Drug Supply Modeling Software: User Manual

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ABSTRACT

The design of multicentre clinical studies consists of several interconnected stages including patient recruitment prediction, choosing a randomization scheme and a statistical model for analyzing patient responses, and drug supply planning. The Research Statistics Unit (RSU) at GlaxoSmithKline (GSK) has developed a risk-based supply modeling tool using statistical principles. The tool predicts drug supply needed to cover patient's demand in a single study with a given risk of running out of stock for a patient. In order to support Clinical Trials Supply and Global Supplies Operations teams at GSK, the RSU created a user-friendly RExcel interface embedding the risk-based supply modeling tool into the Excel environment. This manual discusses screenshots to guide the user through using the interface.

1. Introduction

The design of multicentre clinical studies consists of several interconnected stages including patient recruitment planning, choosing a randomization scheme, the statistical model for analyzing patient responses, and predicting the drug supply required to satisfy patient demand during the recruitment stage. The uncertainties in recruitment and randomization substantially affect the drug supply stage. The drug supply chain process is rather costly and therefore it is essential to use statistical tools to minimize drug supply costs.

Our approach, based on stochastic modeling, allows us to build predictive bounds for the number of patients on different treatment arms in different regions, to predict critical levels of drug supply required to satisfy patient demand, and to evaluate the risk (probability) of running out of stock for a patient. Currently the tool enhanced by RExcel Interface is widely used by clinical teams and has enabled substantial benefits in GSK R&D. In November 2009 the members of GSK's R&D Supply Chain Team won the European Supply Chain Excellence Award for Innovation, where the organizers made a specific reference to the crucial role of the "risk-based prediction modelling tool" within GSK's overall proposal,

recognizing the innovative way to address the problem of supply overages and the development and use of a mathematical model at the project level to provide an innovative solution.

Our risk-based approach to drug supply prediction for a single study uses the notion of an acceptable risk of a stock-out [Anisimov (2009b)]. An acceptable risk δ means that with probability $1-\delta$ all patients in a particular study will receive the assigned treatment at the time of randomization. Correspondingly, with probability δ in a particular study, at the time of randomization the assigned treatment assignment may not be available for one of the patients and these patients will therefore be excluded from the study protocol. Note that for typical scenarios, the probability of supply shortage for more than one patient has magnitude much less than δ. Thus, for a typical study with 500 patients, risk 5% means that across similar studies only one patient out of (500/0.05)=10,000 may be "out of stock". Another way of looking at this is: for 100 similar studies of 500 patients each, we risk losing one patient in each of 5 studies, but in the other 95 studies all patients will receive the correct treatment assignments. Therefore, in general it is not reasonable to use risk less than 5%. This approach is similar to what is used at the statistical analysis stage: take a decision, based on patient responses and with a given probability of risk, on the tested drug.

There are a few input parameters in the tool considered as basic, and several other secondary parameters which in the current version of RExcel Interface are set by default, but can be changed for any specific scenario. For each Scenario we have the following primary parameters in Table 1.

The description of the Scenario can be expanded to show additional details about the following secondary parameters - distribution of centres between depots, initial period, re-supply interval, delivery time to depots, intervals for prediction, delivery time to local sites, coefficient of variation in recruitment rates, treatment proportions within randomization block. The tool covers two randomization schemes: Stratified by centre and Unstratified (central). It accounts for the variation in patient recruitment between different regions/depots, for the uncertainties caused by randomization scheme, and for specific logistics of re-supply. In particular, it allows prediction of the upper bounds for the number of randomized patients and supply demand in different regions for different time periods, estimation of the probabilities and the number of various critical events in the regions, and selection of the amount of the initial shipment in different regional depots.

The current technique of calculations is based on some approximations by the number of patients and the number of centres (for Stratified by centre randomization). Therefore, to get practically relevant results, the total number of patients should be at least 20 and in each depot the number of patients on average should be at least 5. In the case of Stratified by centre randomization, the number of centres in

TABLE 1. Primary input parameters which define the Scenarios.

Number of Patients	Sample size, total number of patients to be recruited (should be at least 20)
Number of Centres	Potentially available number of centers (must not be smaller than number of depots)
Number of Treatments	Total number of treatments (must be at least 1)
Number of Depots	Total number of regions or depots (must be greater than or equal to number of centres)
Number of Dispenses	Total number of dispenses (must be at least 1)
Risk Level	Probability that in a study for not more than one patient a right treatment is not available (should not be more than 0.5, recommended range is [0.05,0.25])
Recruitment Duration	Time available for recruitment (must be at least 1 day)
Treatment Duration	Time required for enrolment and treatment (must be at least 1 day)

each depot should be at least 5. Furthermore, the recommended range for risk level is between 0.05 and 0.25. However, for studies with some "rare" diseases, if the team would like to substantially decrease the potential opportunity of "running out of stock" and the cost of drug is not so important, the level of risk can be set at lower level, e.g. 0.01. The tool does not encompass commonly observed supply challenges such as batch shipment, import licenses, shelf-life, and production bottlenecks.

To facilitate the use of the Drug Supply Modeling tool and to make it more convenient for clinical teams, the RSU has developed a user-friendly RExcel interface. RExcel [Baier and Neuwirth (2007), Neuwirth et al. (2009)] integrates the powerful statistical and graphical functions in R [R (2009)] into the familiar user interface of Excel [Microsoft (2007)]. 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. By connecting R data frames and Excel data lists, it allows the creation of a stand-alone RExcel workbook which hides R almost completely from the user and uses Excel as the main interface to R.

In this technical report, the focus is on using the software implementing the statistical methodology outlined in [Anisimov and Fedorov (2005)]–[Anisimov (2010)]. Section 2 illustrates the interaction between the user and the individual worksheets in the workbook. We provide concluding remarks in Section 3. In the Appendix, we describe the R package and give detailed instructions on installation.

2. RExcel Interface

This section is an illustration of a modeling session for a clinical trial. We show the complete interaction between the user and the interface program. We specify several Scenarios, defined by values of model parameters such as number of patients and number of centres, to the program. We show the calculation of the anticipated overages for each scenario with the MultiScenario worksheet of the Excel workbook (Figures 1–5). We show the calculation of the sensitivity of the analysis with several additional worksheets in the workbook in Figures 6–16. There are ten scenarios displayed in Figure 1. These have been chosen to reflect the experience of recent GSK trials.

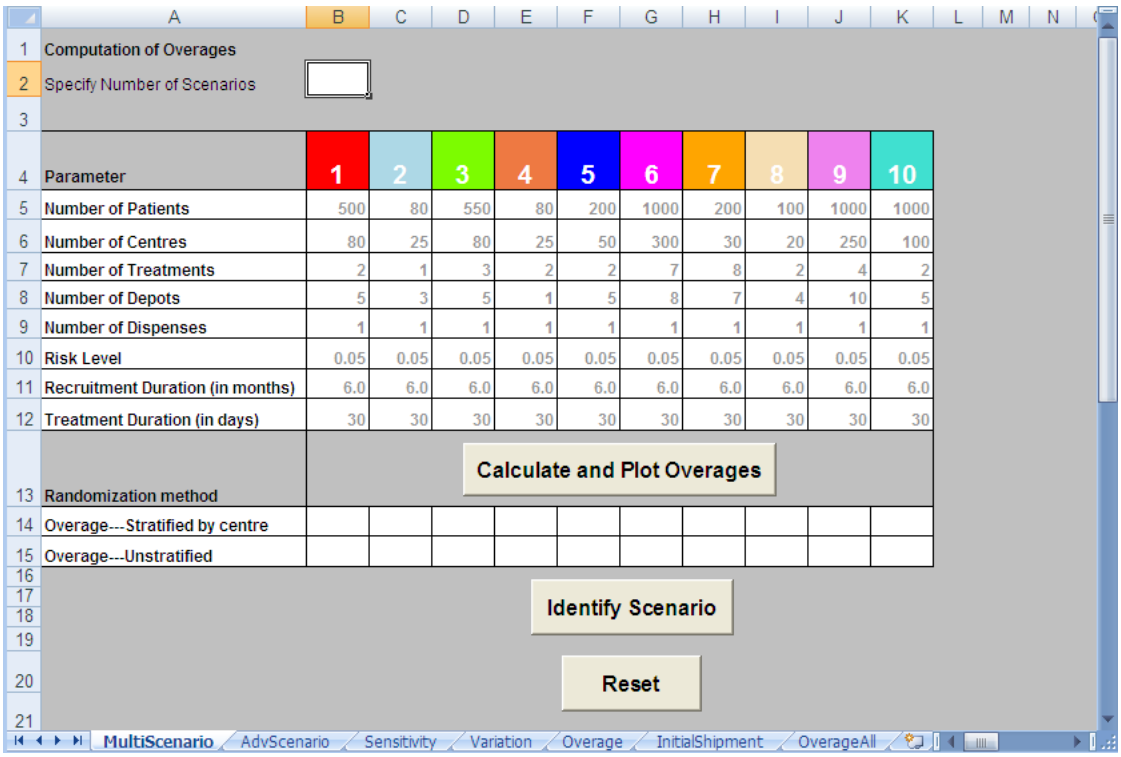
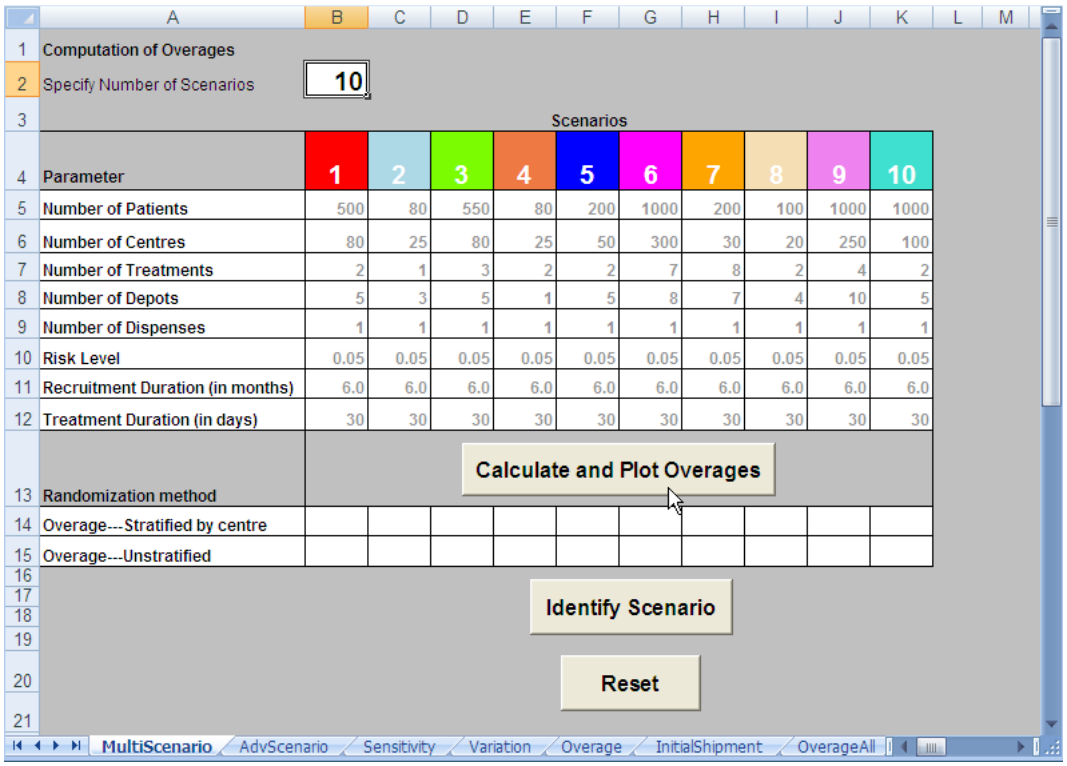


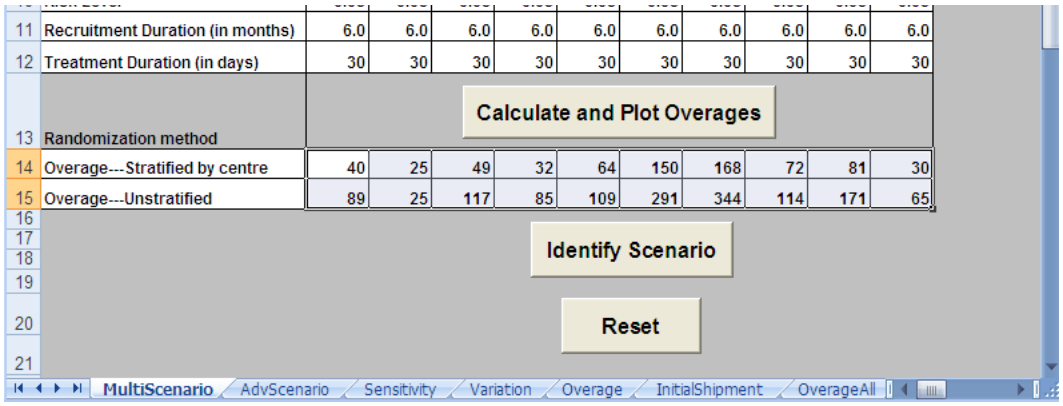
FIGURE 1. The MultiScenario worksheet allows computation of overages for up to ten different scenarios (as specified in cell B2) based on two randomization types, "Stratified by centre" and "Unstratified". The randomization types are described in Section A.3. The Worksheet opens with the primary parameters of the sample scenarios grayed out in Cells B5:K12. These are the cells that will be used to specify the primary parameters for the trial currently under design. When a non-zero value is placed in cell B2, the scenario parameters appear dark (as in Figure 2).



	A	B	C	D	E	F	G	H	I	J	K	L	M
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												
15	Overage---Unstratified												
16													
17													
18		Identify Scenario											
19													
20		Reset											
21													

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

FIGURE 2. We set cell B2 to 10. The button Calculate and Plot Overages in cell D13 is pressed to initiate the overage calculations. The calculated overages for all scenarios are displayed in cells B14:K15 in Figure 3 and plotted in Figure 4.

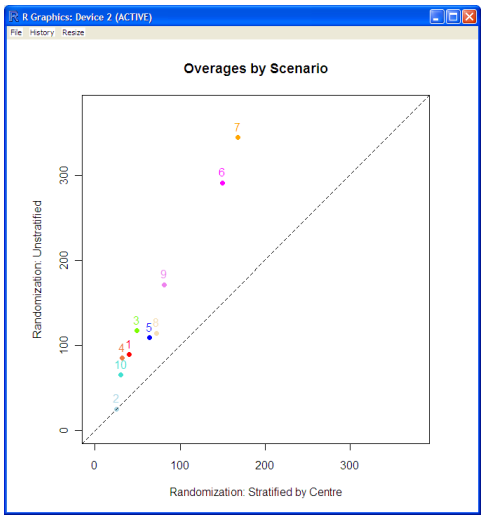


11	Recruitment Duration (in months)	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
12	Treatment Duration (in days)	30	30	30	30	30	30	30	30	30	30
13	Randomization method	Calculate and Plot Overages									
14	Overage---Stratified by centre	40	25	49	32	64	150	168	72	81	30
15	Overage---Unstratified	89	25	117	85	109	291	344	114	171	65
16											
17											
18		Identify Scenario									
19											
20		Reset									
21											

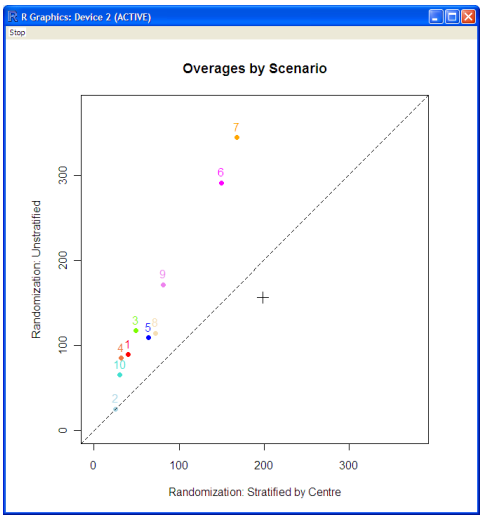
MultiScenario | AdvScenario | Sensitivity | Variation | Overage | InitialShipment | OverageAll

FIGURE 3. The overages calculated in Figure 2 are displayed in cells B14 through K15 and plotted in Figure 4.

a. Initial plot from Figure 2.



b. After clicking the Identify Scenario button.



c. After clicking point 9 in Figure 4b.

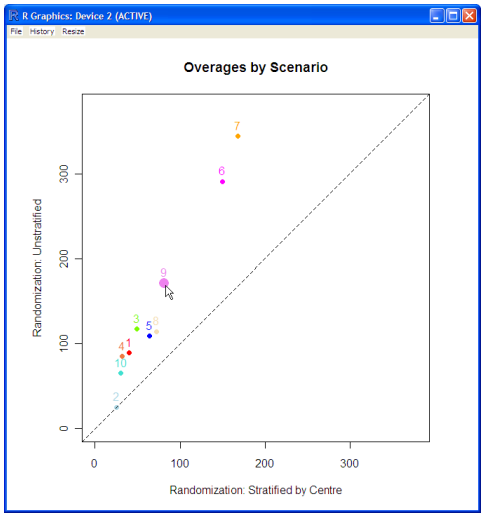
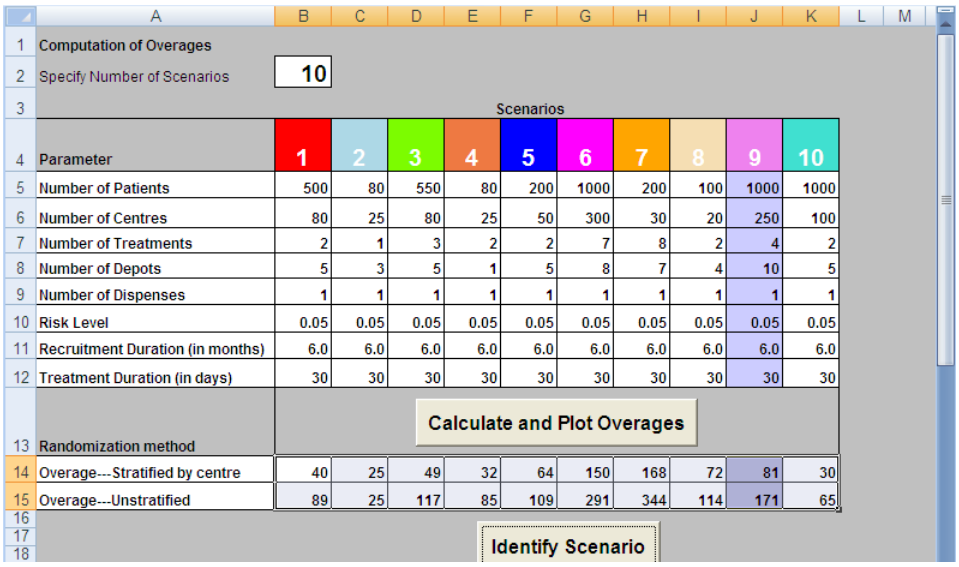


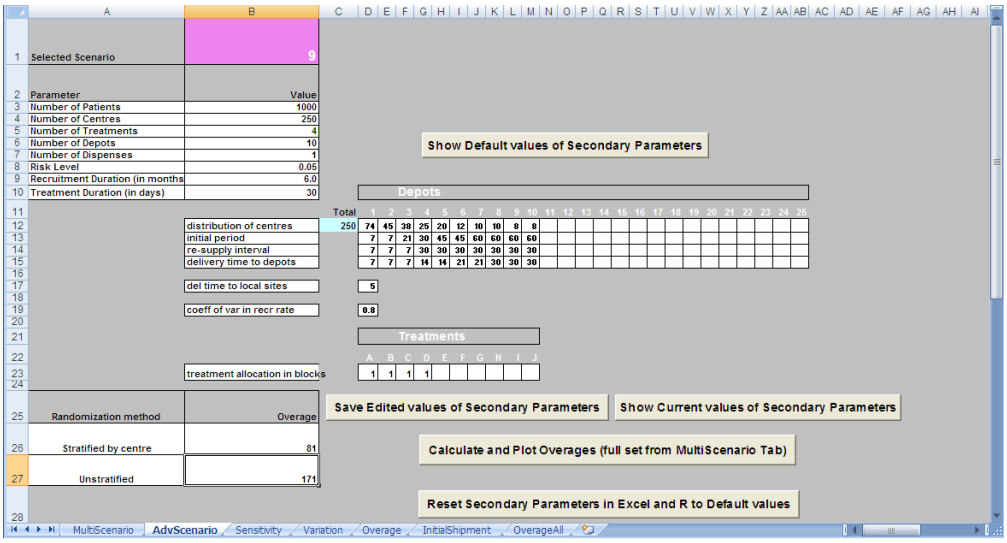
FIGURE 4. Plot of predicted overages calculated in Figure 2 by the "Stratified by centre" and "Unstratified" randomization schemes. As seen in this example, and supported by theoretical results [Anisimov (2009b), Anisimov (2009c)], the overages from the "Stratified by centre" scheme are always smaller than the ones from the "Unstratified" scheme.

Let us investigate Scenario 9 further by looking at, and possibly changing, its secondary parameters. Press the button Identify Scenario in Figure 2 to show the selection cross-hairs in the plot (Figure 4b). Click on a point (in this example, the point associated with Scenario 9) to get Figure 5. After clicking, the dot for Scenario 9 is enlarged in the same color (Figure 4c).



	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		Identify Scenario									
18											

FIGURE 5. After clicking point 9 in Figure 4, the input parameters and the overage values for Scenario 9 are highlighted in a lighter shade of the color displayed in the column header. In addition, the secondary parameters for the highlighted scenario are available for display and/or changing in Figure 6.



	A	B
1	Selected Scenario	9
2	Parameter	Value
3	Number of Patients	1000
4	Number of Centres	250
5	Number of Treatments	4
6	Number of Depots	10
7	Number of Dispenses	1
8	Risk Level	0.05
9	Recruitment Duration (in months	6.0
10	Treatment Duration (in days)	30
11		
12	distribution of centres	
13	initial period	
14	re-supply interval	
15	delivery time to depots	
16		
17	del time to local sites	
18		
19	coeff of var in recr rate	
20		
21		
22		
23	treatment allocation in blocks	
24		
25	Randomization method	Overage
26	Stratified by centre	81
27	Unstratified	171
28		

Show Default values of Secondary Parameters

Depots

Total	1	2	3	4	5	6	7	8	9	10
250	74	45	38	25	20	12	10	10	8	8
	7	7	21	30	45	45	60	60	60	60
	7	7	7	30	30	30	30	30	30	30
	7	7	7	14	14	21	21	30	30	30

5

0.8

Treatments

A	B	C	D	E	F	G	H	I	J
1	1	1	1						

Save Edited values of Secondary Parameters | Show Current values of Secondary Parameters

Calculate and Plot Overages (full set from MultiScenario Tab)

Reset Secondary Parameters in Excel and R to Default values

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

FIGURE 6. The AdvScenario worksheet allows the user to change the values of the secondary parameters for the selected scenario as displayed in cell B1. The Show Default button displays the default parameter values for the selected scenario. We show the changes in Figure 7.

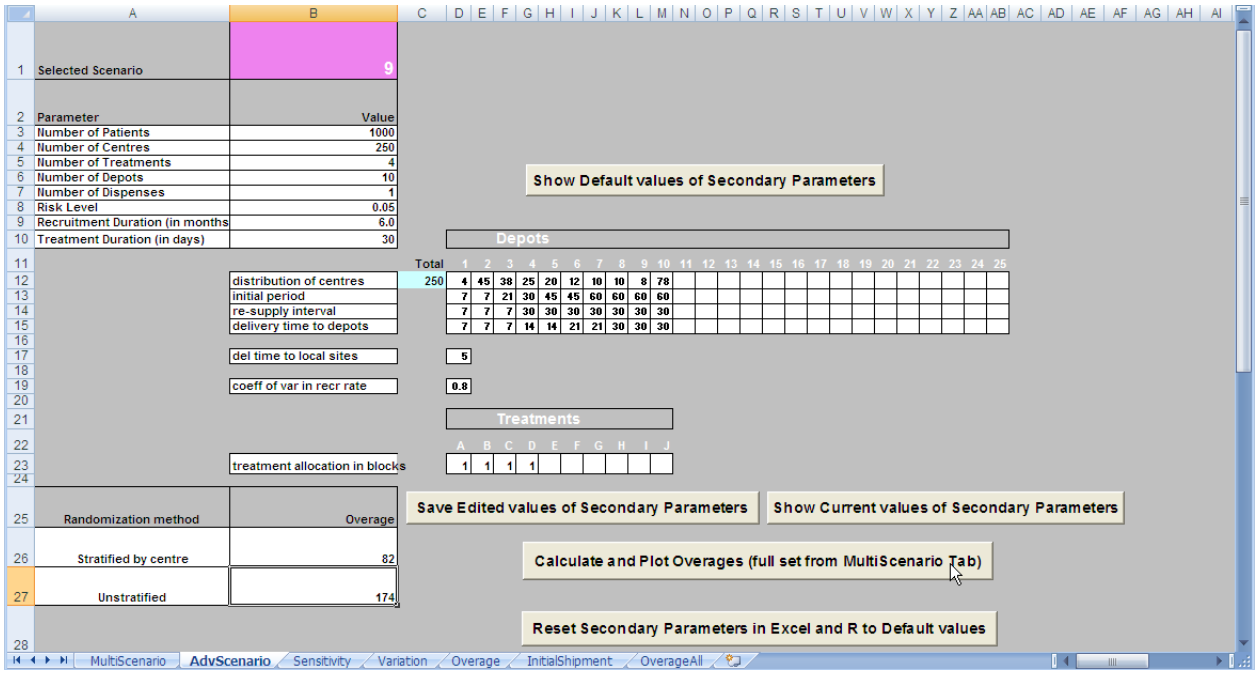
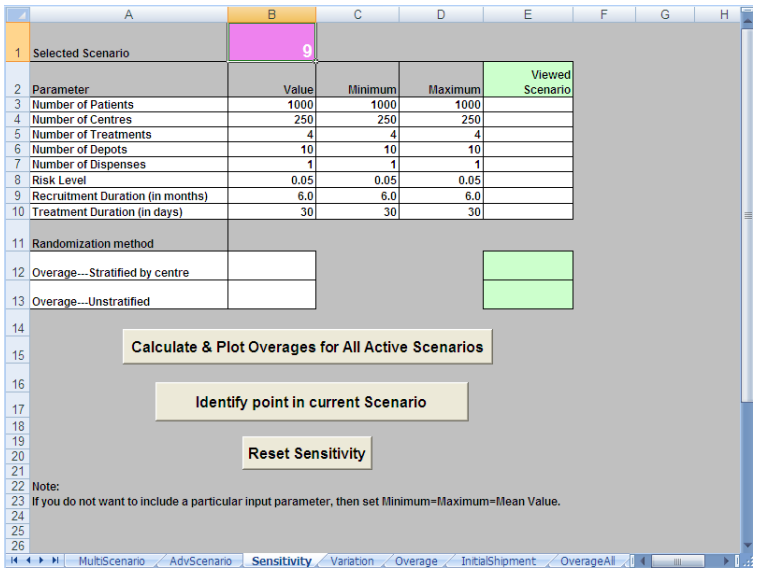


FIGURE 7. The user can change the secondary parameter values displayed in Figure 6 and then click on the button Save Edited values of Secondary Parameters. In this example, we illustrate changing the distribution of centres for Depots 1 and 10. In Figure 6 we had values 74 and 8; in this figure we have values 4 and 78. The changed secondary parameters will be used after the user clicks on button Save Edited values of Secondary Parameters and button Calculate and Plot Overages (full set from MultiScenario Tab)

.

The parameters in rows 12:15 are depot-related. The parameters in rows 17 and 19 are trial-related. The parameter in row 23 is treatment-related. The new overage values calculated using these changed secondary parameters are displayed in cells B26 and B27 of the AdvScenario worksheet. The cells B14:K15 in the Multiscenario worksheet and the graph in Figure 4a are also updated.

The button Show Current values of Secondary Parameters displays the edited values of the secondary parameters while the button Reset Secondary Parameters in Excel and R to Default values sets the secondary parameters back to their default values.



	Selected Scenario	9			
	Parameter	Value	Minimum	Maximum	Viewed Scenario
	Number of Patients	1000	1000	1000	
	Number of Centres	250	250	250	
	Number of Treatments	4	4	4	
	Number of Depots	10	10	10	
	Number of Dispenses	1	1	1	
	Risk Level	0.05	0.05	0.05	
	Recruitment Duration (in months)	6.0	6.0	6.0	
	Treatment Duration (in days)	30	30	30	
	Randomization method				
	Overage---Stratified by centre				
	Overage---Unstratified				

Calculate & Plot Overages for All Active Scenarios

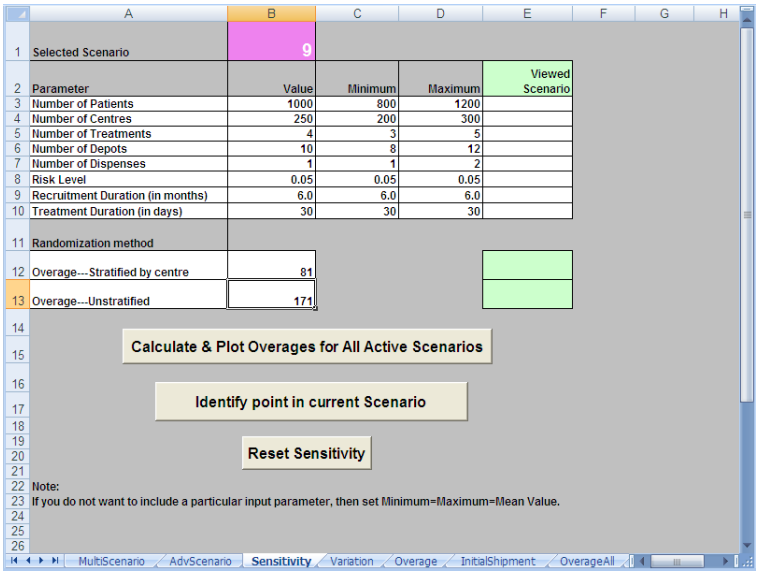
Identify point in current Scenario

Reset Sensitivity

Note:
If you do not want to include a particular input parameter, then set Minimum=Maximum=Mean Value.

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

FIGURE 8. The Sensitivity worksheet is used to perform sensitivity analysis based on the primary parameters for the selected scenario displayed in cell B1. By default the minimum and maximum values for each parameter are set to their input values. In Figure 9 we change some of the minimum and maximum values and run the Sensitivity Analysis.



	Selected Scenario	9			
	Parameter	Value	Minimum	Maximum	Viewed Scenario
	Number of Patients	1000	800	1200	
	Number of Centres	250	200	300	
	Number of Treatments	4	3	5	
	Number of Depots	10	8	12	
	Number of Dispenses	1	1	2	
	Risk Level	0.05	0.05	0.05	
	Recruitment Duration (in months)	6.0	6.0	6.0	
	Treatment Duration (in days)	30	30	30	
	Randomization method				
	Overage---Stratified by centre	81			
	Overage---Unstratified	171			

Calculate & Plot Overages for All Active Scenarios

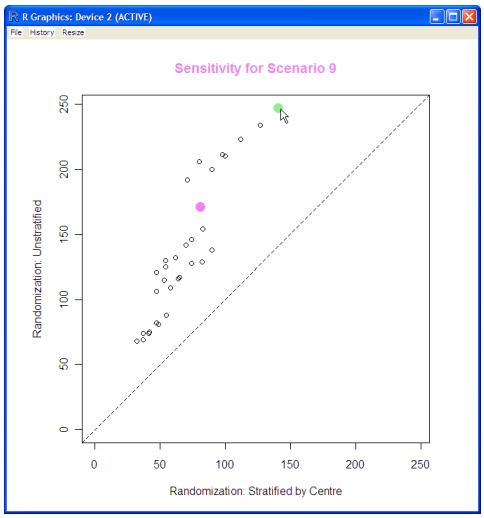
Identify point in current Scenario

Reset Sensitivity

Note:
If you do not want to include a particular input parameter, then set Minimum=Maximum=Mean Value.

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

FIGURE 9. In this figure we change the minimum and maximum values for the number of patients, centres, treatments, depots and dispenses. Then click the Calculate & Plot Overages for All Active Scenarios button followed by Identify point in current Scenario button.



	A	B	C	D	E
1	Selected Scenario	9			
2	Parameter	Value	Minimum	Maximum	Viewed Scenario
3	Number of Patients	1000	800	1200	800
4	Number of Centres	250	200	300	300
5	Number of Treatments	4	3	5	5
6	Number of Depots	10	8	12	12
7	Number of Dispenses	1	1	2	1
8	Risk Level	0.05	0.05	0.05	0.05
9	Recruitment Duration (in months)	6.0	6.0	6.0	6
10	Treatment Duration (in days)	30	30	30	30
11	Randomization method				
12	Overage---Stratified by centre	81			141
13	Overage---Unstratified	171			247

Calculate & Plot Overages for All Active Scenarios

Identify point in current Scenario

Reset Sensitivity

Note:
If you do not want to include a particular input parameter, then set Minimum=Maximum=Mean Value.

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

FIGURE 10. The top panel shows the Sensitivity plot consisting of a colored dot indicating the overages for the initial values in column B of Figure 9, and open circles indicating the overages for the set of scenarios at the 2^k points specified by the minimum and maximum values in columns C and D of Figure 9. The bottom panel shows the Sensitivity worksheet containing the parameter values corresponding to the scenario which the user clicked in the top panel. In this example, we change the minimum and maximum values for the number of patients, centres, treatments, depots and dispenses, hence $k = 5$ and we see 32 open circles. In the top panel we clicked on one point. It turned green and placed the parameter values corresponding to its scenario in column E of the bottom panel.

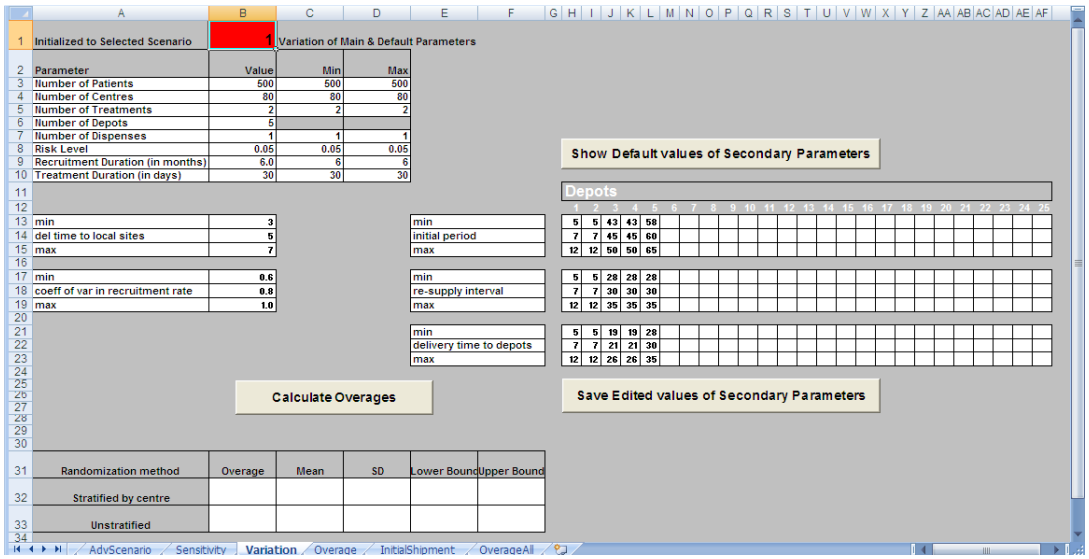


FIGURE 11. The Variation worksheet is used to perform sensitivity analysis based on both primary and secondary parameters. The user can provide minimum and maximum values for the primary and secondary parameters. The button Show Default values of Secondary Parameters displays the current secondary parameter values with their default minimum and maximum values. The user can change these minimum and maximum values of the secondary parameter values and then click on the button Save Edited values of Secondary Parameters.

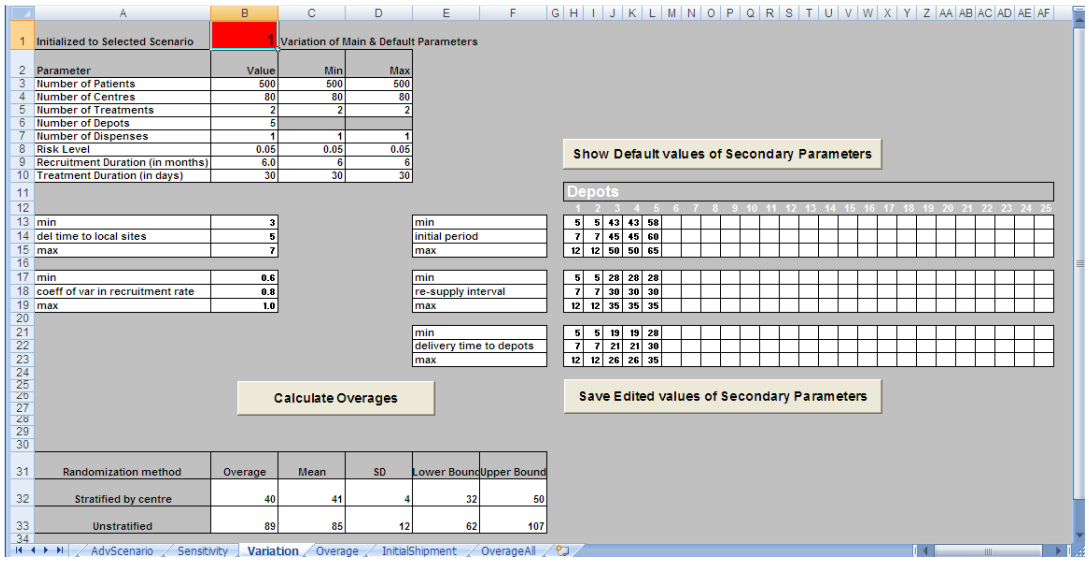
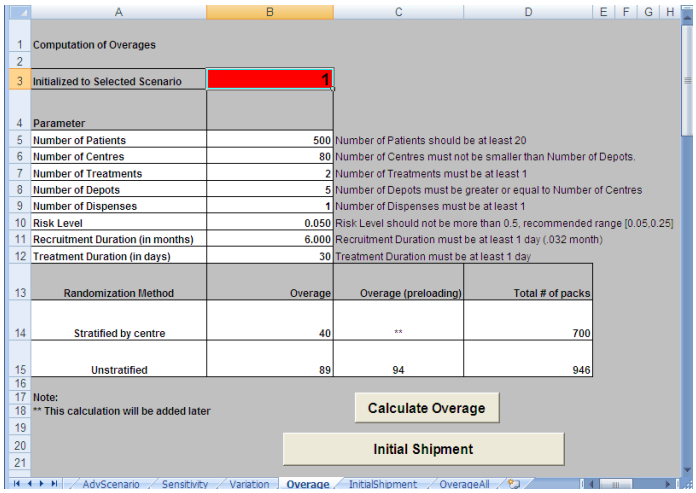


FIGURE 12. Upon clicking the button Calculate Overages, the overages, means, standard deviations, and lower and upper 95% confidence boundaries of the overages are displayed in cells B32:F33.



Computation of Overages			
Initialized to Selected Scenario	1		
Parameter			
Number of Patients	500	Number of Patients should be at least 20	
Number of Centres	80	Number of Centres must not be smaller than Number of Depots.	
Number of Treatments	2	Number of Treatments must be at least 1	
Number of Depots	5	Number of Depots must be greater or equal to Number of Centres	
Number of Dispenses	1	Number of Dispenses must be at least 1	
Risk Level	0.050	Risk Level should not be more than 0.5, recommended range [0.05,0.25]	
Recruitment Duration (in months)	6.000	Recruitment Duration must be at least 1 day (.032 month)	
Treatment Duration (in days)	30	Treatment Duration must be at least 1 day	

Randomization Method	Overage	Overage (preloading)	Total # of packs
Stratified by centre	40	**	700
Unstratified	89	94	946

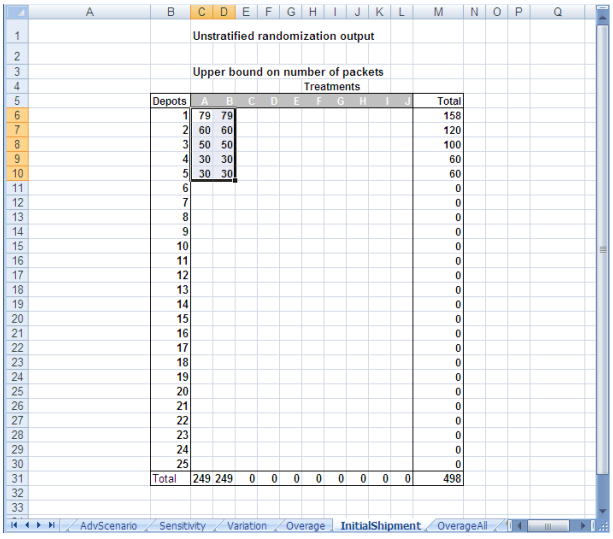
Note:
** This calculation will be added later

Calculate Overage

Initial Shipment

AdvScenario | Sensitivity | Variation | Overage | InitialShipment | OverageAll

FIGURE 13. The Overage worksheet displays information about anticipated overages and total number of packs for each treatment for the single scenario as specified on this worksheet (the Overage worksheet does not inherit parameter values from the Multi-Scenario worksheet). 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. Clicking on the button Initial Shipment takes the user to the InitialShipment worksheet as shown in Figure 14.



Unstratified randomization output

Upper bound on number of packets

Depots	Treatments		Total
	A	B	
1	79	79	158
2	60	60	120
3	50	50	100
4	30	30	60
5	30	30	60
6			0
7			0
8			0
9			0
10			0
11			0
12			0
13			0
14			0
15			0
16			0
17			0
18			0
19			0
20			0
21			0
22			0
23			0
24			0
25			0
Total	249	249	498

AdvScenario | Sensitivity | Variation | Overage | InitialShipment | OverageAll

FIGURE 14. This figure is generated when the user clicks on the button Initial Shipment in Figure 13. In this example, we specified two treatments and five depots in Figure 13. The highlighted cells show the upper bound on the number of packets for each treatment and depot combination for the "Unstratified" randomization scheme.

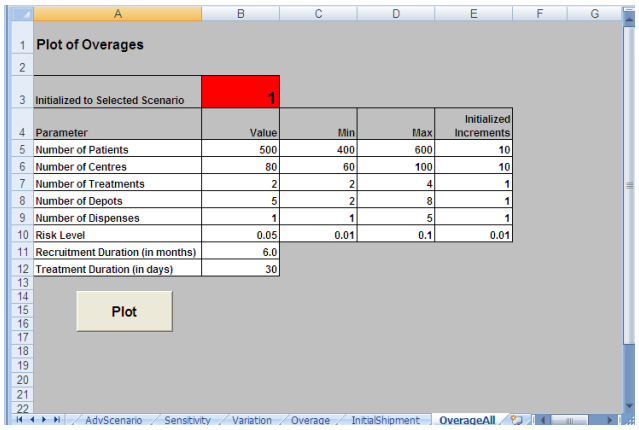


FIGURE 15. The OverageAll worksheet is used to generate six different plots of overages by the following variables: number of patients, number of centres, number of treatments, number of depots, number of dispenses, and risk level. After specifying the minimum, maximum, and increment values for the six variables and clicking the Plot button, the overage values corresponding to "Stratified by centre" and "Unstratified" randomization are plotted in Figure 16. In each plot, the other five variables are held constant at the values shown in column B.

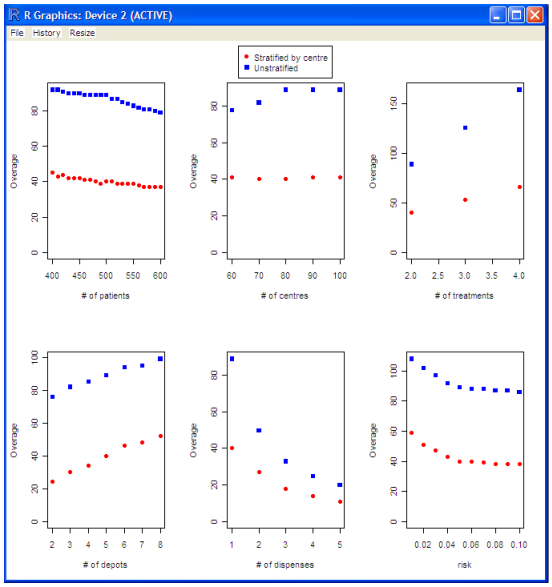


FIGURE 16. Plots of Overage vs number of patients, number of centres, number of treatments, number of depots, number of dispenses, and risk level. As seen from the plots, the overage values are smaller with the "Stratified by centre" randomization.

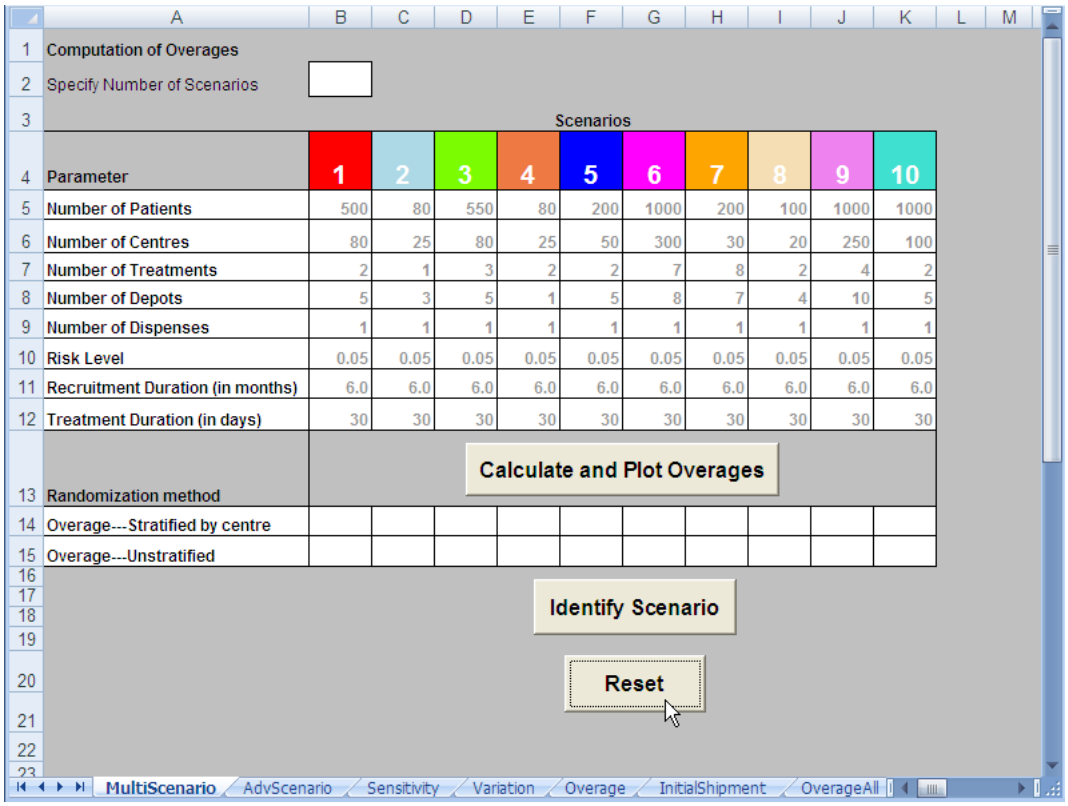


FIGURE 17. When we are ready to examine a different set of scenarios, we click the button Reset to erase the output values in cells B14:K15 and the subsequent worksheets (AdvScenario and Sensitivity).

3. CONCLUSION

The statistical approach to drug supply planning and prediction is based on using the concept of the accepted risk of "running out of stock" for a patient in a single study [Anisimov (2009b)]. Using this approach, as developed in the statistical methodology sections of [Anisimov and Fedorov (2005)]–[Anisimov (2010)], a risk-based supply modeling tool is developed. The tool is programmed in the **R** language and is linked to a user-friendly RExcel interface. The tool provides at the design stage a prediction of the upper bounds for the amount of drug supply required for a single study given the accepted risk of "running out of stock" and, correspondingly, prediction of the upper bounds for supply overages. The tool allows for two types of randomization of patients ("Stratified by centre" and "Unstratified"), equal or different treatment proportions within the randomization block, different shipment intervals in regional depots, single or multiple dispense studies, and some other factors. Future directions for further development of the tool include provisions to account for other supply challenges such as batch shipment, import licenses, shelf-life, and production bottlenecks.

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Appendix A. Documentation of Risk Based Supply Modeling Tool

A.1. **Description.** The RiskBasedSupplyModelingTool toolbox consists of a workbook written in Excel that communicates through the RExcel interface with a package written in R. Download and installation instructions are in Section B. The R functions in the RiskBasedSupplyModelingTool package calculate the overages for central (unstratified) and centre-stratified (stratified by centre) randomization schemes in multicentre clinical studies. The SupplyModelingInterface workbook, written in Excel, is the user interface to the RiskBasedSupplyModelingTool package. The Excel workbook communicates with the R package using the RExcel interface.

A.2. **Usage.** The SupplyModelingInterface workbook is an RExcel interface into the RiskBasedSupply-ModelingTool package written in R. The RiskBasedSupplyModelingTool package calculates anticipated drug supply overage required to satisfy patient demand (given the accepted risk) during the recruitment and follow-up (in case of a multiple dispense) stages of a clinical study.

The calculations of supply overage depend on the arguments

`pts`	the total number of patients to be recruited
`N`	planned total number of centres
`K`	the number of treatments
`S`	number of depots
`ND`	number of dispenses
`risk`	risk level
`TIME`	recruitment duration in months
`durtreat`	treatment duration in days
`Scenario`	number indicating which scenario of the ones on the MultiScenario worksheet
`ParScen`	vector of primary parameters of a scenario

`NumberOfScenarios`	number of scenarios

The workbook has seven user-level worksheets for specification of the arguments. The worksheets, and the situations each is designed for, are described here.

`MultiScenario`	Initial entry into the workbook. Several scenarios (defined by `pts`, `N`, `K`, `S`, `ND`, `risk`, `TIME`, `durtreat`) may be specified. Initially, each scenario is assigned default values of the secondary parameters associated with the individual treatments and depots. The secondary parameters may be changed on the `AdvScenario` worksheet. The worksheet calculates overages under two randomization schemes and prepares arguments for later worksheets in the workbook. The worksheet plots the overages for each scenario and for each randomization scheme.
`AdvScenario`	This worksheet displays, and gives the option to change, the depot and treatment level secondary parameters.
`Sensitivity`	This worksheet calculates sensitivity to the primary parameter settings by estimating the overage over a set of 2^k scenarios centered on one of the scenarios on the MultiScenario worksheet (where k is the number of modified primary parameters).
`Variation`	This worksheet calculates sensitivity to not only the primary parameter settings but also to the default values of the secondary parameters associated with the individual treatments and depots.
`Overage`	This worksheet calculates overage for only one scenario. It is not connected with the other worksheets.
`InitialShipment`	This worksheet displays the output from the Initial Shipment button on the MultiScenario worksheet.
`OverageAll`	This worksheet displays a set of six plots of overages (for the two randomization schemes) vs each of `pts`, `N`, `K`, `S`, `ND`, `risk`.

A.3. **Details.** The underlying R functions estimate the percentage of supply *overage*. For example, an overage value of 46 means: for every 100 units of medication required for patients assigned to treatment A, we will need to prepare in advance and distribute 146 units.

The estimation of the upper prediction bounds for supply overage is based on the technique described in papers [Anisimov and Fedorov (2005), Anisimov (2007), Anisimov and Fedorov (2007), Anisimov (2009b), Anisimov (2009c)] listed in the References. The technique predicts the numbers of patients who will be

recruited and randomized to particular treatments in different centres and regional depots during specified time intervals and subject to other specified input parameter values. It incorporates evaluation of the additional uncertainties generated by critical events (situations when several patients are registered in one centre within a period of time less than the delivery time from the depot to the local centre). By using these predictions at two different stages (initial shipment and the remaining period) the upper bounds of the total supply needed to cover patient's demand are evaluated for any given risk of a patient stock-out.

The results allow comparison at the design stage of two recruitment randomization schemes (*unstratified* and *stratified by centre*). Unstratified (or central) randomization means that the patients entered into the study are randomized to treatment arms according to independent randomly permuted blocks of a fixed size without regard to clinical centre. Centre-stratified (or stratified by centre) randomization means that the patients are randomized according to independent randomly permuted blocks of a fixed size separately in each clinical centre.

The theoretical results [Anisimov (2009b), Anisimov (2009c)] and the results of calculation show that stratified by centre randomization is much more cost-efficient than unstratified randomization and normally generates much smaller overages. Thus, we recommend using stratified by centre randomization in clinical trials.

Appendix B. Installation of Software

The RiskBasedSupplyModelingTool toolbox consists of a workbook written for Microsoft Excel on Windows that communicates through the RExcel interface with a package written in R. The *Download and Installation* section gives detailed instructions on

(1) downloading R with RExcel and related packages included. The instructions assume that you have Excel on your Windows computer, but do not yet have R on your computer.
(2) downloading and installing the RiskBasedSupplyModelingTool toolbox.

B.1. **Download and Installation.**

R and RExcel. Although R by itself can be installed on any computer, RExcel requires administrator privileges for installation. Go to the RExcel website `http://rcom.univie.ac.at`, click the Download tab, and download the RAndFriendsSetup* installer file. This is a Windows executable .exe file that installs R and several related packages. Run the installer from an account with administrator privileges. Accept almost all defaults. The exception is that you *must* check the checkbox

Use Internet Explorer http proxy

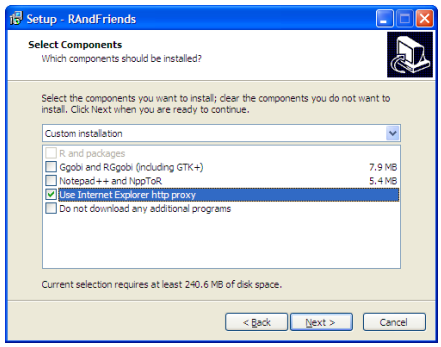

FIGURE 18. You *must* check the "Use Internet Explorer http proxy" checkbox when installing RAndFriends.

on the installation dialog box as in Figure 18. If you forget, then you will not be able to get through the GSK firewall, you will get messages like `"Unable to execute file c:\...\RExcelInst.latest.exe"`, and you will need to cancel the installation and start over.

RiskBasedSupplyModelingTool Package and Workbook. The RiskBasedSupplyModelingTool Package and Workbook are provided as a single ZIP file containing three files. Download the ZIP file to a directory on your computer. Unzip it and it will create an RiskBasedSupplyModelingTool subdirectory with three files.

`RiskBasedSupplyModelingTool_version.zip`

`SupplyModelingInterface-version.xlsm`

`RiskBasedSupplyModelingTool_version.tar.gz`

Install the RiskBasedSupplyModelingTool by starting R from the R icon. In the R Console window, click

Packages > Install package(s) from local Zip files...

Navigate the Select Files window to the RiskBasedSupplyModelingTool directory and double-click on

`RiskBasedSupplyModelingTool_version.zip`

Close R with the File > Exit > No menu item.

The software is now installed and ready to use.

B.2. **Using the RiskBasedSupplyModelingTool Toolbox.**

Open Windows Explorer to the RiskBasedSupplyModelingTool directory and double-click

SupplyModelingInterface-version.xlsm for Excel 2007

The file will open in Excel and start R.

Questions. If you need additional help, please contact Sourish Saha sourish.c.saha@gsk.com and include two necessary pieces of information.

(1) The information that you get from clicking About RExcel.
In Excel 2007, click on the main Excel menu
Add-Ins > RExcel > About RExcel > Copy to Clipboard
Paste that information into the email.

(2) When RExcel is running, the R Console is visible on the Windows Taskbar.
Click the R Console icon and enter the line
`packageDescription("RiskBasedSupplyModelingTool")`
into the R Console. Copy and paste the lines it displays into the email.

R. R is a freely available language and environment for statistical computing and graphics which provides a wide variety of statistical and graphical techniques: linear and nonlinear modelling, statistical tests, time series analysis, classification, clustering, etc. Please consult the R project homepage: http://www.r-project.org for further information.

The current version of R (R-2.11.0) was released April 22, 2010. The RiskBasedSupplyModelingTool software will not work with earlier releases of R. It will work with future releases of R. As we write, GSK's AIT is still distributing a very old version of R (R-2.8.1 from December 2008).

RExcel. RExcel is an Excel add-in using statconn (D)COM or rcom to allow Excel to call R from within Excel. The RExcel website is http://rcom.univie.ac.at. Much detail is available at the Wiki there.

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