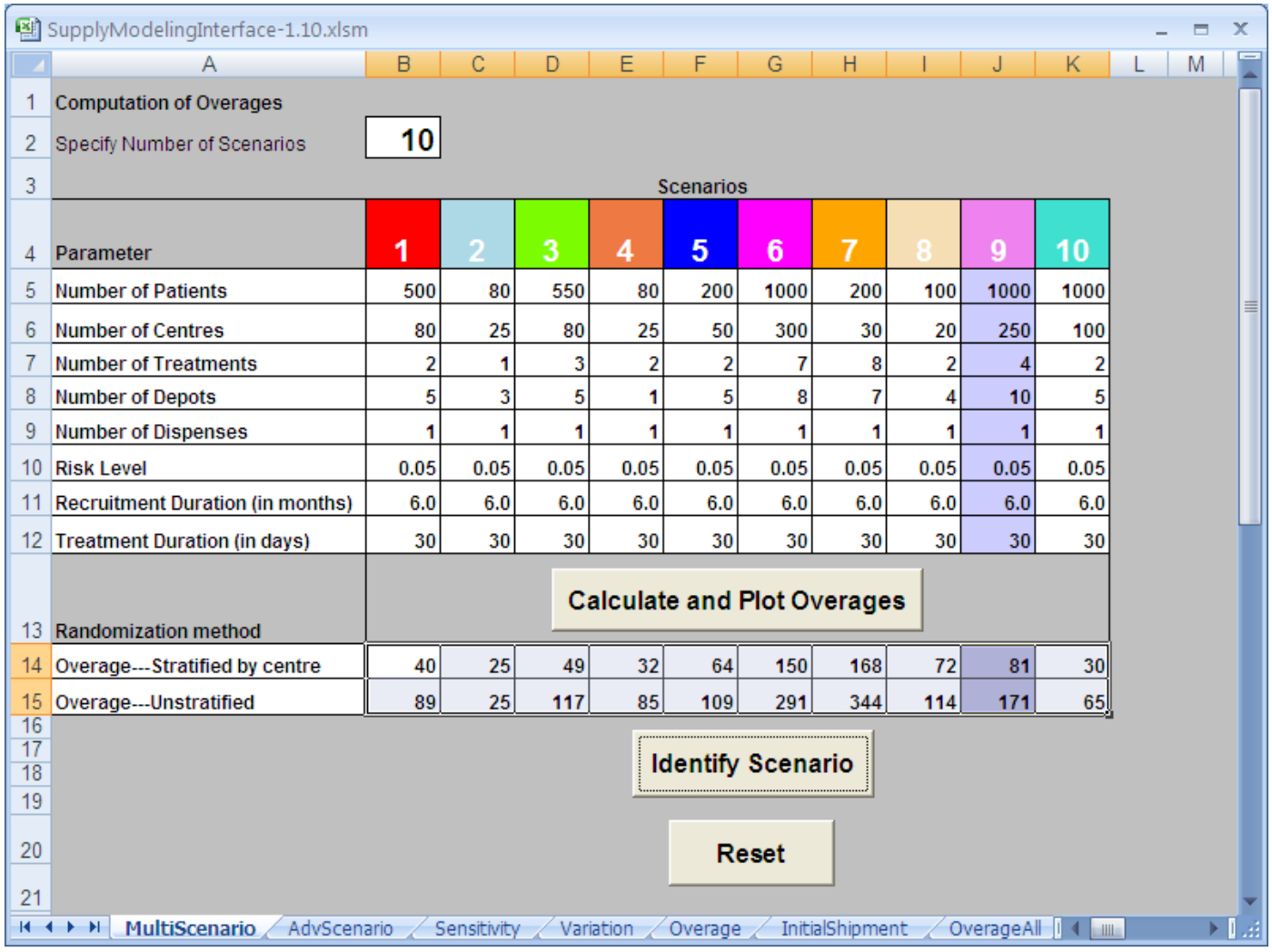


Identification of a Scenario

Scenario 9



Scenario 9 is Highlighted

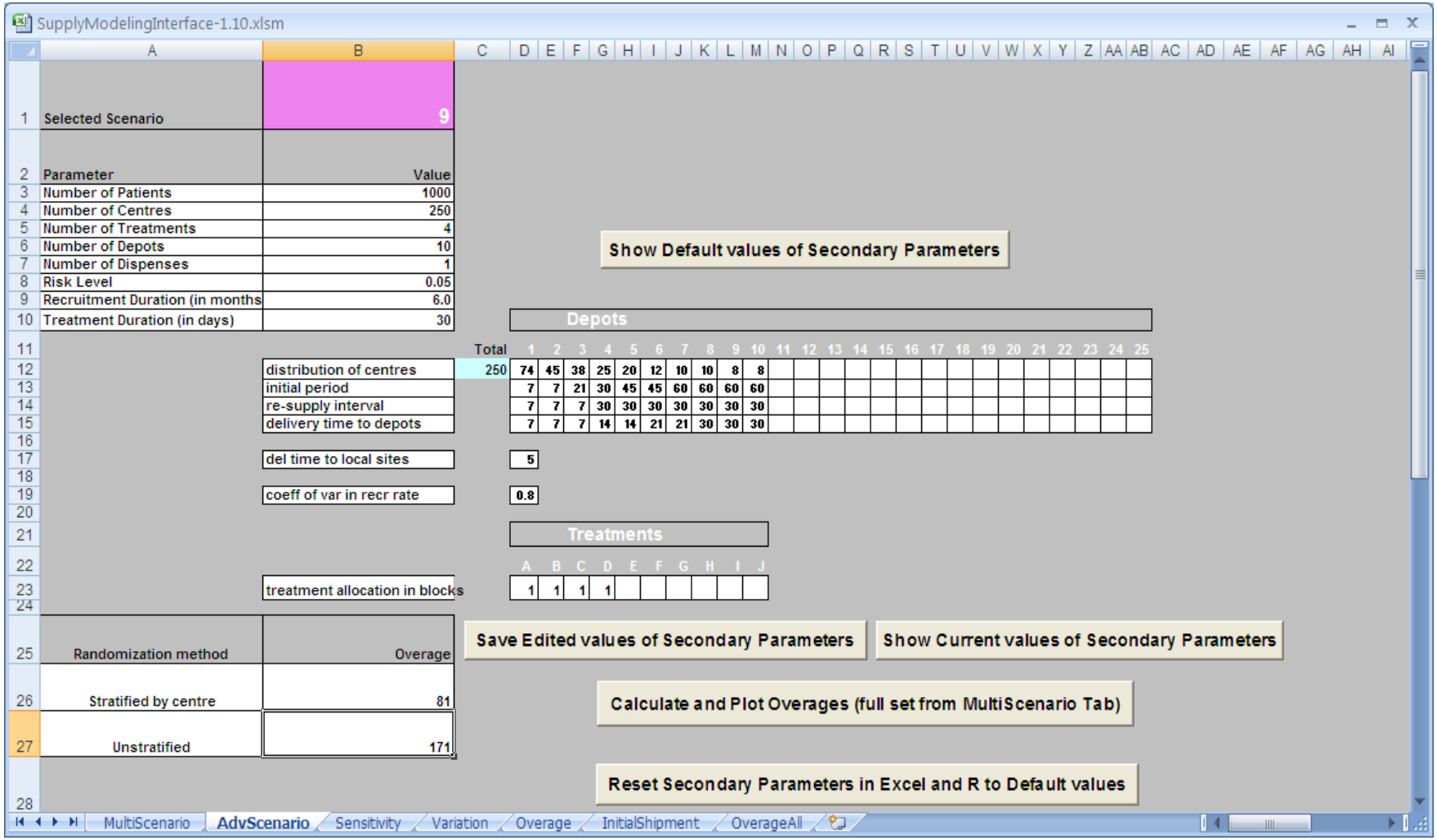


SupplyModelingInterface-1.10.xlsm

	A	B	C	D	E	F	G	H	I	J	K
1	Computation of Overages										
2	Specify Number of Scenarios	10									
3						Scenarios					
4	Parameter	1	2	3	4	5	6	7	8	9	10
5	Number of Patients	500	80	550	80	200	1000	200	100	1000	1000
6	Number of Centres	80	25	80	25	50	300	30	20	250	100
7	Number of Treatments	2	1	3	2	2	7	8	2	4	2
8	Number of Depots	5	3	5	1	5	8	7	4	10	5
9	Number of Dispenses	1	1	1	1	1	1	1	1	1	1
10	Risk Level	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
11	Recruitment Duration (in months)	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
12	Treatment Duration (in days)	30	30	30	30	30	30	30	30	30	30
13	Randomization method	Calculate and Plot Overages									
14	Overage---Stratified by centre	40	25	49	32	64	150	168	72	81	30
15	Overage---Unstratified	89	25	117	85	109	291	344	114	171	65
16											
17											
18		Identify Scenario									
19											
20		Reset									
21											

MultiScenario | AdvScenario | Sensitivity | Variation | Overage | InitialShipment | OverageAll

Advanced Scenario Worksheet (1)



Advanced Scenario Worksheet (2)

- This worksheet displays, and gives the option to change, the depot and treatment level secondary parameters for the selected scenario as displayed in cell B1.
- The Show Default button displays the default parameter values for the selected scenario.
- The user can change the secondary parameter values and then click on the button Save Edited values of Secondary Parameters.
- The changed secondary parameters will be used after the user clicks on Calculate and Plot Overages (full set from MultiScenario Tab).

Conclusions

- An innovative statistical methodology and a risk-based supply modelling tool were developed in R to predict the drug supply needed to cover patient demand during a clinical study.
- A user-friendly RExcel Interface was created to be used by the study manager.
- The implementation in CTS R&D led to substantial drug and cost savings.

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