



# Stimulation by Simulation: Learning from the Adaptive Supply Algorithm

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The ability to project the requirements of clinical trial supplies is something Tom Parke at Tessella values highly; he breaks down the advantages of modelling ahead of trials

Tom Parke joined Tessella in 1996, and has worked on supporting adaptive clinical trials since 1998. He managed the development of the system that allowed Pfizer to run their ground-breaking ASTIN trial, and has worked on three further dose response adaptive trials. He has overseen the development of algorithms, simulation tools and systems to support adaptive trials, as well as integrating adaptive algorithms with existing central randomisation and electronic data capture systems. Whilst currently working on his fifth dose-response adaptive trial, Tom is consulting with a number of international pharmaceutical companies; helping them to define the software systems they require to run adaptive clinical trials.

The development of tools to support clinical trial supply has lagged behind the development of tools for other parts of the clinical trial process – such as trial data storage, electronic data capture and clinical trial modelling. As trials become more complex and trial compounds become more expensive, the cost-benefit case for investing in these tools becomes stronger and stronger.

## SUPPLYING CLINICAL TRIALS

There are many pressures on the supply of drugs during a clinical trial; the first is that the drug must always be available at a centre when a subject is randomised into a trial or when a subject returns for a follow-up visit and needs to be resupplied. Losing a subject because they can't be randomised de-motivates the centre, making them less likely to recruit subjects, causing the trial to take longer. Every extra day spent running the trial is a day less of the compound's patent life once it reaches the market. For a blockbuster drug, a day's patent life is equivalent to millions of dollars in revenue. Being unable to re-supply a subject on a follow-up visit is worse, not only losing the subject's involvement in the trial but also breaking the agreement between the pharmaceutical company and the subject who has agreed to participate in the trial and jeopardising their treatment.

This pressure is longstanding, and has been addressed by keeping the resupply as simple as possible and ensuring there was more than enough supply for the trial, an oversupply of 100 per cent being quite typical. Supply was kept simple by 'pre-randomising' the treatment packs supplied to each centre so that they were simply given out in order to the subjects as they were recruited into the trial. Consequently, a centre didn't need resupplying until it was close to giving out its last treatment pack.

Trials range in size from a single centre, to tens of centres in several countries, to over a 100 centres in countries all over the globe. The determining factors are the number of subjects the trial needs to recruit and how easy it is to recruit people suffering from the condition in question. Phase I, safety trials may only need 30-50 subjects, whereas big Phase III trials to prove to regulators that a compound is safe and clinically effective, may require thousands of subjects. To recruit these sorts of numbers in reasonable time will require using many treatment centres spread across many countries.

In some trials, recruiting subjects is easy and relatively predictable; for example, finding patients to study an obesity treatment ought to be straightforward, but recruiting patients within six hours of them having had a stroke in order to test a neuro-protectant is very difficult and the recruitment process is unpredictable.

For many types of trial we do not know ahead of time how many subjects each centre will recruit into a study. Typically, around half of the centres will recruit no subjects or only one subject, whereas it's common for a small number of centres to be jointly responsible for over half the total number of subjects recruited. This uncertainty as to where the supply will be needed is the biggest in drug supply management.

**The current supply solution for centrally randomised trials is typically to have a two-tier supply chain – a central supply depot and regional supply depots supplying centres in a particular country. Country depots allow the drug supplies to a country to be batched up to reduce the overheads that are sometimes associated with importing clinical trial drugs.**

### NEW PRESSURES

There are new pressures now arising from the difficulties experienced by the pharmaceutical industry. Effective new compounds are becoming harder to find and develop – the number of new drug registrations is falling, and the time and cost of development is climbing (1). Society and regulators are becoming increasingly sensitive to potential safety issues; the diseases where there is still no effective treatment are usually the ones that are harder to study, and the compounds being found are typically harder and more costly to manufacture.

One of the ways in which pharmaceutical companies are trying to redress the balance is by running smarter and more sophisticated clinical trials and these require central randomisation to assign a subject to a dose at the last possible moment. Initially this was designed to allow the randomisation to be balanced not just across the whole trial but also within potentially significant sub-groups of the subjects (old and young, male and female and so on). Increasingly, it is to allow the randomisation to select which dose to give at the last possible moment, in order to optimise the way the trial learns about the dose-response of the compound.

One consequence for the drug supply is that a centre needs resupplying as soon as they are close to giving out the last treatment pack of any one of the different types. If a trial has four treatment arms, and each centre is initially supplied with two treatment packs of each type, with a pre-randomised scheme a centre hasn't run out of supplies until eight subjects have been randomised. With central randomisation, a centre may have run out of one of the treatment arms and need resupplying after only two randomisations.

A further pressure is the changing nature of the compounds being tested. They tend to be increasingly expensive to manufacture and may only be available in a limited amount, making it important to optimise the usage of the

drug on trial. This is the biggest opportunity for delivering benefits to the business through improving the way drug supply is performed during the trial. If we can develop sophisticated ways of supplying trials that still minimise the risk of losing a subject, whilst reducing the level of oversupply required, we can either reduce the amount of drug required to run a particular trial or increase the number of subjects the trial can plan to recruit. Further complexities are introduced if the treatment packs have a shelf-life shorter than the duration of the trial or if the supply is dependent on batches of treatment packs that are only being manufactured after the trial has started.

### SUPPLY REGIMES FOR CENTRAL RANDOMISATION

The current supply solution for centrally randomised trials is typically to have a two-tier supply chain – a central supply depot and regional supply depots supplying centres in a particular country. Country depots allow the drug supplies to a country to be batched up to reduce the overheads that are sometimes associated with importing clinical trial drugs. The supply regime also has two streams. There is resupply to meet predictable need – subjects who should be returning to receive their next treatment pack – and supply to meet the unpredictable need for subjects being randomised. This latter supply stream is usually managed by setting initial, floor and ceiling stock levels and resupplying centres whenever an item of stock reaches its floor level, so that all their stock is back at the ceiling level. The levels are set for each centre depending on how fast it is expected to recruit. Typically, a number of families of levels (for



example ‘fast’, ‘moderate’ and ‘slow’) are set up and centres are pre-assigned to a level.

The biggest weakness of this scheme is when the supply stream for ‘unpredictable’ demand is used to cope with the expiry of batches. This leads to a spike in demand from the depots and in order to meet it, the depots have to hold large stocks (have large ceiling levels). Once the expired batch has been replaced, the depots will be restocked to these ceiling levels, even if there are no more batches that are due to expire. This is inefficient and wasteful. A second weakness of the scheme is its inflexibility; the floor and ceiling stock levels for a centre remain the same unless manually altered.

## TOOLS TO HELP

There are two ways in which software can help with this situation, both ideas coming from software developed for controlling the randomisation in clinical trials. The first is to implement a software model of the supply in a clinical trial, so that the supply can be simulated, and the second is to develop adaptive resupply algorithms.

A simulator for supply in a clinical trial will model the randomisation of patients at centres, the resupply of patients and the shipment of treatment packs from the central pharmacy to depots and then on to centres. The modelling of the dispatch of shipments will follow the rule of the actual supply system. The modelling of when patients turn up for randomisation, and the time shipments take to arrive, will use random sampling from an appropriate probability distribution (to reflect the unpredictability of the real world).

By simulating the trial a large number of times (say 1,000) we can obtain statistics of how well a particular supply solution is likely to cope with the actual trial – that is the odds of failing to recruit a subject, the likely number of shipments that will be made, and the likely total number of treatment packs that will have to be shipped. We may wish to gather data over a number of scenarios in which we vary – for example, the number of fast and slow recruiting centres. Having done that, we may want to re-run all these simulations with different trial designs.

What if we use smaller packs so subjects have to return to be re-supplied? What if we use a low initial level but a high ceiling? These simulations help us optimise the supply in the trial, or evaluate the impact of trial design decisions outside the control of the supply team.

The simulator needs to be compatible with the actual system used to control the supply in two ways. First, it must accurately implement its resupply rules so that the results of the simulations can be trusted. Secondly, it should be able to load data from the actual system, so that it can simulate the supply of a trial from some mid-point to the end. This allows the simulator to foresee if there are any likely supply problems given the way the trial is actually progressing. In particular, do we still have enough material and is it in the right places?

An adaptive resupply algorithm is like repeatedly running the simulator during the trial and adjusting things like the floor/ceiling resupply levels. By continuously re-estimating recruitment rates and delivery times based on actual data, the system can build and maintain probability models for these values. This would allow a single resupply rule for the unpredictable demand across all the centres of the form – “when a probability that a centre’s supply will last for the next month drops below 50 per cent, resupply it to raise that probability to 99 per cent”. This replaces the manual, ad hoc, setting of floor/ceiling levels for all the centres and the need to reset them during the trial.

## CONCLUSION

Tools to simulate clinical trials can improve our estimates of the amount of material required for the trial and optimise the design of the supply for the trial. The same simulators can also be used to monitor the trial as it runs so we see what risks we are running if the real world fails to meet our expectations, and assess the likely impact of any interventions to minimise those risks. Using a smarter – self-tuning – adaptive supply algorithm will make the job of optimising the design a lot easier and automatically adjust to some of the risks of unpredictable recruitment. ♦

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### Reference

1. FDA's paper on its Critical Path Initiative  
<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

