Drug Supply Modelling in Clinical Trials (Statistical Methodology)

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Abstract

Drug supply chain is very costly and is a well-recognized bottleneck at the design and managing of clinical trials. The innovative risk-based statistical approach to modelling drug supply demand for a single study is proposed. The approach uses the developed technique for predicting the number of patients randomized to different treatments in different regions, the notion of the accepted risk of stock-out of a required treatment for a patient and accounts for various uncertainties caused by randomness in patient recruitment, by randomization scheme and drug supply logistics. The advanced risk-based supply modelling tool based on this approach has been developed. The tool evaluates the upper prediction bounds for the amount of supply required to cover patient demand with a given risk of stock-out. Currently, the tool is undergoing implementation within GlaxoSmithKline.

Introduction

The design of multicenter clinical studies consists of several interconnected stages including the patient recruitment planning, choosing randomization scheme and statistical model for analyzing treatment responses, and drug supply planning. The drug supply stage is very costly and substantially affected by the patient recruitment/randomization process and supply logistics. Currently, to the best of our knowledge, other pharmaceutical companies do not use analytic/modelling tools for supply planning. The techniques used are mainly deterministic and do not account for various uncertainties. Some companies use direct Monte Carlo simulation to predict patient recruitment and drug supply. However, simulation for multicenter studies may require a substantial computational time, especially for estimating critical amounts of supply for high confidence levels, or while trying to solve multidimensional optimization problems and compare different scenarios. Therefore, it is imperative to develop analytic statistical tools for planning drug supply demand and minimizing costs.

Modeling patient recruitment and randomization process are the key points when developing tools for drug supply planning, as the uncertainties in recruitment and randomization substantially affect the drug supply stage. Using a proper recruitment model helps to account for various uncertainties and in creating the appropriate technique/tools for predicting supply demand.

Drug Supply Logistics

Scenarios of Supply

Consider a typical scenario for drug supply planning for a single study: there are one or two central depots and several regional depots. Delivery time from a central depot to a regional one can vary from a couple of weeks to 2-3 months. Each depot is associated with several local centers/sites. Delivery time from the depot to a local center can be a few days. The incoming new patients after a screening/testing period (may take up to a few weeks) are randomized to a particular treatment according to a specified randomization scheme and then are included/registered into the study.

Randomization Scheme

Randomization is an essential part of clinical trials design. It is carried out with the purpose of allocating patients to treatments randomly, preserving the blind and achieving balance in the number of patients on treatment arms. The choice of randomization may affect the power of statistical tests and the amount of drug supply required to satisfy patient demand. The description and properties of various randomization schemes are studied by many authors, see, for example, books by Pocock [5], Rosenberger and Lachin [6], and Senn [7].

There are two randomization schemes most often used by pharmaceutical companies: unstratified (central) randomization and center-stratified (site-based) block permuted randomization. Unstratified randomization means that the patients registered into the study are

randomized to treatment arms according to independent, randomly permuted blocks of a fixed size without regard to clinical center (or some another stratum). Center-stratified randomization means that the patients are randomized according to independent, randomly permuted blocks of a fixed size separately in each clinical center.

For example, if there are two treatments, A and B, the size of block is 4, and the proportion of treatments within block is 2:2, then 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)

A randomly chosen sequence of blocks forms a sequence of treatments and the patients are assigned to treatments according to this sequence in the order of registration. It is also possible to consider a combined region-based randomization, where the randomization is carried out by randomly permuted blocks separately in each regional depot (or some group of depots).

Clearly, unstratified randomization minimizes the imbalance in the number of patients on treatment arms for the whole study, but increases the imbalance in regions and individual centers compared to center-stratified randomization. The randomization scheme affects the study design and also impacts the strategy of supply and supply overages. In particular, unstratified randomization adds additional uncertainties in individual centers and may substantially increase the predicted supply overage.

Strategy of Supply

Before the study starts, the initial amounts of supply (initial shipment) are sent to each regional depot to cover the expected patient demand for some initial period until the next shipment will arrive. The amount of the initial shipment should account for the predicted variation in recruitment and randomized patients, time for delivery to the different regions, as well as the frequency of re-supply. Afterwards, on a regular basis (say, monthly) additional supply is sent from the central depot to the regional depots to cover the amount of supply used in the depots during the previous period.

Levels of Uncertainty

There are two basic levels of uncertainty in supply prediction caused by patient recruitment, randomization scheme and special logistics of supply. The first level of uncertainty is caused by two main factors and has to be accounted for both randomization schemes:

a) Variation of the patients over time and between different regions due to stochastic recruitment process

b) Variation of patients between different treatment groups (in centers/depots) due to randomization scheme.

The unstratified randomization may cause an additional level of uncertainty due to the following factors. Note that in the case of center-stratified randomization, the randomization lists are generated in advance for each center. Therefore, the clinical trial supply team knows which treatment will be randomized to each incoming patient and therefore can send the required treatment from depot to local center on request upon the arrival of the new patient at the center. If the screening period is greater than the delivery time from depot to the local center, then using the strategy "sending on request" the supply team can cover patient demand in a center given that there is enough supply in the regional depot. The same strategy can be applied in the case of a region-based randomization.

However, in the case of unstratified randomization, there are some additional uncertainties. If the patient should get drug immediately at time of randomization and delivery time from regional depot may take a few days, then at time of arrival of the first patient in some center, it is required to send to this center the whole set of treatments to avoid running out of stock evenn at time of randomization, as it is not known in advance which treatment this patient can be randomized to. Correspondingly, let us call a "critical event" the event when several consecutive patients arrive at one center within a time slot less than the delivery time from the depot to the local centre. Then, as all these patients with some probability can be randomized to the same treatment, to avoid the possibility of running out of stock, it is recommended to send in this center the whole set of treatments for each of these patients. Thus, unstratified randomization produces the additional uncertainties, related to the events "first arrival in a center" and "critical events," which leads to the extra drug overages.

Statistical Risk-based Approach

From the considerations above, one can see that the drug-supply chain process is affected by several stochastic factors such as patient recruitment, randomization and also by supply logistics. Thus, in order to use scientific approaches for planning/predicting the drug supply for a particular study, it is necessary to introduce some statistical criteria. The most crucial situation is that some patient may be lost because of running out of stock of a particular treatment assigned to this patient in a clinical center. Thus, the natural approach is to predict supply required to satisfy patient demand in a single study with a given risk of stock-out for a patient. Note that because of stochastic fluctuations it is not possible to avoid completely the possibility of stock-out (to make the risk equal to zero). However, at small values of risk these events may happen very rarely, and thus, the accepted value of risk can serve as some measure of the reliability and quality of drug supply prediction. If it is allowed to lose a few patients in a study, then a similar criterion can be to predict supply for a study given that the number of lost patients on average is not more than some fixed value (say, 2,3 patients).

Risk Concept in Drug Supply Planning

An acceptable risk δ means that in a particular study, with probability $1 - \delta$ all patients will receive the correct treatment assignments. Correspondingly, with probability δ for one of the patients at the time of randomization the treatment assignment may not be available. Note that the probability to get shortage of supply for more than one patient for typical scenarios has the magnitude 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 patients may be "out of stock." Another way of looking at risk 5% is: for 100 similar studies we may lose on average one patient in each of 5 studies, but in the other 95 studies all patients will receive the correct treatment assignments. This approach is similar to what is used at statistical analysis stage: take a decision on the quality of tested drug with a given probability of error, usually 5%. Therefore, in general, it is not reasonable to use risk less than 5%.

Now, as we introduce the criterion, the problem is to predict the amount of supply required to satisfy this criterion using the statistical technique.

Statistical Technique

The considerations above show, that, for predicting the amount of supply required to satisfy patient's demand given the accepted risk of stock-out, it is necessary to evaluate the number of patients randomized to different treatments in different regional depots/centers during different time intervals and also account for the additional uncertainties caused by critical events.

The technique for modeling patient recruitment is developed in the papers by Anisimov and Fedorov [1,2] (see also [3]). However, as one can see, for predicting drug supply demand in centres/depots in the case of more than one treatment, it is necessary to develop a technique for predicting the number of patients (with upper bounds) randomized to different treatments. Therefore, the theoretical results on the analysis of randomization schemes and predicting the number of patients randomized to particular treatments in particular centers/depots during specified time intervals are developed for both randomization schemes in the author's papers [4,5]. In addition, the technique for evaluating the impact of the additional uncertainties generated by critical events is also developed.

Each level of uncertainty produces different overages at different stages of drug supply planning. The upper prediction bounds for these overages can be evaluated separately to ensure a given risk at each stage. The sum of upper bounds for treatment packs at different stages provides us with the total predicted amount of supply required for this study.

There are two basic stages in evaluating drug supply overage with different risk levels at each stage: predicting the initial shipment and evaluating the supply during the remaining period. At the stage of the initial shipment, there is no data about patient recruitment. Thus, the predictive bounds for supply demand are evaluated with very small risk accounting for the variation of patients between different depots and all treatments. After the initial shipment, the team can observe the actual recruitment profile, and therefore, at each time of re-supply there is enough in each depot to evaluate the amount of supply needed to compensate only for the supply taken during the previous period. Finally, the sum of predictive bounds at each stage provides us with the predicted amount of supply needed to cover patient demand given total risk.

In cases where the screening period is longer than the delivery time from a regional depot to local centers, the initial preloading is not required. However, in this case, when the screening period is very short, and the patient has been randomized and immediately administered a required treatment, the initial preloading of each center by a few packs of treatments is required, and this also can be accounted for.

Risk-based Supply Modelling Tool

Using the statistical technique described above, the advanced risk-based supply modelling tool for drug supply planning/predicting has been developed in the Research Statistics Unit, GlaxoSmithKline and in collaboration with R&D Clinical Trials Supply Team the tool has been tuned to cover the vast majority of typical supply scenarios. The tool accounts for the variation in patient recruitment and for additional uncertainties caused by the randomization scheme. The basic version of the tool evaluates the upper predictive bounds for the amount of supply required to cover patient demand for a single study with a given risk of stock-out for a patient. The tool also allows the prediction of the upper bounds for the number of randomized patients and supply demand in different regions for different time periods, the evaluation of the probabilities and the number of various critical events in the regions, the critical probabilities of randomizing the patients within some time slot on the same treatment, the amount of the initial shipment in different regional depots, etc.

The tool covers the following range of conditions: unstratified and center-stratified randomization; equal and different treatment proportions within randomization block; single and multiple dispense study; different delivery times to regional depots; preloading (if needed) of local sites.

There are a few input parameters considered as 'basic' and several others are hidden parameters which in the current version are set by default, but can be changed for any specific scenario.

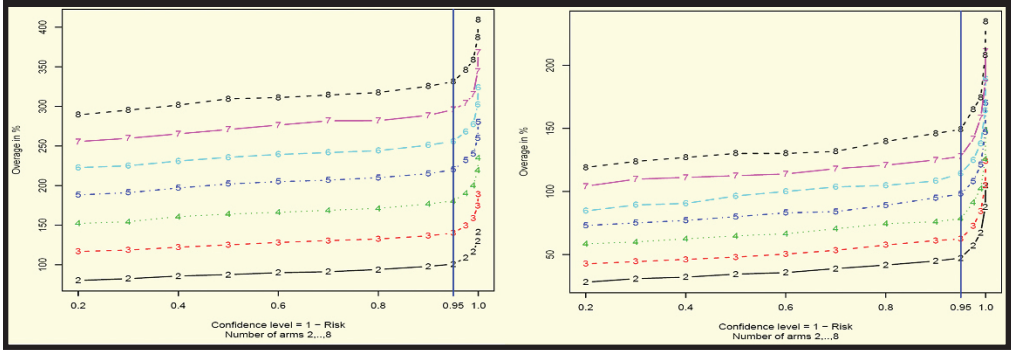
Basic input parameters: the total number of patients 'n' to be recruited; the number of treatments 'K'; randomization type (unstratified or center-stratified); expected duration of recruitment 'T'; expected total number of centers 'N'; number of depots 'S'; number of dispenses; risk level.

The main output: estimated supply overages (in %); total number of treatment packs required at different stages.

The tool is quite flexible and can be adjusted to calculate supply levels in different depots, for different time periods, etc. The software for the tool is written in programming language R and all calculations use the derived closed-form expressions, no Monte Carlo simulation is involved. Thus, the evaluation of particular scenarios takes less than a second. The developed tool provides a variety of opportunities for project teams for comparison at the design stage the different recruitment scenarios using multiple criteria including supply overage and various costs. Currently, the RSU is working on enhancing the tool by a user-friendly RExcel interface with extended features and graphical tools.

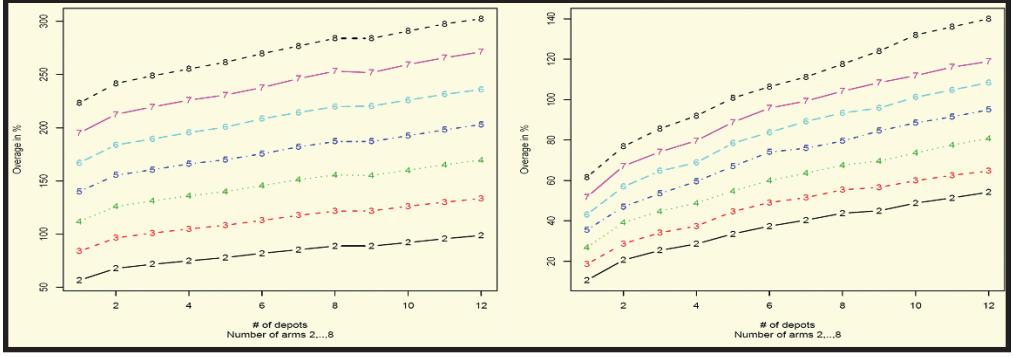
The following figures illustrate the wide possibilities of the developed technique and provide some conclusions on the dependence of supply overages on the main input parameters of the study.

Figure 1. Dependence of supply overage on the confidence level = 1-Risk for different treatment arms.



Scenario: pts=500; N=80, depots=5; time=6 months. Left plot – unstratified randomization, right plot - center-stratified randomization.

Figure 2. Dependence of supply overage on the number of depots for different treatment arms.



Scenario: pts=1000; centers=120; time=6 months, risk= 5%. Left plot – unstratified randomization, right plot - center-stratified randomization.

Here the line with number –k– corresponds to the case of k treatment arms. Figure 1 shows that overages are rising steeply when the risk is less than 5%. The number of treatment arms substantially increases supply overages. Figure 2 shows that the number of depots also increases supply overages. For any particular scenario the overages can be precisely evaluated.

Theoretical results [4,5] and the results of calculation (see Fig. 1 and 2) show that center-stratified randomization in general requires much less drug supply compared to unstratified randomization and therefore is cost efficient. Thus, in the cases when choice of randomization is not dictated by the type of data, it is beneficial to use center-stratified randomization more often in clinical trials.

The proposed analytic technique opens a wide range of possibilities for project teams to play with and compare many multiple scenarios in a real-time environment. The developed tool allows at study design stage to use cost-benefit analysis and various criteria accounting for type of randomization, sample size and supply costs.

Implementation

Currently the pilot versions of the advanced risk-based modelling tool are used in GSK for evaluation of supply overages for a wide range of clinical studies. This innovative risk-based statistical approach has been recognized within the supply standards industry. In November 2009, the members of GSK's R&D Supply Chain team have won the "European Supply Chain Excellence Award for Innovation" for developing a highly innovative approach and creating a predictive tool to managing the demand and supply process in the clinical trials without increasing supply chain risk. This work already has reduced costs by many tens of millions £ and released a significant amount of capacity.

Conclusions

The advanced analytic modeling tool for predicting drug supply demand in clinical trials is developed. The tool uses a risk-based statistical criterion and the developed technique for predicting the number of patients randomized to different treatment arms in different centers/regions. The tool opens wide possibilities for projects teams and allows comparison of multiple scenarios in real time and use of various criteria accounting for type of randomization, sample size and supply costs. The implementation of pilot versions already has shown great advantages, substantial benefits and costs savings.

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