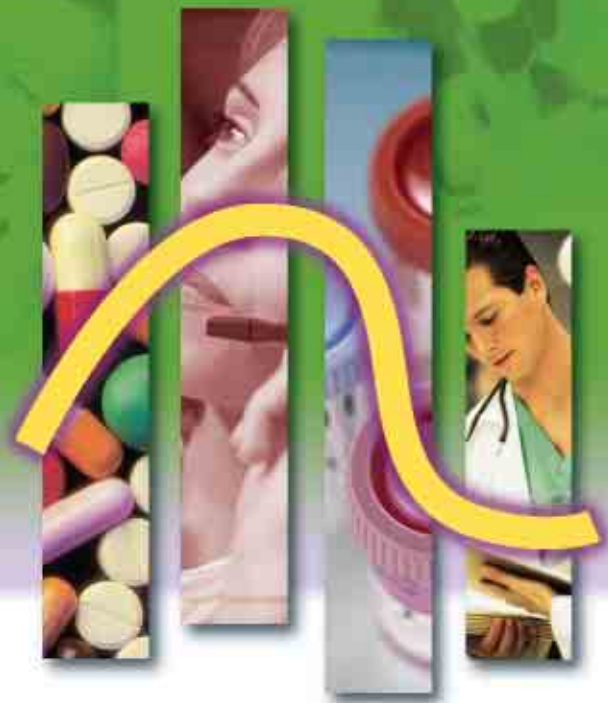


# Optimizing the Supply Chain Through Trial Simulation

Nikki Dowlman, Martin Lang, Damian McEntegart, Graham Nicholls, Stephen Bacon, Jeremy Star, and Bill Byrom



**M**anagement of supplies is an area where sponsor companies are seeing perhaps the greatest changes due to the increased pressure in bringing drugs to market faster.<sup>1</sup> This often means trials start earlier, with fewer supplies. They may be larger, both in terms of numbers of subjects and in the geographic area of trial participants. There is often more competition for the available supplies, since different trials using the same drug run in the same period of time. There may even be a need to pool supplies across studies, making medication units available to a number of concurrent trials.

Interactive Voice Response (IVR) systems provide one possible way of addressing this challenge. IVR systems have been used to significantly reduce the amount of overage and wastage in the clinical supply chain by ensuring efficient targeting of available supplies to the sites that are actively recruiting and retaining subjects. How these systems operate to manage the clinical trial supply chain is well documented elsewhere.<sup>2-4</sup> However, previously it has not been possible to fully estimate the amount of savings in material that can be gained by implementing an IVR-controlled supply chain within a clinical trial. For this reason, the potential savings in drug supply may not be fully realized. By building a simulation model that mimics the medication-conserving supply chain processes implemented by IVR, it was hoped that two main objectives would be achieved. First, it would enable accurate estimates of supply needs for clinical trials using IVR. Second, it would obtain a greater understanding of the IVR-managed supply

chain to further refine and improve the algorithms used within the system itself.

This article describes a simulation model of the clinical supply chain managed by an IVR system and examines the results of the model when applied to an example study.

## Simulation of an IVR-managed supply chain

Optimizing the medication supply chain strategy and then managing it using IVR can be complex, involving many factors. Minimization of study drug requirements, for example, is a nontrivial problem, dependent on the interaction of many factors and variables. (Although this article focuses on simulating an IVR-controlled supply chain, it should be noted that a similar approach could be adopted to consider traditional packaging and manual stocking and re-supply of sites, but would require the model to follow different rules and algorithms.)

Previously, clinical supply teams used the performance of older trials to understand how much material was likely to be required in a new study and to determine their supply chain requirements. They may have examined key performance variables such as subject recruitment rates, the number of drug kits used, countries involved in past studies, and so on. However, such techniques often result in “best guess” estimates for medication management, making the impact of small changes in study design, randomization methodology, medication packaging and labelling or expiry date difficult to account. Simulating the IVR management of a clinical trial allows the supplies group to experiment with a variety of strategies and scenarios. In this way, the amount of clinical material required can be identified and the supply chain can be optimized.

**Simulation tools empower sponsors to confidently choose the best drug supply strategies in IVR trials.**

## Modelling real world variability

The simulation builds a model that mimics aspects of the drug distribution process, such as recruitment, withdrawal, shipment times, randomization methodology, etc. This allows for effective optimization of medication management strategies, as well as identification of how much material is required for an upcoming clinical trial by evaluating different supply chain scenarios. Some processes, such as subject recruitment, are variable, so it is important that the modelling approach incorporates variability into the study. This way, a full range of outcomes can be studied.

Monte Carlo simulation<sup>5,6</sup> allows such an approach, sampling values for pertinent variables from underlying specified distributions for some of the input parameters. To explain how Monte Carlo simulation works, consider how this technique applies to predicting subject recruitment. The recruitment for a site is generally modelled to follow a Poisson process<sup>7</sup> (this process describes the number of random events over a defined time period). Thus, while the average study recruitment for a group of sites may be 2 subjects per site per month, there is a chance that an individual site may recruit zero subjects or as many as 6 or 7 subjects in any particular month (Table 1). Monte Carlo simulations account for this variability by using a random number generator to determine the site's recruitment for each month of the simulation (see Figure 1). The process is somewhat similar to rolling a die to mimic real world variability. In reality, though, the random number generator is weighted to return numbers in the proportions that underlie the theoretical distribution. The same concept is applied in the model for other study parameters that add variability into the clinical trial process, such as shipment times or subject variability across stratification factors. In this way, the model can incorporate the variability observed in the real world when performing its calculations.

Using this approach, the results of a number of runs not only show mean values but also the range of possible outcomes with their likelihood, providing valuable information to understand the requirements and behavior of the supply chain strategy under investigation. While deterministic models and simple estimation methods follow an average process that answers "How much drug do I need on average?," the Monte Carlo approach answers "What is the most amount of drug I am likely to need?" or "How can my supply chain perform best with the limited supplies I have available?"

This approach enables the model to answer practical questions and concerns:

- Ideal shipment sizes, to minimize any potential blinding issues versus stock availability at the beginning of the trial
- Optimal trigger/re-supply settings (see sidebar)
- Optimal prediction windows in multiple dispensation studies (see sidebar)
- The impact of trigger and re-supply levels on the number of shipments
- The best time to plan subsequent production runs
- How much material to pack, given a particular study and pack design
- How expiry may impact on a study
- What impact different randomization methodologies will have

on the available supply material

- Investigating the use of local depots versus direct-to-site shipments
- Cost benefit of frequent small shipments or fewer larger shipments versus drug cost and availability
- Benefits of using IVR in a trial.

Experience has shown that the simulations can prove valuable both before a study while planning and midstudy. Using the same method to perform midstudy simulations enables sponsors to test their initial assumptions, refine their supply strategy, establish the optimal timing and content of

**Monte Carlo simulations account for recruitment variability by using a random number generator to determine the site's recruitment for each month, similar to rolling a die.**

additional production runs, and consider the impact of study design changes—new sites or countries, or modification of treatment arms. The principle of these simulations is exactly the same, but whereas prestudy simulations are "best guesses" based on information from monitors or previous studies, midstudy simulations are based upon a snapshot of the real life medication usage data within the active IVR application database. These simulations employ actual information on subject status and medication location and availability to forecast the likely progression for the remainder of the study. Again, the Monte Carlo approach enables the range of possible

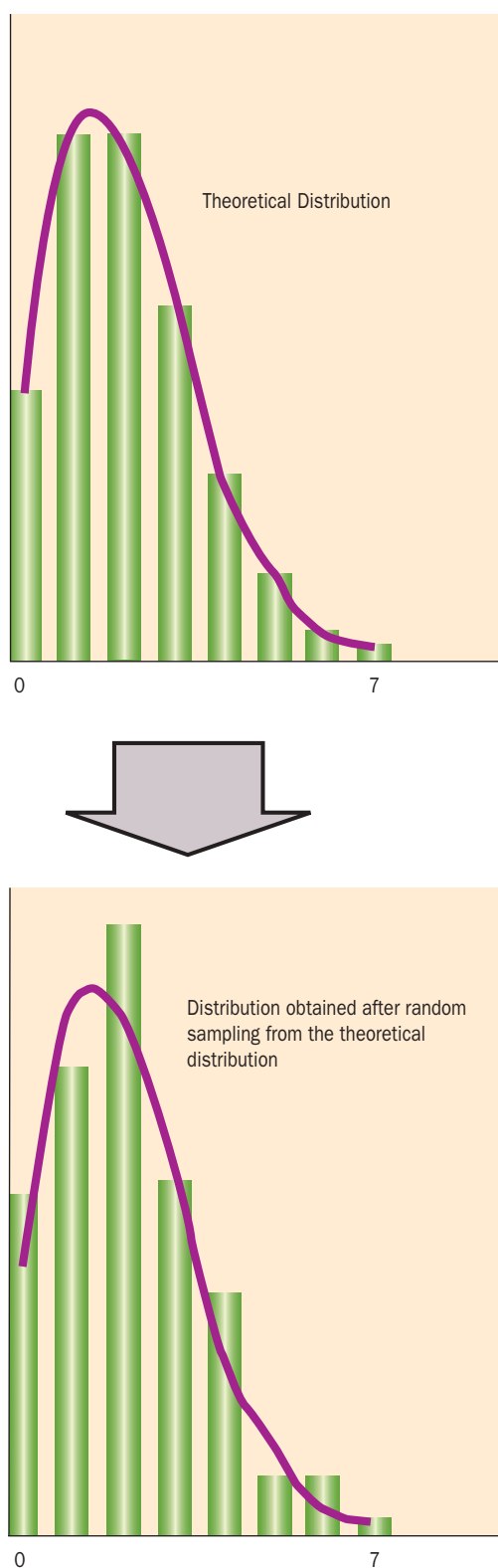
## Supply Chain Management Algorithms

### Trigger re-supply process<sup>2-4</sup>

With this algorithm, each study site is assigned a trigger and stock level for each pack type. These parameters depend on recruitment rate, delivery time, site storage, and study overage. When the number of packs at site falls to (or below) the trigger level, additional packs are automatically re-ordered. In the ordering process, it is usual for all pack-types to be re-supplied up to their assigned stock level. A number of variations of this process exist.

### Predictive re-supply process<sup>2-4</sup>

This algorithm applies to studies where medication is dispensed at more than one visit in a planned predictable way. Site supply needs are assessed relative to the anticipated re-dispensing of active subjects and requirements of possible newly recruited subjects. The length of the prediction window (how far ahead the algorithm looks for scheduled dispensing visits) should be determined by the frequency of potential dispensing visits, the withdrawal rate, expiry date of supplies, and storage at site.



**Figure 1.** Subject recruitment at sites is modelled using a Poisson distribution to model the real world variability observed. In this way, it becomes possible to observe a range of possible outcomes rather than simply an average. The top graph presents the theoretical distribution; the lower graph presents a typical distribution of sampled recruitment rates aggregated over centers.

outcomes to be measured, instead of one single-line extrapolation.

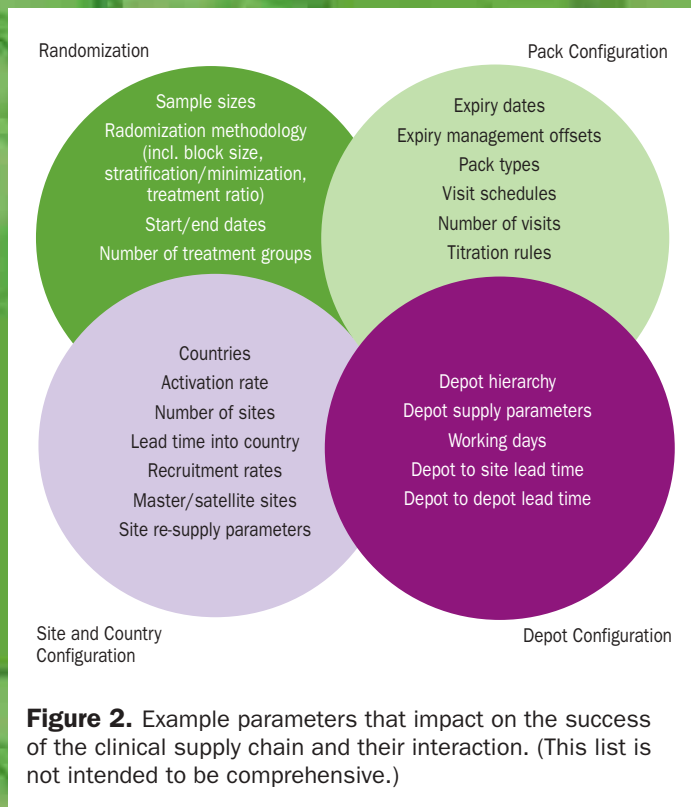
### Model input

The model will need to accept inputs for a significant number of variables that impact on the supply chain and drug availability (Figure 2). Some of these parameters will be fixed for a particular run, by their very nature: method of randomization, block size, pack types, visit schedule, etc. Others are programmed to emulate the “real-world” variation, e.g., recruitment rates, withdrawal rates, and up/down titration rates for each visit. Each simulation runs through every day of the duration of study, mimicking the events that could be expected for that day. So at the start of the trial, countries and sites are activated randomly over a defined period of time and initial supplies are requested in a way identical to that occurring in a real trial using an IVR system. Subjects are recruited on a daily basis using the recruitment rates given for each site. Their subsequent visits are randomly sampled from the target visit date range defined for the study. Subject withdrawals occur in a random manner on a “daily” basis according to the defined withdrawal rates. At the end of each day, site and depot stocks are assessed for the requirements to raise a re-supply order using the predefined re-supply algorithms, mimicking the IVR system. The time taken for medication deliveries to arrive at site are sampled from an underlying uniform distribution. The model must be able to imitate all of the functionality observed in the medication management application used by the IVR system and all of the randomization methodologies that can be applied with IVR. It is also possible to automatically register milestones in the study and make sensible adjustments to input parameters. For example, at the end of recruitment it may be desirable to reduce the buffer stock held at a site as there are no more “new” subjects to recruit and therefore fewer “unexpected” supply events likely to take place.

### Model output

In using the simulation tool, it is important to run a sufficient number of simulations in order to identify any possible outliers. This may mean running the model over a thousand times in order to ensure that all likely outcomes are simulated. As discussed earlier, while each simulation will produce a different result for all of the output variables, the true power of the tool is demonstrated when reviewing the summary statistics as a whole. Examining the data in this way will provide a range (minimum and maximum and confidence interval) as well as a mean estimate. In our experience we have found the most useful summary statistics to be:

- The overage in medication required, i.e., the amount of medication remaining in the supply chain (site or local depot) at the end of the study
- The number of deliveries required
- When additional supplies (from an additional packaging run) will be required to prevent supply chain stocks from running too low
- The probability of being unable to supply one or more subjects (at randomization or dispensing visits)
- The expected incidence of forced randomization,<sup>8</sup> if it is



allowed (i.e., if the desired treatment is unavailable the subject is forced onto an alternative treatment group)

- The number of subjects affected and the length of time before supplies are available at site, if medication is unavailable for dispensation
- The ranges of study durations.

Reviewing these data for each scenario (a single defined set of input variables) enables the end-user to explore “what if” analyses to help understand the behavior of the supply strategy, for example, to help balance overage reductions with increased risk of supply failures to aid in study optimization. The user can also evaluate a particular supply strategy in comparison to others. In generating awareness of an outcome’s likeliness, appropriate contingency plans can be devised or the supply strategy adjusted to reduce the odds of the situation occurring. Sensitivity analyses to test the ability of the strategy to cope with alternative assumptions about the trial progression can provide a valuable measure of the robustness of the model’s results.

### Simulation example

To illustrate the usage of the model, simulations of a 1,000-subject study were performed. The protocol design was chosen to mimic a number of likely practical challenges that one could expect to face in a genuine study. The following overview details these challenges.

### Study overview

**Pack types and dispensations.** Six treatment groups each received two different pack types at randomization and at subsequent re-supply visits; there were five pack types in all. Four re-supply visits occurred at fortnightly intervals.

**Randomization method.** The randomization was stratified at the country level, with recruitment spanning 10 countries in Europe, Asia, and North America.

**Supply logistics.** Local depots were in place to issue supplies to centers in each country. Delivery into two of the countries required import licenses that meant that the shipment times from the central depot to the relevant local depots were prolonged and more variable.

**Subject enrollment.** In some centers of one Eastern European country, all the subjects to be enrolled had the potential to be rapidly entered into the study in batches on a single day of the week, e.g., each subject would be enrolled in the IVR system at 30-minute intervals. There was a high probability that these centers would all have their clinics on the same day of the week. Subjects from other centers and countries were enrolled in a more conventional manner over a period of months; recruitment at these centers was expected to vary and for convenience was grouped into three types—low, medium, and high, with mean recruitment rates of 0.2, 0.4, and 0.6 subjects per week according to a Poisson distribution.

**Medication management algorithm.** The medication management strategy involved trigger-re-supply for the randomization stocks at site, and predictions for the re-supply visits. A trigger-re-supply strategy was also employed to manage the re-supply of local depots.

### Simulation experiment objective

The objective of the simulation was to estimate the total amount of each pack type required for the study while keeping the risk of supply failures to a minimum. This required setting center level supply strategies for the three conventional center types (low, medium, and high recruiting centers) and the batch recruiting centers. Different depot level supply strategies also had to be set taking into account those countries which contained batch entry centers, and those with longer lead times for supply from the central depot.

### Simulation findings

The simulation experiment comprised two stages. The first stage was to investigate the optimal initial supply requirements for the batch recruiting centers. Once this was determined, the simulation was repeated to explore optimal initial supplies and re-supply parameters for the complete study.

**Stage 1: Initial supply requirements for the batch-recruiting centers.** It was assumed each batch-recruiting center would enter 12 subjects per week on any given day in the initial stages

**Table 1.** Distribution of number of subjects recruited at site per month following a Poisson process with rate 2 subjects per month

	Number of subjects recruited in specified month									
	0	1	2	3	4	5	6	7	...	10
<b>Probability</b>	0.135	0.271	0.271	0.180	0.090	0.036	0.012	0.003	...	0.00004

of the trial. Because randomization was stratified at country level, it was possible that, in the worst case, all 12 subjects could be recruited to the same treatment group. In this case a total of 60 packs (12 of each of the five pack types) would be required initially. But in 1,000 simulations, the maximum number of subjects ever randomized to one treatment was seven.

It was, therefore, further informative to examine the maximum usage of each pack type over the 1,000 runs; these could then be used as the optimum buffer stock levels for the sites. The sum of the maxima over all pack types was 51 packs. This would accommodate all possible outcomes observed when the study was simulated 1,000 times. In contrast, supplying only 44 packs to each batch-recruiting site coped with 97.3% of the 1,000 simulation runs. This less conservative strategy may be considered optimal, as the potential supply wastage and site storage requirements were limited with only a small possibility of a pack type being initially unavailable. These data were used as the starting point for defining the supply strategy parameters for the batch recruiting centers further explored in stage 2.

*Stage 2: Overall study supply strategy parameters.* The relative merits of three different strategies were explored in stage 2 of the simulation experiment. For each pack type, different initial supply volumes, trigger levels, and stock levels were assigned for the low, medium, high, and batch recruiting centers. Table 2 illustrates examples for one of the five pack types.

In addition to differences in the trigger and stock level parameters, strategy A employed a longer prediction window than the other two strategies. Using strategy A, when a re-supply requirement is identified, the algorithm looks ahead for 56 days to account for any additional predicted re-supply visits that are scheduled to occur. With strategies B and C, the prediction window was 28 days.

For each strategy, the 1,000 simulations were performed and summary metrics were calculated to measure the total medication requirement, number of shipments, as well as whether sites without inventories were able to accommodate dispensation requirements. These results are presented in Table 3.

As indicated in the table, strategy A is low risk, having no observed instances of medication shortage at site. However, the downside of this approach is that more medication is required in the supply chain to eliminate this risk—20% and

**Table 2. Initial supply volumes, trigger parameters, and re-supply parameters for a single pack type**

Center type	Strategy								
	A (high settings)			B (medium settings)			C (low settings)		
	Initial stock	Trigger level	Stock level	Initial stock	Trigger level	Stock level	Initial stock	Trigger level	Stock level
Low	4	2	4	2	0	2	2	0	2
Medium	8	4	8	3	1	3	2	0	2
High	12	6	12	4	2	4	3	1	3
Batch	12	6	12	10	5	10	9	5	9

24% more than that required by strategies B and C, respectively. Strategy B may be optimal as it enables the study supplies to be managed with less overall medication and only a small possibility of a site inventory shortage.

When performed in reality, this information could then be used as a basis for the packaging campaign.

### Discussion

Simulation models have been used in many other areas of clinical trials,<sup>5</sup> but to our knowledge this is the first simulation to cover a typical clinical trial's complex distribution system. Hamilton<sup>9</sup> describes a previous application where subjects were randomized to receive only one dispensation of four possible treatments. Thus, only the subject characteristics and randomization process were simulated in conjunction with a very simple re-supply system. Nevertheless, this simple exercise demonstrated the value of simulation as well as the tradeoffs between different supply strategies. Building a model to simulate the clinical trial supply chain as controlled by IVR is a way to not only refine the parameters for any given study, but also to better understand the mechanisms by which IVR controls the supply chain, allowing for further developments in the underlying algorithms.

Central computer-controlled supply chain systems are not exclusively delivered using IVR. The telephone helps provide a commonly available and simple-to-use interface to the computer, which enables simple and rapid communication. Another approach uses the Internet as the interface between end-user and computer.<sup>10</sup> Visual display of information can be valuable when reviewing the contents of shipments containing many packs. Fax systems have also been used employing OCR technology to read inputs directly from site faxes. However, these systems have limitations, as transactions can be slowed, delayed, or even fail altogether, which impacts on the effectiveness of the solution.

**A total of 60 packs were required initially. But the sum of the maxima over all pack types was 51 packs, which would accommodate all outcomes in 1,000 simulations. Supplying only 44 packs resulted in a 97.3% figure, which may be optimal.**

## Conclusions

With the drive to get drugs to market faster, sponsor companies are continually evaluating how they run clinical trials to introduce more efficiencies. In relation to clinical trial material, this often means less drug is available over a more sophisticated supply chain with increasingly complicated logistics, resulting in more points for potential failure. More companies are turning to IVR as a possible solution to this problem, with a limited understanding of the potential benefits. Modeling the IVR process enables researchers to understand how much medication is likely to be required by a forthcoming study when managed by IVR.

Some sponsor companies are considering the supply chain design and the use of IVR very early in the planning stage. Helping to design the study protocol and define suitable subject visits and medication supply pack sizes would aid in utilizing either expensive or scarce material.

This approach is still novel within the industry. After a number of test cases to evaluate the output, a few companies are now using this solution extensively in the planning and conduct of their clinical trials. Other sponsor companies are using simulations tactically on an individual study basis.

With this in mind, the types of clinical trials that might particularly benefit from this approach may include the following:

- Where medication is expensive
- Where medication is scarce
- Where there are planned subsequent production runs
- Where medication supplies are pooled across concurrent studies
- Where there is an expiry issue
- Where studies contain complex stratifications
- Where there are planned or possible study changes.

The use of a mathematically sound modeling tool to evaluate clinical supply chains will empower sponsor companies with scientifically sound conclusions on which to base decisions about the chosen supply strategy. Although results may not have any unexpected revelations, simulation will allow quantification of the study supply requirement and optimization of the design and supply chain management strategy. This will provide a new level of confidence in the decision-making process.

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**Table 3. Results of the simulation experiment: metrics for the three supply chain strategies investigated**

Strategy	Summary statistics from 100 simulations: Mean (maximum)			
	Total number of packs shipped	Total number of consignments	Total number of failures to supply desired stock at randomization	Total number of failures to supply desired stock at re-supply visit
<b>Strategy A</b> High trigger re-supply settings. Long prediction window (56 days).	19463 (20047)	730 (762)	0 (0)	0 (0)
<b>Strategy B</b> Medium trigger re-supply settings. Short prediction window (28 days).	16210 (16696)	1268 (1302)	0.11 (2)	0.06 (1)
<b>Strategy C</b> Low trigger re-supply settings. Short prediction window (28 days).	15647 (16134)	1326 (1384)	0.50 (3)	0.39 (2)

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