Predictive Modelling of Recruitment and Drug Supply in Multicenter Clinical Trials

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Abstract

Patient recruitment and drug supply planning are the biggest challenges for clinical study design. The innovative statistical technique for modeling patient recruitment in multicentre clinical trials is proposed. It allows predicting recruitment with confidence boundaries at initial and ongoing stage of the study, evaluating study/centre performance and the minimal number of centres needed to complete recruitment in time with a given confidence, providing adaptive adjustment. Predicting in time the recruitment profile provides the opportunity to evaluate drug supply needed to cover patient demand for a given risk of patient stock out and establishes the basis for a novel approach in optimizing drug supply planning. The developed in R software tools use derived closed-form expressions, no Monte Carlo simulation involved. Technique is validated on real data, case studies are considered. The results are illustrated for several case studies.

Key Words: Patient recruitment, multicentre trial, drug supply, statistical prediction, adaptive adjustment, mixed Poisson process

1. Introduction

The design of multicentre clinical studies consists of several interconnected stages including patient recruitment planning, choosing randomization scheme and statistical model for analyzing patient responses, and predicting drug supply required to satisfy patient demand during recruitment stage. Some controversies in the analysis of multicentre clinical trials are considered by Senn (1997,1998).

Patient recruitment is an essential stage of the drug development process and a well recognized bottleneck for new drug development as randomness in recruitment process together with randomization substantially affect all stages of study design. The drug supply chain process is very costly, depends on recruitment and randomization processes and has many uncertainties. Currently, to the best of our knowledge, the known techniques for recruitment and supply modeling used by other pharmaceutical companies are mainly deterministic, use averages and different ad hoc techniques and do not account for various uncertainties such as (a) the uncertainties in input information (b) stochastic fluctuations of recruitment over time (c) variation in recruitment across centres. Clinical trial phase takes nearly one half of costs for a new drug. However, a large proportion of trials ($\geq 50\%$) fail to recruit in time. Some companies (Cytel, Tessella) use direct Monte Carlo simulation for predicting patient recruitment and drug supply. Nevertheless, simulation may require a substantial computational time especially while estimating bounds for high confidence levels, trying to solve multidimensional optimization problems, etc.

Developing the appropriate technique for patient recruitment modelling will help to analyze various uncertainties and to develop the technique for predicting drug supply.

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An advance methodology for patient recruitment modelling based on stochastic approach is developed in several papers (Anisimov, Fedorov, 2005, 2007; Anisimov et al., 2007; Anisimov, 2009). It allows predicting the number of recruited patients (the mean and confidence bounds) at the initial (design) stage using the planned data provided by study managers and also at any interim time using real recruitment data. It allows also to evaluate the number of clinical centres needed to complete recruitment up to a particular deadline with a given confidence and provide recommendations on adding new centres if required (adaptive adjustment).

In the paper, this technique is used for the evaluation of study performance and site productivity, and it is also extended to predicting the number of patients randomized to different treatment arms in different regions. The latter provides an essential step forward for predicting drug supply needed to cover patient demand at the recruitment stage.

The second part of the paper is devoted to drug supply predictive modelling. Using patient recruitment modelling technique and its extensions to predicting the number of randomized patients, a statistical approach for drug supply modeling/predicting has been proposed and the technique for predicting the amount of supply needed to cover patient demand given an accepted risk of supply shortage has been developed.

2. Patient Recruitment Modelling

Consider a multicentre clinical study where n patients have to be recruited by N clinical centres. Upon registration, the patients are randomized to different treatment arms according to some randomization scheme. At study design stage it is crucial to predict the number of patients to be recruited in different regions and how many of them will be randomized on a particular arm as this may substantially affect the predicted amount of drug supply required to satisfy patient demand in regions. First, let us consider stochastic models for patient recruitment developed in (Anisimov, Fedorov, 2005-2007).

2.1 Poisson and Poisson-gamma Models

Consider a trial where the recruitment starts in a clinical centre when this centre is initiated and there are no patients in databases before study starts waiting for this trial. Then the patient recruitment process in a particular center i can be described by a Poisson process with some in general unknown rate λ_i. This is an accepted in the literature approach (e.g. Senn, 1997,1998; Anisimov et al. 2003).

A large clinical trial usually involves many clinical centres. These centres may have different recruitment rates reflecting the size of centre, population of patients in the region, etc. To mimic the variation in rates it is proposed to use a gamma distribution which is a natural way to describe the variation of positive variables. Therefore, we assume that the rates $\{\lambda_i\}$ in different centers are viewed as a sample from a gamma distributed population with some parameters (α, β) (shape and rate parameters). That means, in each centre the recruitment is described by a mixed Poisson process with random rate (Cox process). This model is called a Poisson-gamma recruitment model (Anisimov, Fedorov, 2005-2007), see also Anisimov et al., 2007; Anisimov, 2009. The model accounts for the natural variation in recruitment over the time and variation in recruitment rates between different centres and has been validated for many real trials with large enough number of centres (≥ 10).

2.2 Verification of Recruitment Model

Consider as an example a case study A. This is a real study with $n = 629$ patients recruited by $N = 91$ centres. The recruitment data can be re-arranged in a special form as follows. Denote by $\nu(j)$ the number of centres recruited exactly j patients. Then the data for study A is a vector $\bar{\nu} = (\nu(1), \nu(2), ...)$, where $\bar{\nu} = (7, 11, 8, 8, 9, 8, 9, 7, 2, 4, 1, 3, 3, 4, 0, 0, 2, 1, 1, 2, 1, 0, 0, ..)$. That means, 7 centres recruited only 1 patient, 11 centres – 2 patients,.., 2 centres – 20 patients, and finally 1 centre recruited 21 patients. Assume that the recruitment follows a Poisson-gamma model. Then, using an approach proposed in (Anisimov, Fedorov, 2005, 2007), one can calculate that the maximum likelihood estimator of a parameter α is $\widehat{\alpha} = 2.84$.

Consider now a hypothetical study with n patients recruited by N centres and denote $m(n, N, \alpha, j) = \mathbf{E}[\nu(j)]$, where α is a shape parameter of a gamma distribution modelling the rates. It is proved in (Anisimov, Fedorov, 2005, 2007) that

$$m(n, N, \alpha, j) = N \binom{n}{j} \frac{\mathcal{B}\Big(\alpha + j, \alpha(N-1) + n - j\Big)}{\mathcal{B}\Big(\alpha, \alpha(N-1)\Big)}, j = 0, 1, .., n, \qquad (1)$$

where $\mathcal{B}(a, b) = \int_0^1 x^{a-1}(1-x)^{b-1}\mathrm{d}x$ is a beta function.

Figure 1 shows that for study A the theoretical curve $m(n, N, \widehat{\alpha}, \cdot)$ fits well real data $\bar{\nu}$. This is a typical behaviour and the results for many other studies are similar. Therefore, this model can be accepted as a working model when the number of centres $N \geq 10$. For trials with a few centres the rates should be estimated separately in each centre.

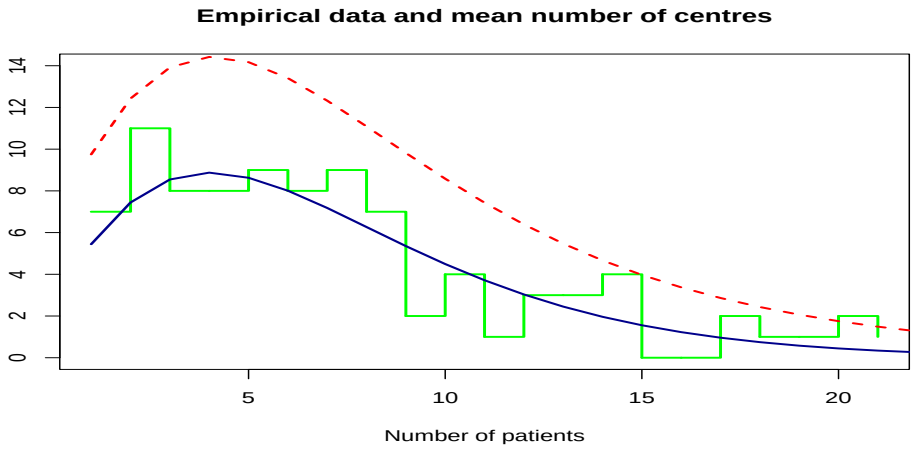

Figure 1: Study A. Graph of empirical data (vector $\bar{\nu}$) – step-wise line, mean number of centres with j patients (theoretical function $m(n, N, \widehat{\alpha}, j)$) – solid line, the mean + 2sd – dashed line.

3. Recruitment Prediction

There are two basic stages of recruitment prediction: the initial (design) stage before study start and the ongoing stage (interim look).

3.1 Prediction at the Initial Stage

At this stage there is no data about the recruited number of patients and therefore a standard practice is to use the planned data provided by study managers based on their experience and possibly comparing with historical data. The planned data as usual has the form: for each country – the number of centres to be initiated in particular time intervals and the number of patients to be recruited by these centres.

Using this data, the empirical mean m and sd σ of the planned rates can be calculated. Parameters (α, β) of a Poisson-gamma model are calculated using simple relations: $\alpha = 1/C_v^2$, $\beta = \alpha/m$, where $C_v = \sigma/m$ is the coefficient of variation of the rates.

Consider the prediction of the recruitment process. Denote by $n_i(t)$ the predicted number of recruited patients in centre i during time interval $[0, t]$, by $n(I_s, t)$ – in some region I_s. Let $n(t)$ be the number of patients recruited by all N centres, and $T(n, N)$ be the total recruitment time. Assume that centre i is initiated at time u_i where u_i is uniformly distributed in a given interval $[a_i, b_i]$. Then $n_i(t) = \Pi_{\lambda_i}(t - u_i)\chi(u_i \le t)$, where $\Pi_\lambda(t)$ stands for an ordinary Poisson process with rate λ and $\chi(A)$ is the indicator of the event A ($\chi(A) = 1$ if A is true, and $\chi(A) = 0$ otherwise). Thus, $n_i(t)$ is a doubly stochastic Poisson process with two levels of mixing. Using known formulae for calculating the expectation and the variance of a doubly stochastic variable, one can calculate that

$$\begin{aligned} \mathbf{E}[n_i(t)] &= M(t, a_i, b_i, m), \\ \mathbf{Var}[n_i(t)] &= M(t, a_i, b_i, m) + S^2(t, a_i, b_i, m, \sigma^2), \end{aligned} \tag{2}$$

where the functions $M(t, a, b, m)$ and $S^2(t, a, b, m, \sigma^2)$ are calculated as follows:

$$M(t, a, b, m) = \begin{cases} 0 & \text{if} \quad t \le a \\ m(t-a)^2/(2(b-a)) & \text{if} \quad a < t \le b, \\ mt - m(a+b)/2 & \text{if} \quad t > b, \end{cases}$$

$$S^2(t, a, b, m, \sigma^2) = \begin{cases} 0 & \text{if} \quad t \le a, \\ m^2(t-a)^3(4b-a-3t)/(12(b-a)^2) + & \\ +\ \sigma^2(t-a)^3/(3(b-a)) & \text{if} \quad a < t \le b, \\ (m^2+\sigma^2)(b-a)^2/12 + \sigma^2(t-(a+b)/2)^2 & \text{if} \quad t > b. \end{cases}$$

Therefore, as $n(I_s, t) = \sum_{i \in I_s} n_i(t)$ and $n_i(t), i \in I_s$, are independent,

$$\begin{aligned} \mathbf{E}[n(I_s, t)] &= \sum_{i \in I_s} M(t, a_i, b_i, m), \\ \mathbf{Var}[n(I_s, t)] &= \sum_{i \in I_s} \Big(M(t, a_i, b_i, m) + S^2(t, a_i, b_i, m, \sigma^2) \Big). \end{aligned} \tag{3}$$

Thus, an approximate p-confidence limit $z_p(I_s, t)$ for $n(I_s, t)$ can be computed for any probability p using relations (2), (3) and a normal approximation as $z_p(I_s, t) = \mathbf{E}[n(I_s, t)] + z_p\sqrt{\mathbf{Var}[n(I_s, t)]}$, where z_p is a p-quantile of a standard normal distribution. Denote by $z_p(N, t)$ an approximate p-confidence limit for the total number of recruited patients in all N centres at time t. Then the intersection of the line $z_p(N, t)$ with the horizontal line $Y = n$ defines the approximate T_{1-p}-confidence limit for the recruitment time $T(n, N)$. Therefore, the event $T < T_{1-p}$, where T is the planned recruitment deadline, means that $\mathbf{P}(T(n, N) \le T) < 1 - p$.

These relations provide us with the criterion for how to select the minimal number of centres required to complete recruitment before deadline with a given confidence $1-\delta$. For N initially planned centres we need to compute $z_\delta(N,t)$ confidence line and the value $T_{1-\delta}$. If $T < T_{1-p}$, then it is necessary to add in some countries the additional centres and repeat calculations until the relation $T_{1-\delta} \le T$ is satisfied.

3.2 Study and Centre Performance

According to empirical observations, large studies with many centres have some particularities, e.g. as usual there are many low performing centres and a large fraction of patients is recruited by a small fraction of highly productive centres. These particularities lead to largely unbalanced study which may cause also a decrease of statistical power and increase of recruitment time and drug supply costs.

In this section we prove using recruitment modeling that these particularities can be explained by the natural statistical fluctuations.

Consider a mean fraction of the centres recruited exactly j centres. According to (1), it has the form $m(n,N,\alpha,j)/N$.

Theorem 1 *Assume that $n \to \infty$, $N \to \infty$ and $n/N \to q > 0$. Then*

$$m(n,N,\alpha,j)/N \to Q(\alpha,q,j) = \frac{\Gamma(\alpha+j)}{j!\Gamma(\alpha)} \frac{q^j \alpha^\alpha}{(\alpha+q)^{\alpha+j}},\ j = 0,1,... \qquad (4)$$

To prove this result, one need to use the expression (1), the relation $\mathcal{B}(a,b) = \Gamma(a)\Gamma(b)/\Gamma(a+b)$ and Sterling formula for factorials and gamma functions. One can also prove that the variance of this fraction tends to zero.

Therefore, study performance for large number of centres (enough to have $N > 10$) is mainly determined by only two factors: the mean number of patients in a centre $q = n/N$ and a shape parameter α or the coefficient of variation C_v in recruitment rates across centres.

The right-hand side in (4) is a negative binomial distribution, and there is also a probabilistic proof of Theorem 1. The mean fraction is asymptotically equivalent to $\mathbf{P}(n_i = j)$, where n_i is the number of patients recruited by some centre i. Under a Poisson-gamma model assumptions, n_i has a beta-binomial distribution with parameters (n, p_i), where $p_i = \lambda_i/\Lambda$, $\Lambda = \sum_k \lambda_k$. It is known that at fixed and small probability p_i a binomial distribution is approximated by a Poisson one with rate np_i. Furthermore, at large N, $np_i \approx \lambda_i q/m$. So, n_i is approximated by a Poisson variable with gamma distributed rate $\lambda_i q/m$. This mixed Poisson variable has a negative binomial distribution (4).

Relation (4) allows to investigate the performance of different centres with regard to their load for rather general scenarios.

Figure 2 shows the behaviour of the fraction of empty centres for different values of C_v. As $\alpha = 1/C_v^2$, the corresponding values of α are $(2, 1.5, 1.2, 1, 0.8)$. The value $C_v = 0.9$ ($\alpha = 1.2$) corresponds to the medium variation. Figure 3 shows the behaviour of the fraction of low performing centres (recruited not more than two patients). As it can be seen, the variation in rates increases the fraction of empty and low performing centres.

For example, in trials where on average not more than 4 patients per centre (as in some oncology studies) it is common to achieve ∼15-20% of empty centres if do not make interference of the recruitment on the way (e.g. closing low performing

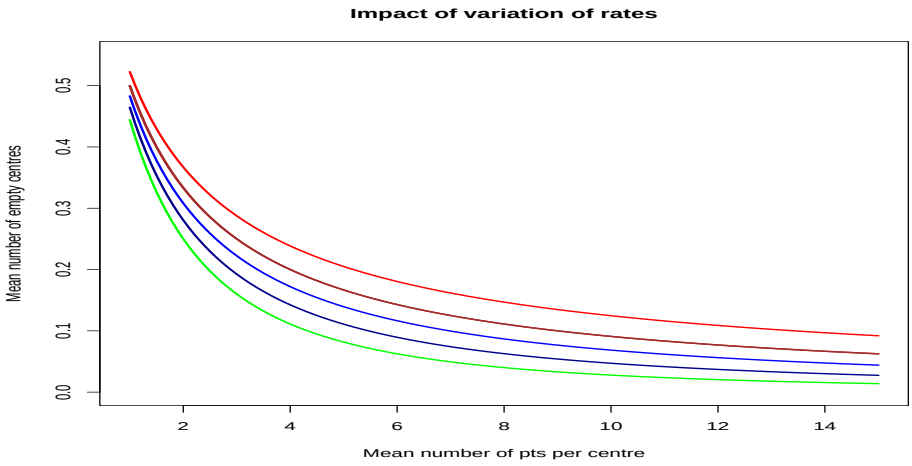

Figure 2: Fraction of the number of empty centres as the function of $q = n/N$ for different values of $C_v = 0.7, 0.8, 0.9, 1.0, 1.1$. Low curve corresponds to $C_v = 0.7$.

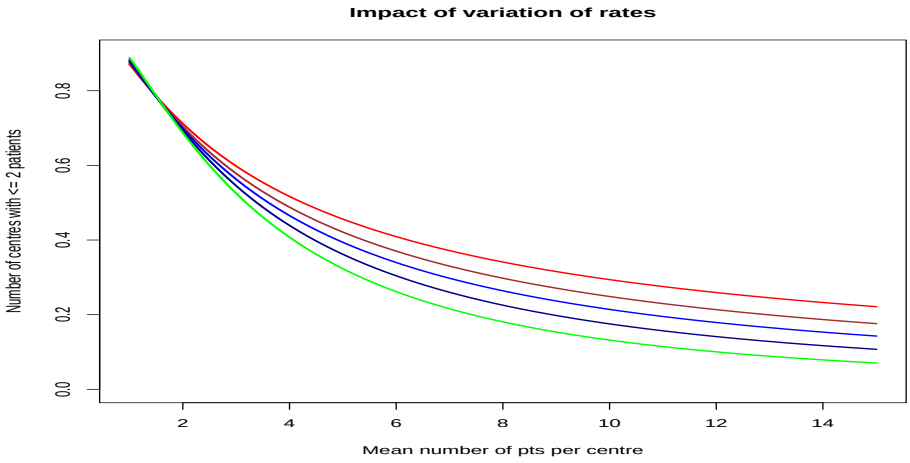

Figure 3: Fraction of the number of centres recruited not more than two patients as the function of $q = n/N$ for different values of $C_v = 0.7, 0.8, 0.9, 1.0, 1.1$.

sites, etc.). This provides an explanation of the empirical observations that in trials with small number (on average) of patients per centre the number of empty centres is often substantial.

These results allow us to evaluate the productivity of different groups of centres at the design stage of the study.

Let us investigate the impact of the most productive centres. Using relation (4) it is possible to calculate numerically the fraction of patients recruited by the most productive centres. Figure 4 illustrates this behaviour for study A (see Section 2.2) compared with the theoretically calculated curve. As one can see, both curves practically coincide. This fact can serve as an additional verification of the Poisson-gamma model.

For this study, 50% of patients recruited by $\sim$ 22% of centres; 80% of patients recruited by $\sim$ 52% of centres. The results are similar for other typical scenarios, e.g. half of patients is recruited by ~15-20% of the most productive centres, 80% of patients are recruited by ~40-50% of the most productive centres, which is in agreement with empirical observations.

Therefore, the observed heterogeneous behaviour of recruitment in large trials

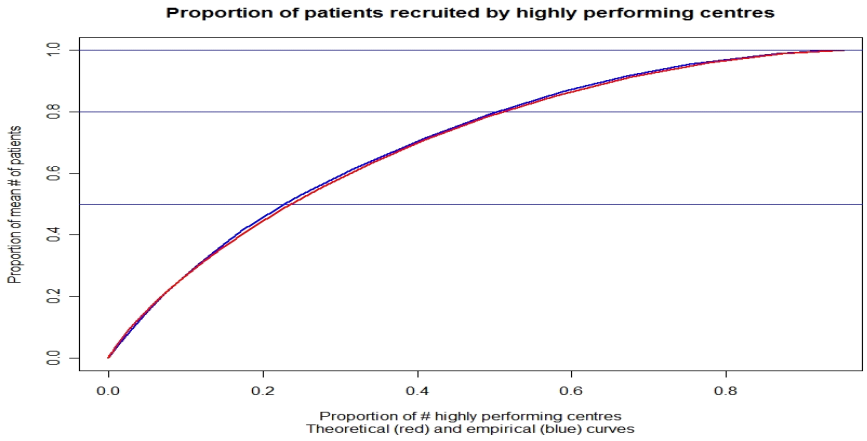

Figure 4: Study A. Fraction of the number of patients recruited by the most productive centres.

is not a result of a bad planning, but a Statistical Law following from stochastic modelling.

3.3 Prediction of the ongoing study

Consider an ongoing study at some interim time point t_1 and construct the predictions for the remaining recruitment process and recruitment time following the technique proposed in (Anisimov, Fedorov, 2007).

The recruitment data at time t_1 has the form: for each centre i it is known the date of centre initiation u_i and the number of recruited patients k_i. The algorithm of prediction consists of several steps:

1. Estimating parameters of recruitment model (α, β) (shape and rate parameters of rates) using maximum likelihood approach.
2. Using in each centre a new posterior recruitment rate that has a gamma distribution with parameters $(\widehat{\alpha} + k_i, \widehat{\beta} + v_i)$ (Bayesian approach), where $v_i = t_1 - u_i$ is an actual duration of recruitment in center i.
3. Compute the mean and the variance of the predicted remaining number of patients (over the time) similar to Section 3.1.
4. Compute the confidence bounds for the remaining recruitment time.

If the probability to complete in time is less than some prescribed probability, then similar to Section 3.1, an adaptive adjustment of recruitment (calculating the number of additional centres to be initiated with the purpose to complete in time with a given probability) can be provided.

In particular, if all centres initiated at the same time with actual duration of recruitment v, then the predictive remaining recruitment time can be expressed in the form

$$\widehat{T}(K_2, N) = \frac{\gamma(K_2, 1)}{\gamma(\widehat{\alpha}N + K_1, \widehat{\beta} + u)},$$

where K_1 is the number of recruited patients, K_2 – the number of patients left to recruit. This is a Pearson type VI distribution (Johnson et al., 1994, p. 381).

3.4 Patient Recruitment Modelling Tool

Using this technique, the modelling tool in R-language is created. The tool computes the mean and confidence bounds for the predicted number of recruited patients over time and for the total recruitment time at any stage of the study. The tool has many additional features: evaluating the minimal number of centres required to complete recruitment in time with a given probability, providing adaptive adjustment, predicting performance of centres/countries, predicting recruitment in countries/regions. These features allow to use decision making approaches and cost benefit analysis for optimal study planning.

The tool has been validated for many real studies and currently is on the way of implementation in GSK.

3.5 Case Study

Consider as an example a real completed study. The initial plan was to recruit 366 patients by 75 centres. Finally, 109 centres were initiated.

The retrospective analysis of the study was performed. The recruitment duration was divided on 4 equal periods (64 days): after 1st period – 15 patients were recruited, after 2nd period – 118 patients, after 3d period – 254 patients. Using data after each period, the predictions were constructed and compared with the real course of recruitment.

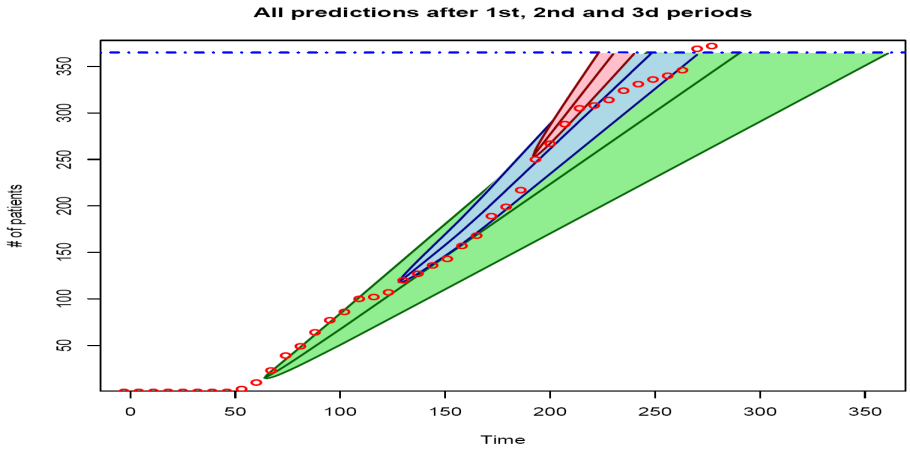

Figure 5: Combined plot of predictions constructed at three interim times and the real data shown by dots, 90% confidence areas.

Figure 5 shows the 90% confidence areas constructed after each period. As one can see, the predictions become narrower as the number of patients increases and pretty good cover the real data. Some slowdown in recruitment after 220 days was caused by closure of one dose out of four due to some medical indications not related to recruitment itself. To account for such situations, it would be necessary to adjust recruitment rates as soon as a new information becomes available.

4. Supply Chain Process

The drug supply chain process is rather costly, depends on recruitment and randomization and has many uncertainties.

A typical scenario of drug supply planning for a single study means that there are one or two central depots and several regional depots. Delivery time from a central depot to a regional one can vary up to a couple of months. Each depot is associated with several local centers. Delivery time from the depot to a local center can be a few days. The incoming patients are registered and after a screening period (may take up to a few weeks) are randomized to a particular treatment and then should get a prescribed treatment. A typical strategy of supply assumes that before study starts, the initial amount of supply is sent to each regional depot to cover the patient demand for some initial period until the next shipment will be delivered. Afterwards, on a regular basis (say, each month) the additional supply is sent to the regional depots to cover the amount of supply used in the depots during the previous period.

The main problem is to minimize the risk of stock out for a patient and reduce the amount of unused drug.

4.1 Drug Supply Modelling

The main uncertainties in predicting supply demand are caused by the variation of patients over time and between different regions due to random recruitment and also by the variation of patients between different treatment groups (in centers/depots) caused by randomization.

The technique for modelling patient recruitment can serve as the basic methodology for drug supply modelling. In addition, for predicting supply needed to satisfy patient demand we need to predict the number of patients randomized to different treatment arms in centres/depots. Therefore, a randomization scheme may add a substantial variation in these numbers.

The two most often used in clinical trials randomization schemes are: unstratified and centre-stratified block permuted randomization. Unstratified randomization means that the patients after screening are randomized to treatment arms according to independent randomly permuted blocks of a fixed size without regard to clinical centre (a common randomization list). Centre-stratified randomization means that the patients are randomized separately in each clinical centre according to independent randomly permuted blocks of a fixed size (separate randomization lists in each centre).

Randomization schemes and their properties are investigated in (Pocock, 1983; Lachin, 1988; Matts and Lachin, 1988; Rozenberger and Lachin, 2002). The randomization scheme affects the study design and also influences the strategy of supply and supply overages. In particular, unstratified randomization leads to extra uncertainties in local centres/depots and substantially increases supply overage.

Therefore, the technique for patient recruitment modelling described in sections above is extended to predicting for both randomization schemes the number of patients randomized to different treatment arms in centres/depots. The extended technique can be used for predicting supply demand (in depots and in total) and for evaluating the risk of stock out of a patient.

4.2 Statistical Criterion

It is proposed to use a statistical risk-based criterion for predicting the amount of supply needed to cover patient demand during the recruitment stage.

An acceptable risk δ means that in a particular study, with probability $1 - \delta$ all patients will receive the correct treatment assignments and 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 subject out of 500/0.05=10,000 patients may be "out of stock". This approach is similar to what is used at the statistical analysis stage: take a decision on the quality of drug based on patient responses with a given probability of risk. Therefore, in general it is not reasonable to use risk less than 5%.

4.3 Risk-based Supply Modelling Tool

Using the statistical approach described above, the pilot versions of the tool for drug supply modelling are created. The tool uses R-language and covers both randomization schemes. The basic features are the following: the tool evaluates the upper confidence bounds for required supply (for a given risk), the upper confidence bounds for the number of treatment packs needed at different stages, in depots, etc. The tool uses the direct computations based on derived closed-form expressions, no Monte Carlo simulation involved. Thus, it allows to compare many scenarios in seconds, evaluate the impact of risk, of the number of depots and other supply logistics parameters on supply overage, and compare costs.

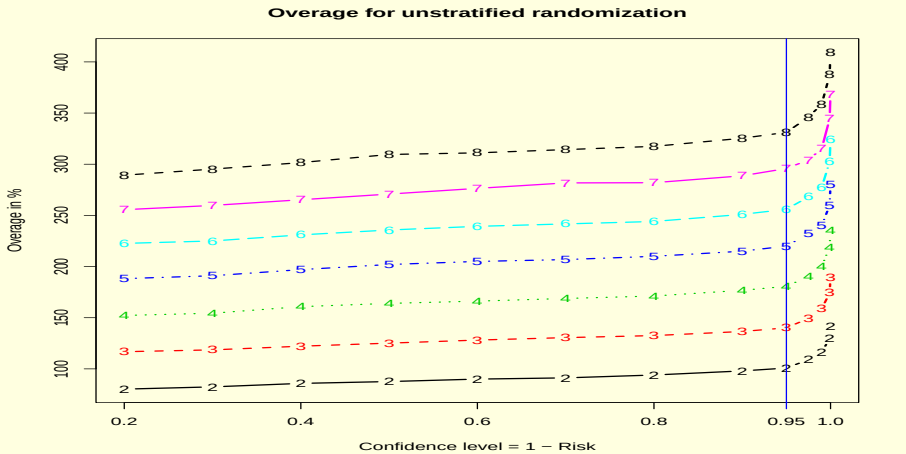

Figure 6: Dependence of overage on confidence level. Unstratified randomization.

4.4 Case studies

Consider a design for a hypothetical study where it is planned to recruit 500 patients by 80 clinical centres. There are 5 depots with the following distribution of centres among depots $(28, 20, 16, 8, 8)$, and the planned recruitment time is 6 months.

Figures 6 and 7 show the dependence of supply overage on the confidence probability $= 1 - risk$ for different treatment arms (2,3,..,8) and for both randomization schemes. As one can see, the overage is sharply going up for risk $< 5\%$, and using unstratified randomization may increase overage for more than 100%.

Figure 8 illustrates the dependence of overage on the number of depots for different treatment arms while using a centre-stratified randomization for the following scenario: 1000 patients, 120 centres, recruitment time is 6 months, risk is 5%.

As one can see, the increase in the number of depots leads to substantial increase of overage. For all these cases the number of treatment arms is a crucial factor, e.g.

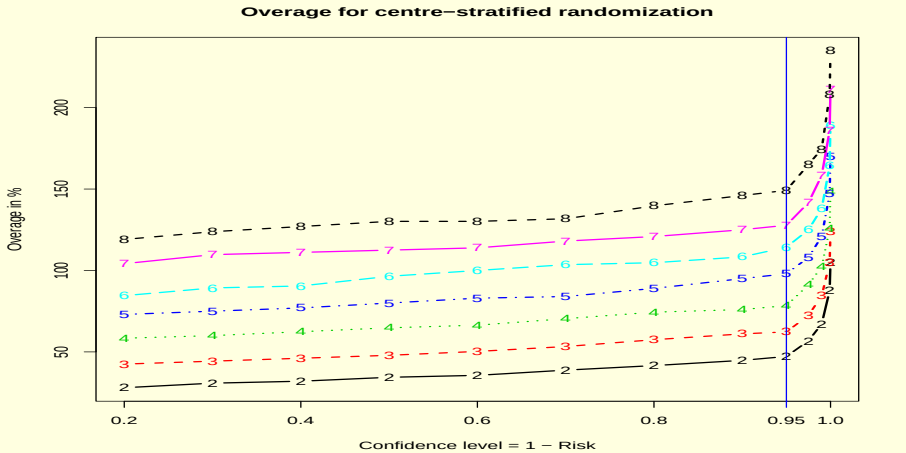

Figure 7: Dependence of overage on confidence level. Centre-stratified randomization.

increasing the number of arms from 2 to 4 may lead to overage increase up to 50% and more percents.

These plots illustrate the broad possibilities in using modelling tool for clinical teams at the design stage.

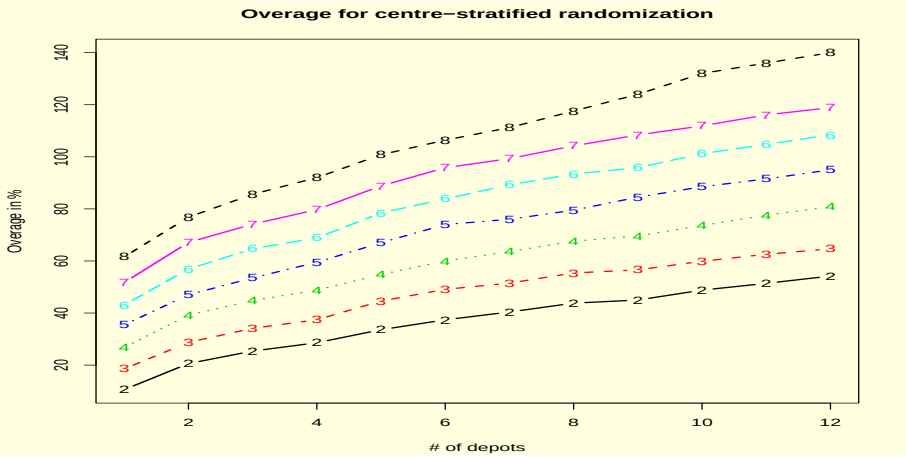

Figure 8: Dependence of overage on the number of depots for different treatment arms. Centre-stratified randomization.

5. Conclusions

The statistical methodology for predictive patient recruitment and drug supply modelling is developed. Software tools in R-language based on this methodology are created. The tool for modeling patient recruitment allows predicting patient flows with statistical confidence at any stage of the study (using planned or real data), adaptively adjusting recruitment and the number of clinical centres needed at any interim time, evaluating study performance and site productivity. The tool for drug supply modeling uses the recruitment modelling technique and allows predicting drug supply required to cover patient demand for a given risk of stock out. Using statistical tools opens wide opportunities for clinical teams at design and any interim

stage and allows to compare different scenarios using various criteria accounting for the recruitment time, randomization scheme, costs (per recruitment, supply) and different risks of delays and stock out.

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