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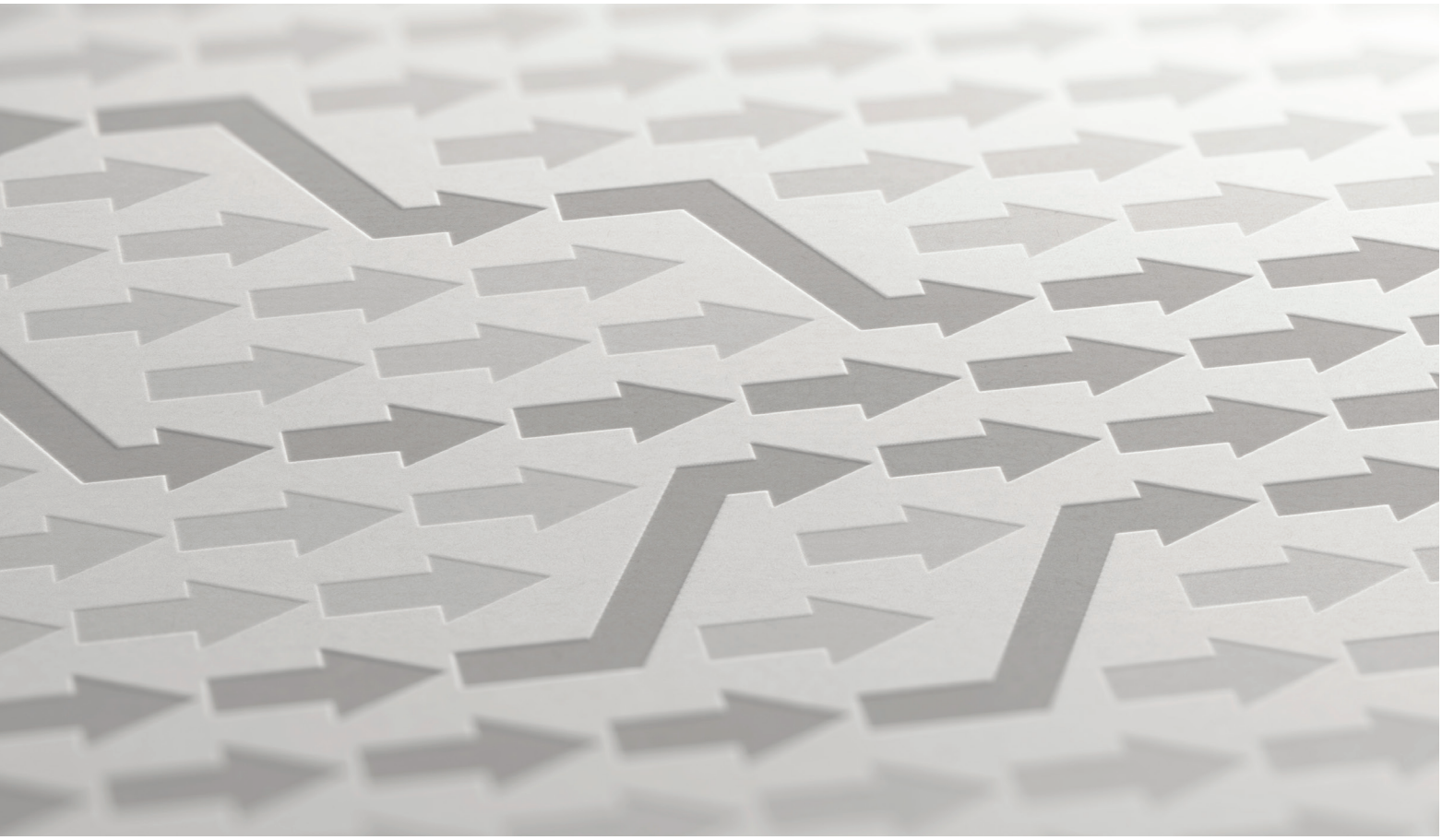

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WHITEPAPER

Clinical trial simulation: Advanced modeling techniques enable data-driven supply chain planning

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Abstract

The logistical challenges of matching drug supply to research needs in clinical trials have increased by an order of magnitude in recent years. To manage the growing complexity and respond to competitive pressures, drug sponsors are increasingly looking to technology to optimize drug supply planning. The integration of supply chain simulation into early clinical trial planning minimizes risk in an uncertain supply chain environment, improves supply chain outcomes, and helps streamline time-to-market for innovative therapies.

Executive summary

Matching drug supply to research needs in clinical trials is an ongoing challenge. Every step of the clinical development process has some degree of uncertainty—from the drug itself and how it's manufactured to the patients enrolled in the clinical trial. The complexity of supply chain planning is further exacerbated by the evolving clinical trial ecosystem which is subject to changing import/export regulations, inventory and storage considerations, patient recruitment challenges, aggressive timelines, cost constraints, and unforeseen pressures exerted by the COVID-19 pandemic.

Keeping all the moving parts well coordinated to get investigational therapies to patients on time and on budget with as little waste possible requires careful planning and accurate forecasting of clinical supplies. This white paper will provide a roadmap for sophisticated supply chain modeling using advanced simulation tools in which all the possible scenarios that could affect the supply chain are accounted for in the strategy. Specifically, the report will offer critical insight into how simulation supports evidence-based decision making to achieve the following objectives:

- Accurate planning of initial trial supplies
- Optimization of the entire clinical supply chain to reduce costs and support patient centricity
- Maintenance of supply chain robustness/integrity in the face of change
- Risk mitigation

Simulation tools can transform clinical supply chain management by helping teams set the right priorities from the outset, anticipate the likelihood of disruption, and find the best balance between risk and budget.

Introduction

Simulation is a critical tool across industries for gaining insight into complex systems and behaviors. The use of algorithms and equations to create digital models of process operations provides a safe, efficient, and cost-effective way to explore multiple "what if" scenarios for planning and decision making.

Ensuring uninterrupted supply and quality assurance of products while minimizing cost and waste is the holy grail of clinical trial supply chain management.

In pharmaceutical manufacturing, this "future vision" is especially valuable to the management of clinical trial supply chains, which are inherently unpredictable and complex. Ensuring uninterrupted supply and quality assurance of products while minimizing cost and waste is the holy grail of clinical trial supply chain management. Achieving that goal requires planning for the ideal state in which the planned clinical trials is conducted with no deviation from the approved protocol with no discrepancies between the supplies needed and the supplies available to conduct them. In this version of reality, patient recruitment is predictable, visit attendance is 100%, timelines are met, and planned budgets represent the upper limits of trial costs. However, the growing complexities of the clinical trial space necessitate planning that considers and incorporates a number of contingencies that could affect supply chain management, ranging from protocol revisions, recruitment delays, and changing import/export regulations to the supply chain disruptions caused by a global pandemic.

COVID-19 and the supply chain

At no other time has there been such an unexpected and disruptive global event as the COVID-19 pandemic. Concerns about the SARS-COV-2 virus swept their way to the top of industry priority lists as clinical trials in other areas were disrupted and emergency production, emergency shipments, and high resource demand contributed to what felt like chaos across the board. Disruptions in supply chains and uneven availability across countries left companies waiting for their materials, patients waiting for their medications, and many patients and companies unprepared to handle the subsequent increased costs. Since the beginning of the pandemic, clinical trials have been ramping back up [Adams 2021], but new strains of the SARS-COV-2 virus along with the industry's heavy reliance on hard-hit areas of the pandemic for raw materials, intermediates, and active pharmaceutical ingredients (APIs) are likely to remain substantial concerns for quite some time.[2, 3, 4]

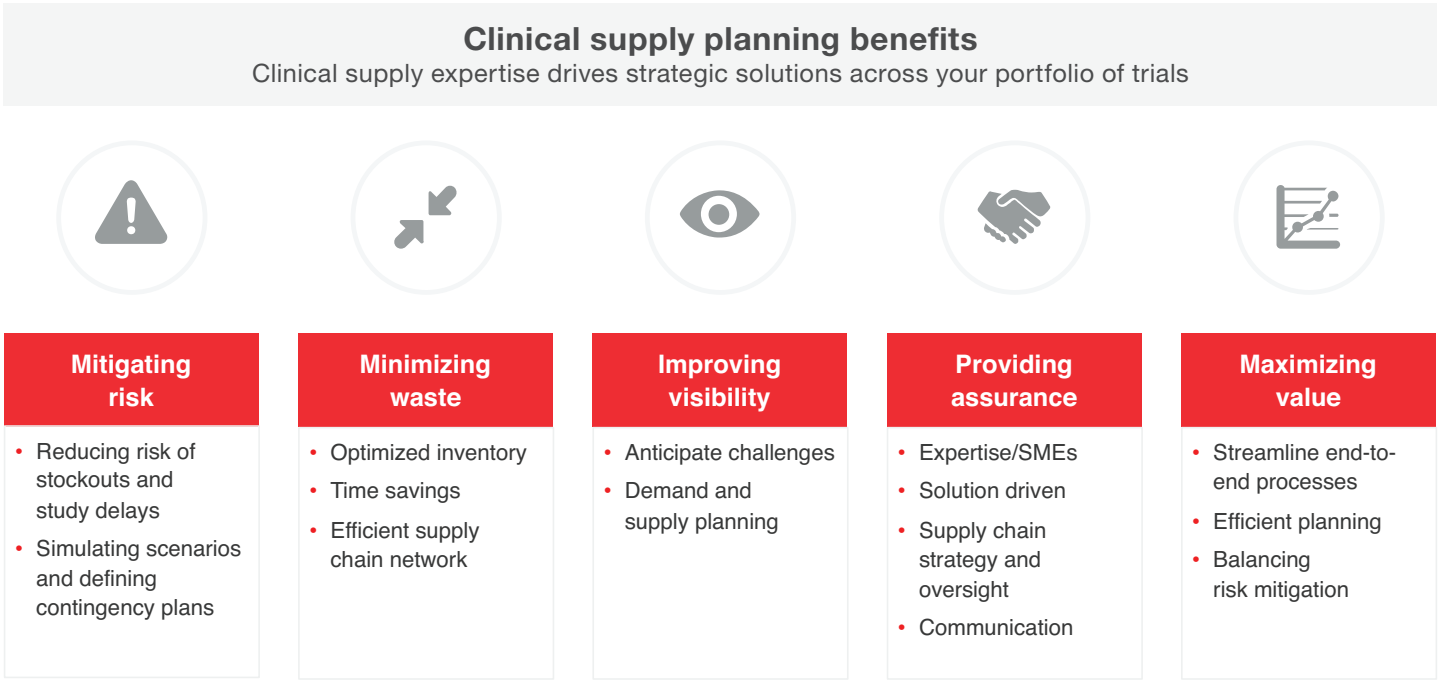
In addition to the COVID-related contingencies, pharmaceutical companies must also be prepared for the supply chain implications of the increasing complexity of the new drugs in development, compressed timelines, changes in the regulatory environment, and specific human factor and safety concerns.

Successfully navigating the evolving clinical trial supply landscape requires early planning and close collaboration with supply chain strategy and logistics experts who can guide accurate forecasting and simulation. From risk mitigation to value maximization, the benefits of integrating clinical supply expertise early in the planning process are described in Figure 1.

Clinical trial simulation: A key component in successful early planning

A simulation is an exercise that allows study teams to plan for what is likely to happen versus what might happen. One well known example of simulation in drug development is molecular modelling. Another use is Monte Carlo simulation of clinical trials. Unlike traditional simulation which treats the model parameters as fixed values, Monte Carlo simulation treats them as random variables.

Figure 1



Monte Carlo methods are used to determine the probability of certain outcomes based on uncertain circumstances. Essentially, numerous scenarios are generated by running iterations of known parameters, and the outcomes are then observed. The value of these computer algorithms is that they allow planning teams to proactively identify risks to desired outcomes and test the effectiveness of various mitigation strategies. The process generally includes several rounds of fine-tuning to reach an optimized supply plan that covers all phases of the study and balances risk and cost.

Simulation for trial planning and supply chain optimization

With the growing volume and complexity of clinical trials, supply chain planning should begin at the earliest possible stage, ideally during the creation of the first version of the study synopsis.[6] The most meaningful value from a trial planning simulation is optimizing the balance of risk, overage, shipments, and cost across the entire life cycle of the trial, from first patient in to last patient treated.

Input for the planning simulations may come from previously completed protocols, examined separately, or pooled to determine similarities to the needs of the current trial. Considerations at this phase may include visit schedule design, comparator choices, and blinding strategies, each of which could influence risk and/or cost.

Clinical study planning teams can derive value from the simulation of various supply chain scenarios. All possible scenarios that could affect the supply chain should be accounted for in the strategy (see “Strategic partnerships add value to simulations” on page 8). Experienced simulation teams can offer tailored visualizations based on statistical analysis to advise on the optimization of packaging design, supply network, and visit intervals. Other components, such as quantities, dates, settings, ancillaries, enrollment scenarios, and patient behavior scenarios, can also be considered and planned through simulation, leading to a better understanding of the potential impact of these factors and supporting evidence-based decision-making in the project plan and supply chain strategy.

Case study: Early planning with simulation cuts planned bulk drug product by half

Thermo Fisher supported a global clinical trial program of three studies conducted at 585 sites and involving 2,049 patients in Europe, the Middle East, Asia, and the United States. The studies utilized the same pack type, but with separately labelled supplies. Enrollment for the studies ranged from 9 – 12 months, and dosing lasted for 12 months.

The strategy for optimizing the supply for this program included use of a study simulation tool early in the planning process to assess demand, including what quantities would be needed and on what timeline. Clinical supply chain and simulation experts collaborated to create a simulation, which was repeated multiple times based on milestone and demand assumptions.

The resulting simulation led to a **54% planned reduction of bulk drug product** while mitigating risk across the supply chain. This represented a substantial reduction in the supply chain budget, including **cost savings of 180,000€ in packaging** alone and another **370,000€ in shipping costs**.

Simulation for supply chain management and agility

Nearly 20 years ago, Peterson et al. described a set of simulation experiments to investigate supply strategies and their effect on overage[7]. Output from the simulations showed that their proposed automated system for supply management yielded overages as low as 47% compared to that of traditional non-automated systems with overages as high as 75%. They were also able to compare site- versus country-stratified delivery schemes to reduce the probability of supply failures. Today, those simulations would need to account for modern changes in supply chain dynamics- including the increased use of interactive response technology (IRT) and the effects of unforeseen events such as the COVID-19 pandemic. The beauty of using a simulation to plan for supply chain management is that, as new circumstances arise, analytics teams can change the inputs to the simulation (in near real-time) to predict how those changes will ultimately affect outcomes. At this point, course corrections can be considered, and a new optimal scenario can be envisioned.

Simulation for risk mitigation

A few studies have been conducted using simulation to optimize study costs against the risk of stockouts but few have considered fluctuating inventory policies, demand, and other dynamic factors.[8, 9]

Simulations can show the study team how changes in one or more of these factors affect the others (see example in Figure 2). These outputs are critical for budget planning, in particular. Running simulations using variations of these factors will illustrate the effect of that variation on overall risk and costs to guide decision-making.

Figure 2

KPI	Scenarios		
	SCN6	SCN3	SCN2
Missed visits	5.19	9.24	15.85
Comparator overage	53.91%	46.65%	43.50%
IMP overage	53.99%	49.47%	48.55%
Depot shipments	120	111	104
Site shipments	2,369	2,365	2,363
Total cost	26,012,357.96	24,939,888.24	24,384,583.42

Summary			
Category	A	B	C
Risk	Lowest	Optimized	Highest
Budget	Highest	Optimized	Lowest

Scenario	Descriptions
A	Lowest risk, highest coverage, shipments and cost
B	Balance of risk, overage, shipments and cost
C	Highest risk, lowest coverage, shipments and cost

Strategic partnerships add value to simulations

In most simulation exercises, the inputs are as important as the outputs. The more informed the simulation is, the more accurate its predictions about outcomes can be.

A contract development and manufacturing organization (CDMO) that has demonstrated expertise in clinical trial simulation can add value at this stage. Some CDMOs not only house experts in the conduct of simulation methods, but they also maintain an extensive network of contacts and trusted relationships with subject matter experts and suppliers who can help inform a high-performing simulation. In addition to a knowledge of the fundamentals of simulation development, study teams should look for partner who understands the limitations (e.g., size and complexity requirements) of clinical trial simulations and how to manage around them. An experienced CDMO should be able to support both small and large biopharma companies through trial simulations.

Conclusion

Accurate forecasting is critical, especially in today's clinical research ecosystem. When resources are limited and time is essential, good planning and monitoring during execution can minimize resource needs, streamline processes, and reduce costs. In addition, the models provide a powerful tool for setting and managing leadership expectations, communicating with internal and external stakeholders, determining realistic timelines, and calculating budget.

With the right set of inputs and assumptions, coupled with expertise in data analysis and visualization, simulations in early clinical trial planning can be a game changer for getting investigational therapies to patients when they need them.

For more information about using clinical trial simulation and global clinical trial solutions, visit Patheon.com

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About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. Built on a reputation for scientific and technical excellence, we provide pharma and biotech companies of all sizes instant access to a global network of facilities and experts across the Americas, Europe, Asia and Australia. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ programs for large and small molecules help you balance speed and risk during early development so you can file your IND quickly and successfully. Digital innovations such as our mysupply Platform and Pharma 4.0 enablement offer real-time data and a streamlined experience. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

Simon Caviezel

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Simon is a program director in EMEA for Thermo Fisher Scientific's Clinical Supply Optimization service. Bringing more than nine years of industry experience to the business, Simon has a broad knowledge and a wealth of experience managing clinical study supply on both local and global trials. During his time in the industry, Simon has developed a thorough understanding of how supply chain planning must align with risk mitigation to be able to reliably provide the right product to the right patient at the right time.

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As senior clinical supply chain manager, Benedict leads a global team of clinical supply chain specialists supporting customers in the setup and optimization of supply strategies, including the execution and analysis of supply chain simulation. He holds a master's degree in biology with a deep specialization in computational neuroscience and has extensive experience in demand forecasting and planning for global studies from inception to closure.

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Published 09/21

ThermoFisher SCIENTIFIC