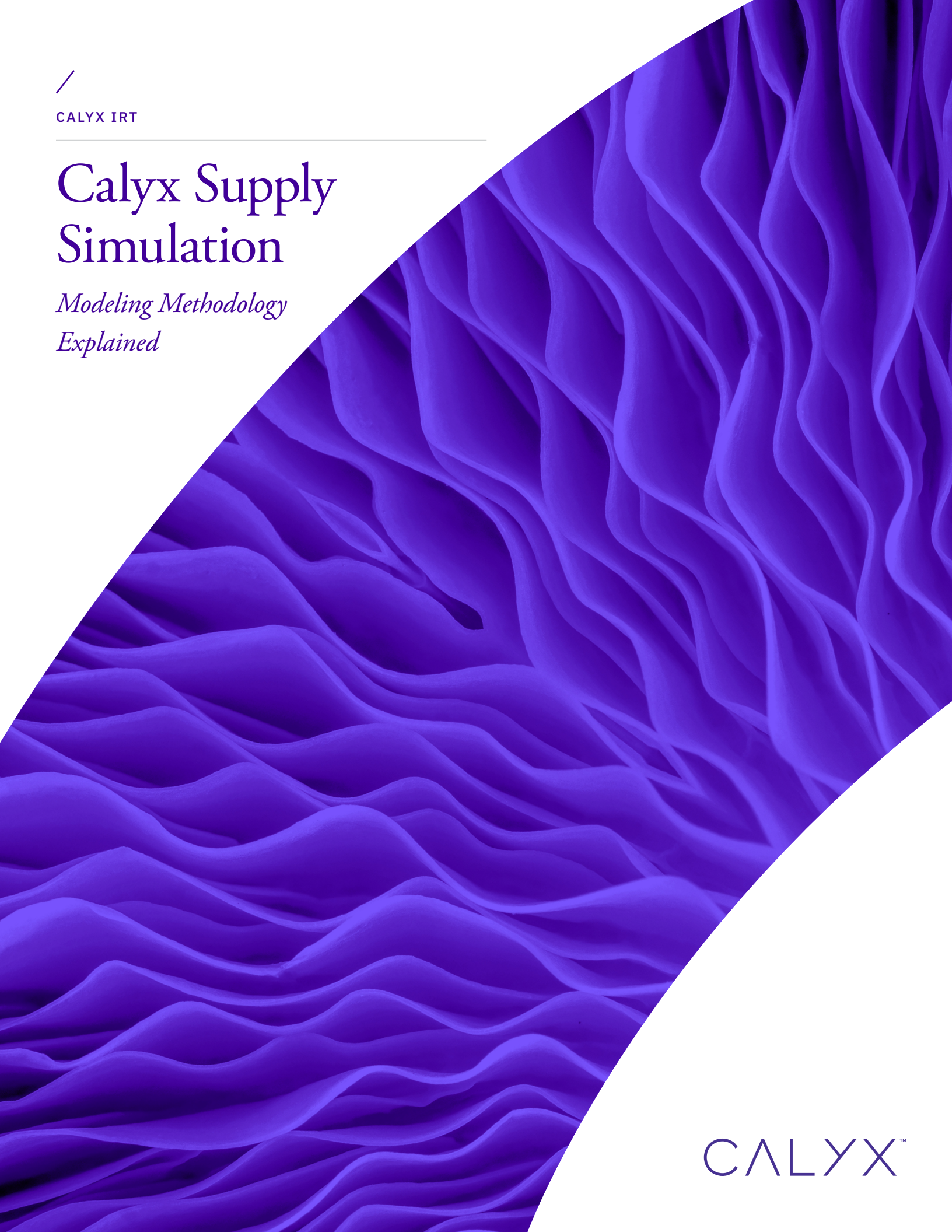
CALYX IRT

Calyx Supply Simulation

Modeling Methodology Explained



CALYX™

Optimize with Supply Simulation

Calyx provides a Supply Simulation service to help sponsors and CROs estimate the right quantity of medication that should be packaged and when, both to start the study and overall.

The aim is to find the optimal supply chain and site and depot stock amounts needed to ensure patient dispensation while reducing wastage.

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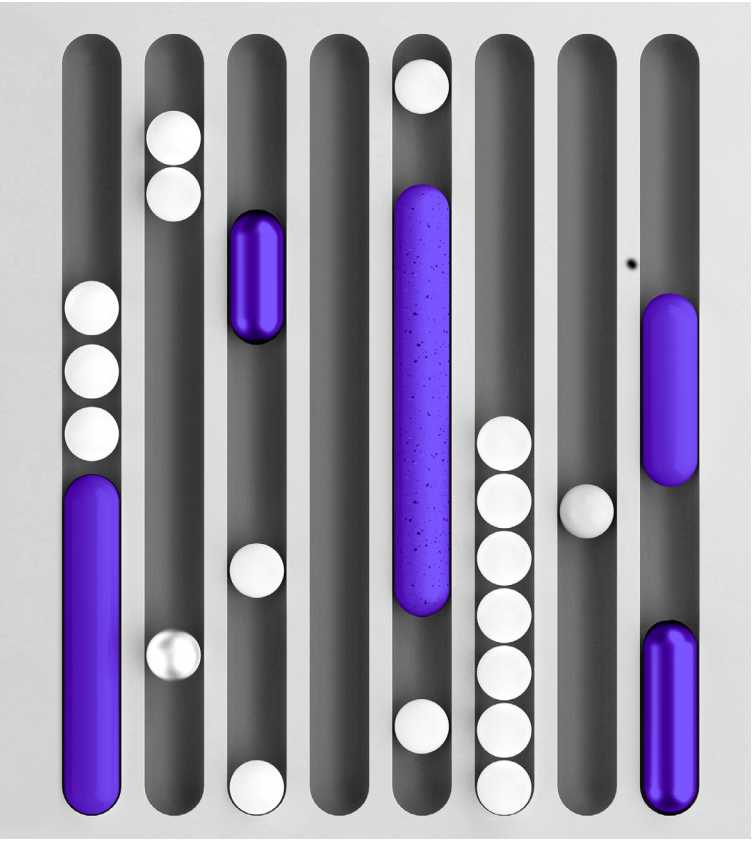


Calyx will estimate study supply requirements based upon sophisticated simulation modelling methodology, which:

- Simulates patient progression through the dispensing events of a trial
- Considers real-life variability and "what if" scenarios
- Uses 50+ design parameters closely mimicking an IRT system, including:
  - Fixed parameters, e.g., trial design, supply chain, IMP types
  - Variable parameters, e.g., titration, visit windows, % of damaged IMP

Simulation or Forecast?

Forcast

A forecast is defined as a prediction or estimate of a future event or trend. A forecasting tool takes data as a point of entry and creates a likely state of the data in the future.

Simulation

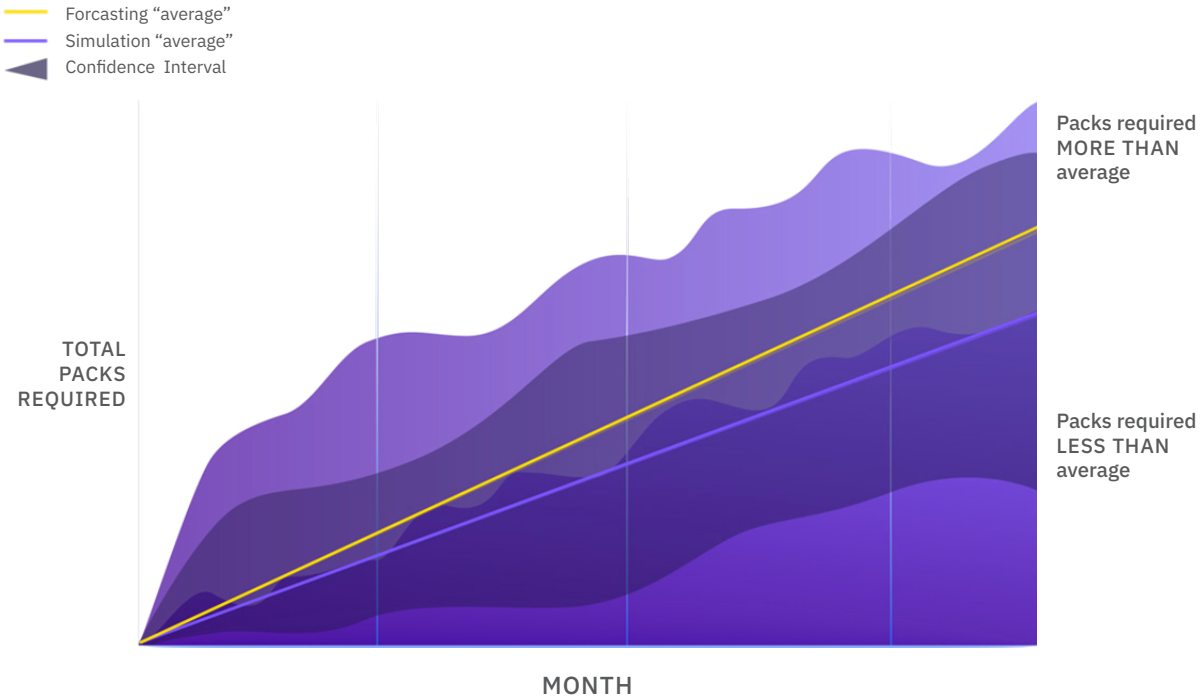
A simulation considers variable factors that could impact the data used as entry point. In clinical supplies, a simulation considers the likelihood of some events occurring, and how they affect medication consumption.

Based on multiple simulations, averages are obtained on parameters such as overage, number of shipments and the risk of not being able to supply patients – these estimates are more accurate than forecasting estimates since we consider more factors and real-world variability.

Simulations provide us with ranges (or confidence intervals) that give us a sense of what we can expect to happen in the study with certain degrees of confidence. Therefore, simulations can be used to define what the optimal supply strategy should be e.g., how much buffer stock should be held at sites and depots.

Simulations also allow us to investigate several "what if" scenarios – since some parameters will be unknown up-front i.e., educated guesses – which is not possible with static forecasting.

Below is a Plot of Total Kits Required Over Time



Simulation Run

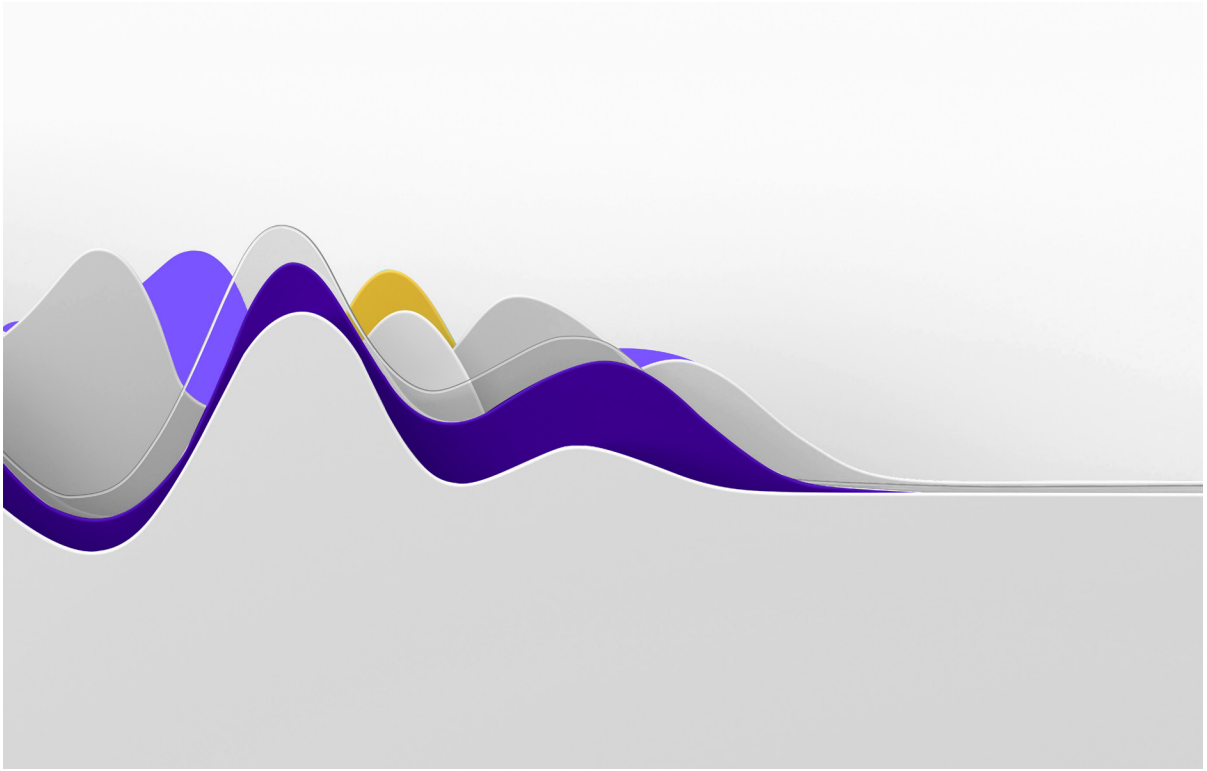
We refer to a simulation "run" as a single representation of what might happen in the study, resulting in the estimation of the total kits required over time for the execution of the study.

By running multiple simulations (multiple runs), we can obtain an "average" for the total kits required, which is more precise than a simple forecasting average.

Let us suppose that we decided to base the number of kits required for the study on the simulation average, then:

- If the actual study behaved similarly to any of these *lower* simulation runs, we would be producing more kits than would be required
- If the actual study behaved similarly to any of these *higher* simulation runs, we would have insufficient kits produced

It is vital that we do not only consider the average, but also information provided across the many simulation runs. This cannot be achieved via a static forecasting approach.



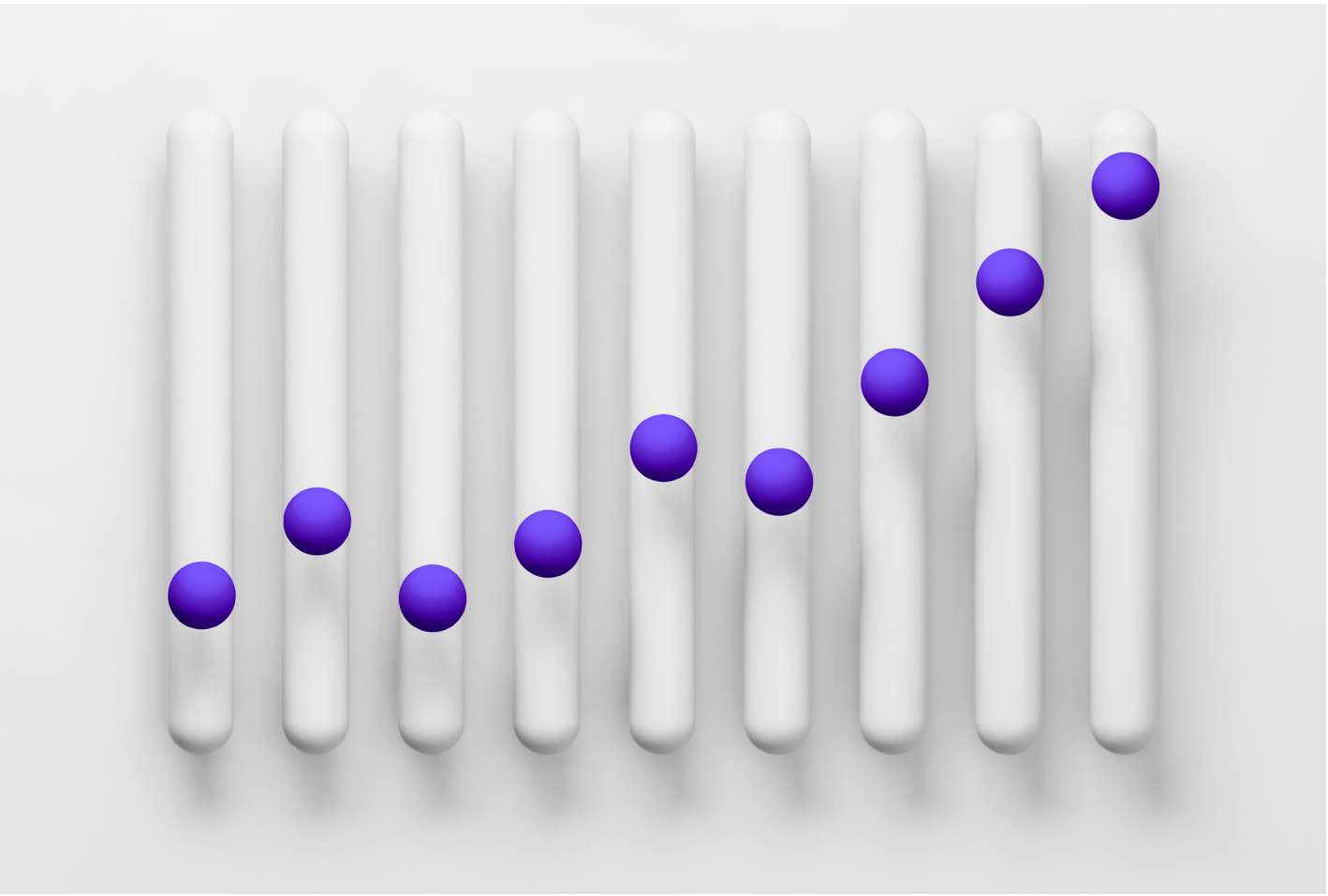
Monte Carlo Simulation Technique

Some of the key elements of a clinical trial are variable, such as patient recruitment. It is important that the modelling approach incorporates variability into the study simulation so a full range of outcomes can be studied. Monte Carlo simulation allows such an approach, sampling values for key variables from underlying specified distributions of some of the input parameters.

Monte Carlo simulation applied to patient recruitment

While the average study recruitment for a group of sites may be e.g. two patients per site per month, there is a chance that an individual site may recruit zero patients or as many as six or seven patients in any month.

Monte Carlo simulations account for this variability by using a random number generator to determine each site's recruitment for each month of the simulation. The random number generator is weighted to return numbers in the proportions that underlie the theoretical distribution. This process is like rolling a die to mimic real-world variability.



Simulating the Trial

Simulations are based on underlying, distributional assumptions which help incorporate real-world variability into our evaluation of future trial supply requirements.

We will simulate the patient pathway through the trial for all patients; this will then be repeated many times pre-study start.

Each simulation run replicates a running of the entire trial on a day-by-day basis; this includes:

- Activation of new countries, with activation of new sites within these countries with dates chosen randomly with a defined activation period
- Shipping of initial supplies at site activation, selecting the delivery time from a predefined range and randomly damaging any packs should there for instance be temperature sensitive material
- Patient visit registrations, from screening, to randomization to scheduled dispensing visits as per protocol time windows, to withdrawal and completion
- Patient up and down titrations, if applicable
- Dispensation at each visit according to the protocol schedule of assessments
- Resupplying sites and depots as their stocks get low and hit the triggers

Parameters

Calyx Supply Simulation estimates study supply requirements based upon sophisticated simulation modelling methodology which uses 50+ parameters that closely mimic an IRT design.

The parameters can be classified as either fixed or variable:

- Fixed parameters relate to trial design, supply chain or study performance. Study design parameters include things such as the sample size, the number of countries and sites, the treatment groups and their allocation ratio etc.
- Fixed supply chain parameters include the pack types and the dispensing schedule, the central and local depot configuration, the supply scheme parameters, dates that packaging campaigns will come on stream and the expiry dates associated with the medication etc.
- Variable parameters are those that are subject to random variation and are defined in one of two ways:
  1. A range from which values are sampled. Examples include visit windows surrounding patient visits or the duration of delivery from depot to site
  2. A probability or rate. Examples would be the rate of titration from one visit to another, the withdrawal rate etc.

Some of these parameters are shown below:

FIXED PARAMETERS	VARIABLE PARAMETERS
STUDY DESIGN PARAMETERS	
Sample size	Patient visits /schedule of assessments
Number of countries	Visit windows
Number of sites	
Treatment groups	
Allocation ratio	
Randomization method	
SUPPLY CHAIN PARAMETERS	
Pack (IMP) types	Depot-to-depot shipment delivery times
Patient dispensing schedule	Depot-to-site shipment delivery times
Patient visit prediction windows	Damaged shipments (percentage)
Central and Local Depot configuration	Damaged packs (percentage)
Site and Depot trigger levels	
Packaging campaigns	
Expiry dates	
STUDY PERFORMANCE PARAMETERS	
Country activation	Recruitment rates
	Withdrawal rates
	Titration rates
	Center activation

If information is not known, for example recruitment rate, Calyx can support with finding plausible rates given our experience that meet the expectation of the estimated study timelines. Alternatively, Calyx can simulate different values for the unknown setting to investigate the impact of a low, medium, or high value.

Simulation Process: Understanding Expectations

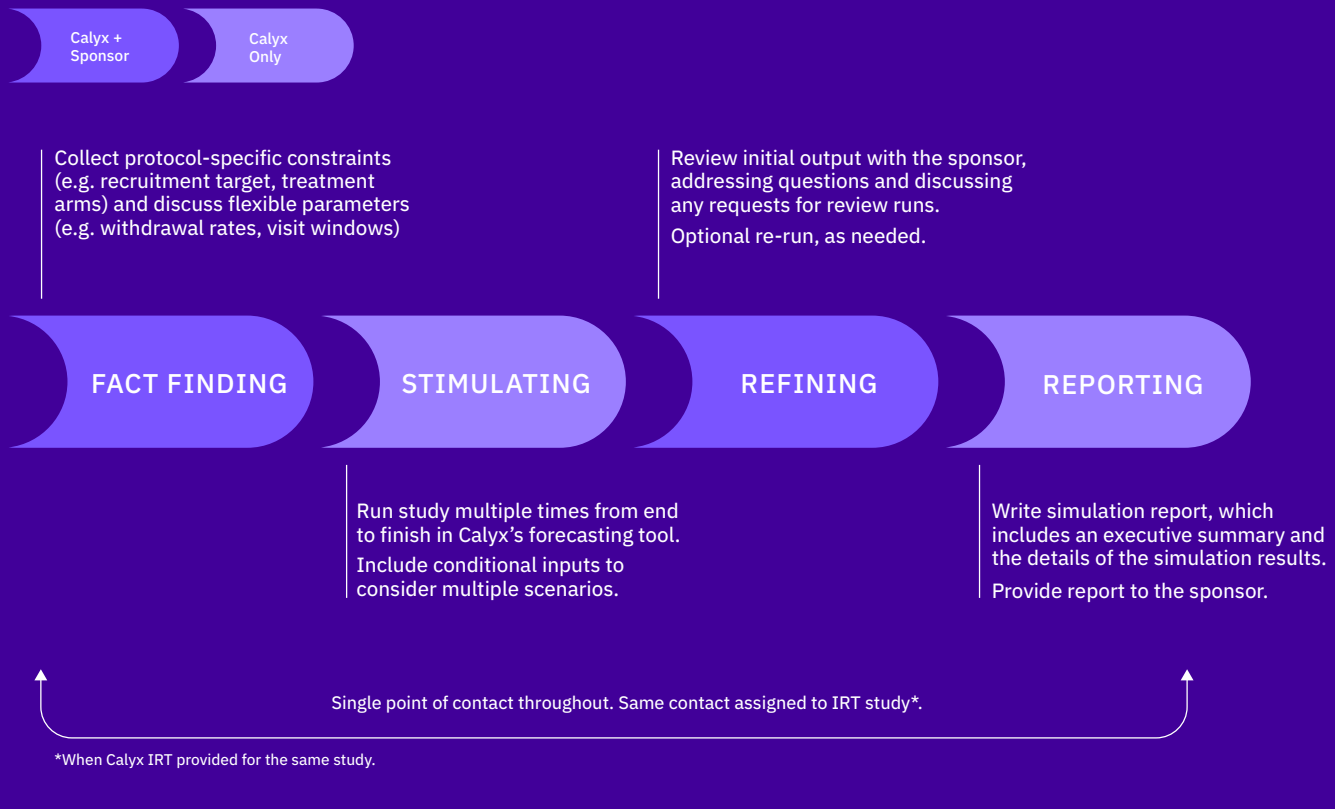
The simulation process is an iterative one, based on inputs from the sponsor and understanding of their expectations and constraints.

The output of a simulated scenario is reviewed against the expectations and settings altered before providing results to the sponsor. For example, if the numbers of supply failures are too high, or if a local depot could be removed to reduce wastage.

The process of amending inputs and considering outputs continues until the sponsor is satisfied with the solution.

Calyx's supply chain analysts will work with the sponsor/drug supply team to:

- Consult on choice of 'estimated' parameter values
- Understand key factors and objectives important to the sponsor
- Determine ideal scenarios to meet the sponsor's objectives



Output

Many different situations could arise randomly as part of a simulation, and we report out the summary measures across all those simulated outcomes. This allows the study team to understand:

- What is the maximum amount of medication that might be needed, or the amount needed to cover 95% of the simulation runs
- The average amount of medication needed
- The minimum amount of medication needed

Calyx will provide a report following all simulation runs, which will include:

- The quantity of medication needed of each pack type for the packaging run dates confirmed by the sponsor
- Stock-out measures of failed randomization and failed visits, with the medication quantities needed to support these measures, which indicates both the maximum number of kits utilized by the study design and the 95th percentile, which we would normally consider in relation to determining the quantity of kits to manufacture

Key information and recommendations will include:

- Optimal IRT settings that reduce failed visits and failed randomization, in addition to maintaining an ideal shipment frequency – these include:
  - Buffer stock amounts (covering randomization and replacements)
  - Trigger and resupply settings for site (and depot) – appropriate supply strategies for the study based on dispensation plan and recruitment rate
  - Prediction lookahead values for shipments – the number of days ahead the IRT should ensure needed medication is on site for
- Additional target measures can also be reviewed, such as overage percentage and number of shipments for a design where shipping costs are high relative to the medication cost.

Reporting

An example of the results reported:

STOCK-OUT SUMMARY						
FAILED RANDOMIZATION						
	Mean	Median	Standard Deviation	Minimum	95th pct	Maximum
Runs with >=1 Failed Randomisation (%)	20.00	20.00		20.00	20.00	20.00
Number of Failed Randomisations / Run	0.20	0.00	0.45	0.00	0.80	1.00
Number of Unique Patients with Failed Randomisations	0.20	0.00	0.45	0.00	0.80	1.00
FAILED VISITS						
Runs with >=1 Failed Visit (%)	100.00	100.00		100.00	100.00	100.00
Number of Failed Visits / Run	2.00	2.00	0.00	2.00	2.00	2.00
Number of Unique Patients with Failed Visits	1.00	1.00	0.00	1.00	1.00	1.00

Medication needed to support the above stock-out measures, which indicates both the maximum number of kits utilized by the study design and the 95th percentile, which we would normally consider in relation to determining the number of kits to manufacture:

MEDICATION SUMMARY							
PACKS UTILIZED							
Pack Type	Batch	Mean	Median	Standard Deviation	Minimum	95th PCT	Maximum
ACTI_150	1001A	4,140.40	4,201.00	162.93	3,922.00	4284.00	4,286.00
ACTI_150	1002A	2,316.20	2,255.00	133.47	2,192.00	2492.60	2,522.00
PLAC_150	1001B	3,146.00	3,139.00	111.77	3,006.00	3283.00	3,308.00
PLAC_150	1002B	2,018.80	1,982.00	115.79	1,909.00	2169.60	2,194.00
PACKS DISPENSED							
ACTI_150	1001A	1,307.80	0.00	0.00	0.00	2,832.60	4,140.40
ACTI_150	1002A	1,803.00	0.00	0.00	0.00	513.20	2,316.20
PLAC_150	1001B	1,643.60	0.00	0.00	0.00	1,502.40	3,146.00
PLAC_150	1002B	1,762.80	0.00	0.00	0.00	256.00	2,018.80

Summary

Calyx's trial supply simulation and forecasting consultancy service is provided by our in-house expert supply chain analysts to evaluate:

- Amount of study medication required, both to start the study and overall
- Optimal site supply settings
- Optimal site and depot buffer stock levels to ensure dispensation whilst reducing wastage
- Timing and content of packaging campaigns
- How long the planned quantity of study medication will last

Contact hello@calyx.ai to learn how Calyx Supply Simulation can help improve efficiencies in your clinical development program.

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Reliably solving the complex.

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Contact us at: hello@calyx.ai