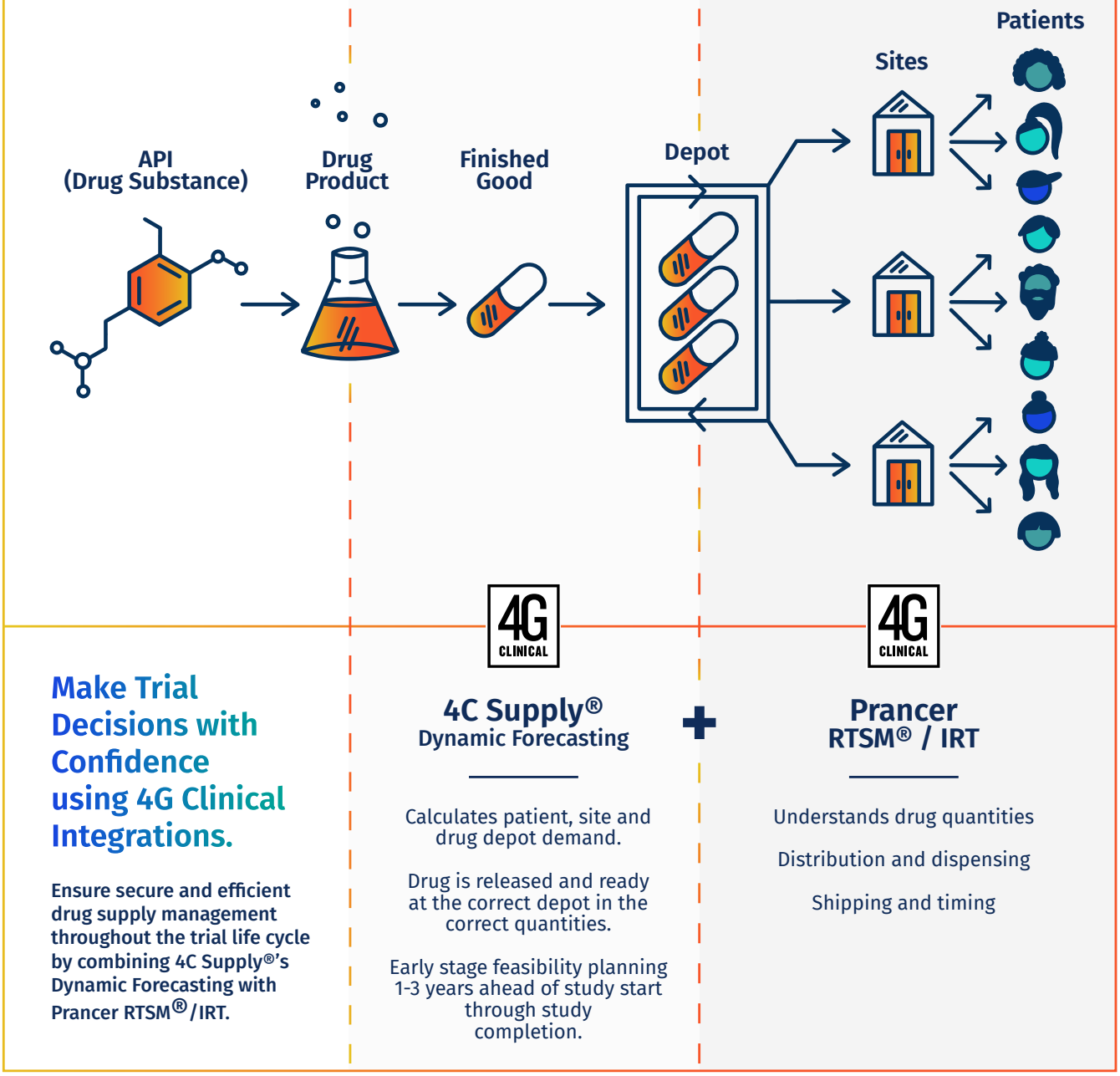
Integrated Technology for End-to-End Clinical Trial Supply Management

Knowledge Sharing Series

There's more to drug supply than just the RTSM

Drug Supply Value Chain



Make Trial Decisions with Confidence using 4G Clinical Integrations.

Ensure secure and efficient drug supply management throughout the trial life cycle by combining 4C Supply®'s Dynamic Forecasting with Prancer RTSM®/IRT.

4C Supply®
Dynamic Forecasting

Calculates patient, site and drug depot demand.

Drug is released and ready at the correct depot in the correct quantities.

Early stage feasibility planning 1-3 years ahead of study start through study completion.

+

Prancer
RTSM® / IRT

Understands drug quantities

Distribution and dispensing

Shipping and timing

For end-to-end management of the investigational medicinal product (IMP) in a clinical trial, the RTSM must be combined with a long term demand and supply forecasting tool, such as 4C Supply®. This can model the demand and supply well before the first patient is screened to define an efficient supply strategy from IMP production to patient dispensing. During study conduct, the demand forecasting tool can integrate data from the RTSM in real time to forecast the remainder of the study based on the current situation, allowing the drug supply strategy to be adapted when necessary as the trial unfolds.

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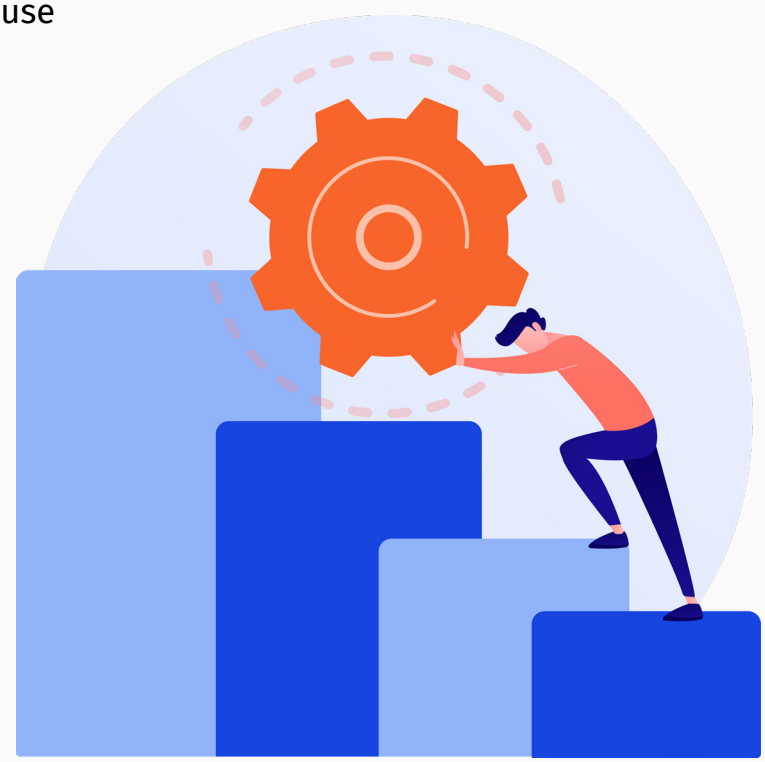
Each clinical trial can bring many challenges for drug supply managers

Each and every trial can bring its own unique challenges, but there are a few things that drug supply managers end up dealing with even when everything goes to plan. Additionally, drug supply managers are often sent requests to provide comparisons or answers to what-if scenarios for all the things that might happen. When using a forecasting tool like 4C Supply®, the drug supply team can leverage the forecast to make data driven decisions and move forward with confidence knowing the decisions around study drug production and resupply settings are based on real forecasting models. There's no need to rely on spreadsheets with patient demand plus an aligned percentage of overage, or old fashioned speculation.

Supply managers can also use the integrated reporting engine to communicate the rationale for supply strategy decisions with external stakeholders. The graphs below are examples of such a report. They show snapshots of the primary depot over the duration of the trial, with data on the incoming supplies, inventory level, buffer level, demand and expected expiries.



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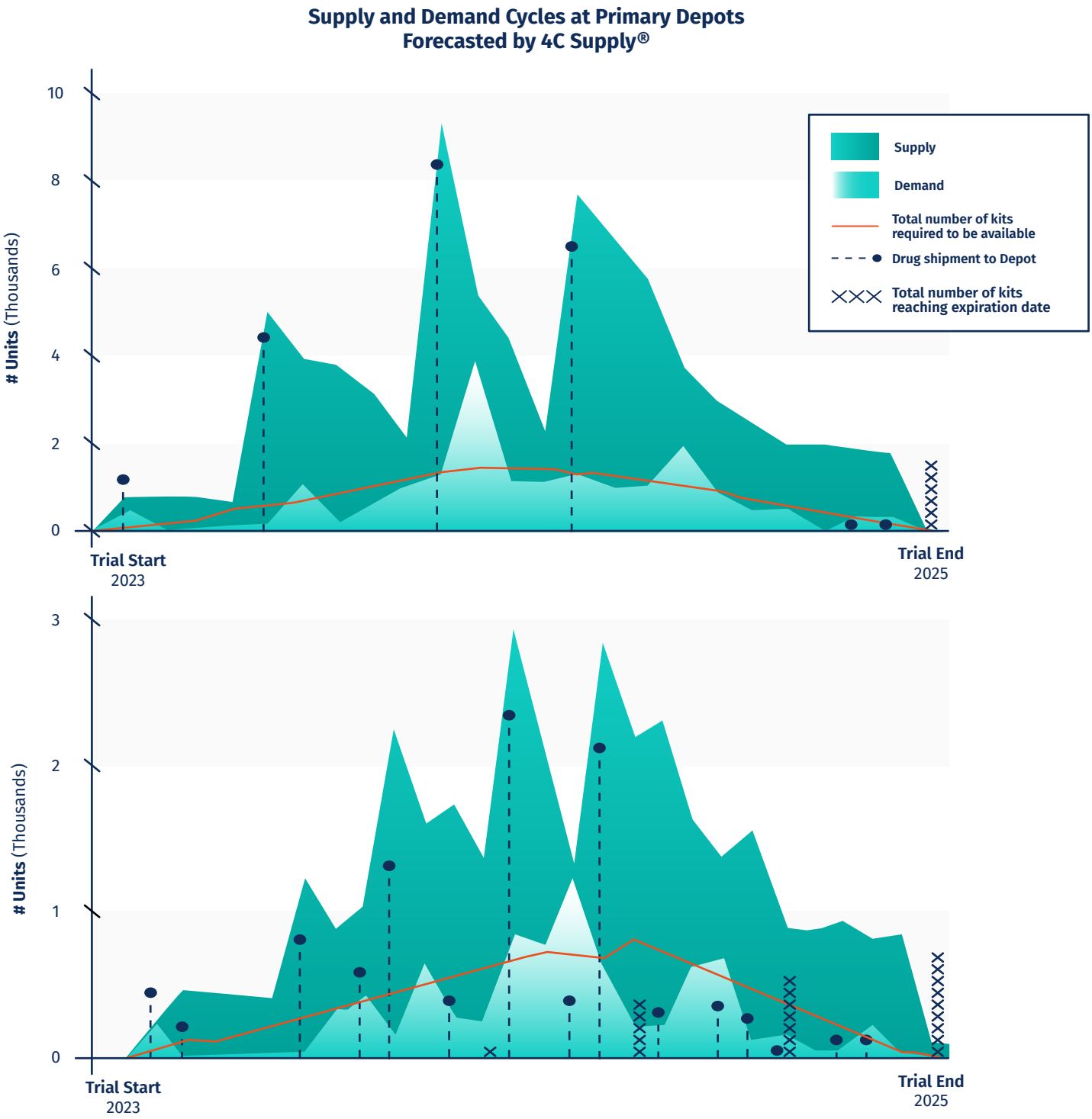
Using 4C Supply® to visualize production demand and the flow of clinical drug supplies



Shipments *- the blue bars signify incoming shipments to the primary depot.*
Supply *- is the development of the depot inventory over the duration of the trial.*
Demand *- demand for shipments to sites and subordinate depots over time.*
Required Available *- is the number of kits over time which are required to be available as safety stock.*
Expiries *- are the numbers of kits over time which are expected to expire at the depot.*

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What if the expected enrollment rates don't match what is occurring in the study?

There are many, many things that happen in a trial that make the projected enrollment rates change over time. There is also the chance your clinical operations team may not have accurate enrollment information available.
By building multiple scenarios within a forecasting tool, like 4C, drug supply managers can plan ahead for different outcomes. This could be a shift in the number of expected patients per site or it could be a total shift in the number of expected patients in a given country. We have many examples where the study teams thought enrollment was going to be skewed much greater to one country or region and the exact opposite occurred. When this is brought to light proactively using a forecasting tool, the amount of study drug located in a specific depot can be reallocated or additional production runs and distribution shipments can be made to reduce the risk of site stockouts.

Drug supply managers need to know they will be prepared to handle these changes when they occur. When using Prancer RTSM and 4C Supply® together, the actual enrollment data is imported on a regular basis to re-forecast based on the live enrollment rate occurring for each site. This way, forecasting is run with the most relevant enrollment data when the latest scenarios are being planned for.

What resupply values (floor and ceiling values) should we set in the RTSM system?

Finding the 'right' floor and ceiling values is one of those items that can be as much an art as it is a science. Drug supply managers will typically take a look at a given site and consider how many patients are expected to enroll in the time it takes for a shipment to arrive at site. This is a good way to set a potential resupply floor value, but what should the ceiling be? How high should it be set? How will changing it affect the number of shipments and overall inventory levels? Does the site have enough temperature appropriate storage space for all of this drug? 4C Supply® can act as the tool that calculates the drug necessary to meet the floor requirements to avoid site level stockouts, while also helping identify a ceiling value that fits the risk tolerance of the drug supply team. 4C Supply® can also recalculate these values on a regular basis to help optimize the resupply values throughout trial execution as changes in enrollment rates and dosing take place.

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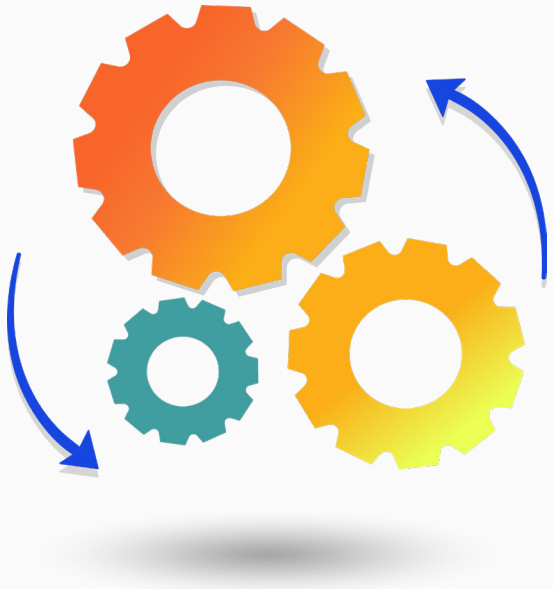
How frequently should site shipments be sent? What happens if we want or need to change frequency?

These questions typically require an answer from the drug supply team, and having access to a tool like 4C Supply® can help. The drug supply manager can run multiple scenarios to illustrate the outcomes of many potential options, facilitating more informed answers.

The data provided in the outputs show the effect shifting the resupply windows will have on the outcome of the forecast. Frequency of site shipments is a second area where the art versus science conversation comes into play.
As drug supply managers, the goal is to provide enough study drug to avoid adding any unnecessary risk into the trial while minimizing study drug waste. Drug supply managers don't want to ship too frequently, driving up costs, but they also don't want to over-stock sites that may have limited storage with too infrequent shipping. They need to know what shipping more or less frequently does to the total shipping costs, total drug manufacturing costs, and average inventory at a given site or site group.?

What does changing resupply parameters do to the number of shipments and overall supply at the depot and total cost for the trial?

When working through different scenarios with the study team, drug supply managers are requested to reduce the number of shipments or lower the amount of distribution spend. They might try to get a balanced approach over the entire duration of the trial, but many tools cannot provide a clear understanding of how or what to change in the forecast to find the best answer to these questions. Using Prancer RTSM® and 4C Supply® together allows drug supply managers to access full visibility of data required to more accurately summarize total costs across various scenarios.



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Do I have enough drug on hand, or will I be able to manufacture enough study drug to support the duration of the trial?

The ultimate goal of any true forecasting tool should be to ensure there is enough drug at the right depot at the right time. Without these production values a forecasting tool is leaving the drug supply manager still guessing how much drug supply to produce. 4C Supply® will create a production plan based on constraints provided by the drug supply manager.

The production plan created by 4C Supply® factors in aspects of the model like DNx settings, expiry dates, shipping lead times, min and max batch sizes, and a target interval between production runs. 4C Supply® can also run a full forecast with only a set amount of study drug which will allow a drug supply manager to estimate at what point they are at risk of stocking out at sites or depots. During trial execution combining 4C Supply® with actual demand data from Prancer RTSM® allows the drug supply managers to revisit the production plan and adjust real time as needed.

> *When a clinical trial kicks off, the only certainty is that nothing will develop quite as planned. Therefore, it's critical to* ***never stop questioning the planning*** *status quo and continuously adapting it to the evolving reality as the trial unfolds.*

Casey Ferrier,
Sr. Forecasting Services Lead

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Prancer RTSM® forecasting is pivotal for a successful trial and patient dosing

While long term forecasting tools such as 4C Supply® focus on the bigger picture, the RTSM is responsible for ensuring that no patient dispensing visit is missed due to inadequate site inventory. To achieve this, the system takes a daily look at each kit type in every active study site, determines whether the site inventory is adequate to meet the forecasted demand and raises a resupply shipment if needed.

This concept is basically quite simple, but forecasting demand can be tricky. The RTSM is aware of the visit schedule and knows how many units of each kit type are dispensed at each visit depending on the treatment arm, weight, titration level, etc. Having all that information already in the system, forecasting the demand of known patients with a clear status (treatment group, weight, titration level, etc.) is more or less straightforward (predictable demand). By contrast, forecasting demand, which is uncertain, such as the demand of a patient who has been screened but not yet randomized to a treatment arm, or demand for projected patients, is a lot more complicated because probabilities of demand must be considered (unpredictable demand). Most RTSM systems work around this challenge by not forecasting unpredictable demand at all, instead leaving it to the user to define and maintain kit quantities (commonly known as buffers) for each site which must be sufficient to cover all types of unpredictable demand.

In the end it is the drug supply manager who manually forecasts unpredictable demand and updates the buffer quantities in the RTSM accordingly.
Manual forecasting of unpredictable demand works well in smaller trials but becomes an extremely complex and arduous task in larger trials with substantial variability in the patient treatment process.

To provide the most appropriate forecasting approach in each trial, Prancer RTSM® supports multiple demand forecasting algorithms. Prancer RTSM® can forecast unpredictable demand automatically, making it unnecessary for users to manually define and maintain buffer quantities. However, this can make the forecasting logic more complex and difficult to predict. In those cases,, Prancer RTSM® can also limit forecasting to predictable demand and leave the management of buffer quantities to the user, which makes the forecasting algorithm less dynamic, but also simpler and easier to predict.

To determine buffer quantities automatically, a probabilistic demand forecasting algorithm is used which considers the different paths each patient can take during randomization, weight collection, titration, etc. and determines the buffer minimum and maximum values accordingly.

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Prancer RTSM® forecasting is pivotal for a successful trial and patient dosing

This algorithm automatically forecasts predictable and unpredictable demand of each kit type at each site on each day and raises resupply shipments to ensure that no dispensing visit is missed because there is inadequate supply.

When the management of buffer quantities is left to the user, Prancer RTSM® forecasts the predictable demand for each kit type at each site and adds the result to the buffer values defined by the user. The sum is the site's total demand. This forecasting approach keeps predictable demand and supply of each kit type consistently aligned at each site, ensuring that no planned dispensing is missed, but relies on the user to cover uncertain demand.

The different options of demand forecasting available in Prancer RTSM® make it possible to choose the one which is the best balance of supply security, efficiency, and complexity for each trial. Choosing the most suitable forecasting logic depends on a number of factors, including patient journey complexity, trial size, IMP cost and distribution cost.
In many cases, smaller trials will benefit most from a forecasting approach with manually defined buffers, while larger trials will work best with probabilistic demand forecasting.

Because each trial is unique, selecting the forecasting approach should be carried out individually for each trial as a joint effort between the sponsor and the RTSM vendor.

To make sure your integrated technology continues to function in unison, all forecasting approaches available in Prancer RTSM® can be modeled in 4C Supply®. This ensures that long term forecast results are aligned with the RTSM supply strategy, but also permits using 4C Supply® to drive the RTSM supply strategy selection process with data evidence.

> *Prancer RTSM®'s probabilistic forecasting algorithm can appear challenging at first sight, but is a game changer for ensuring supply security in large, complex trials, while at the same time substantially reducing the workload of clinical supply managers.*

Benjamin Etschmann
Senior Forecasting and Resupply Operations Lead

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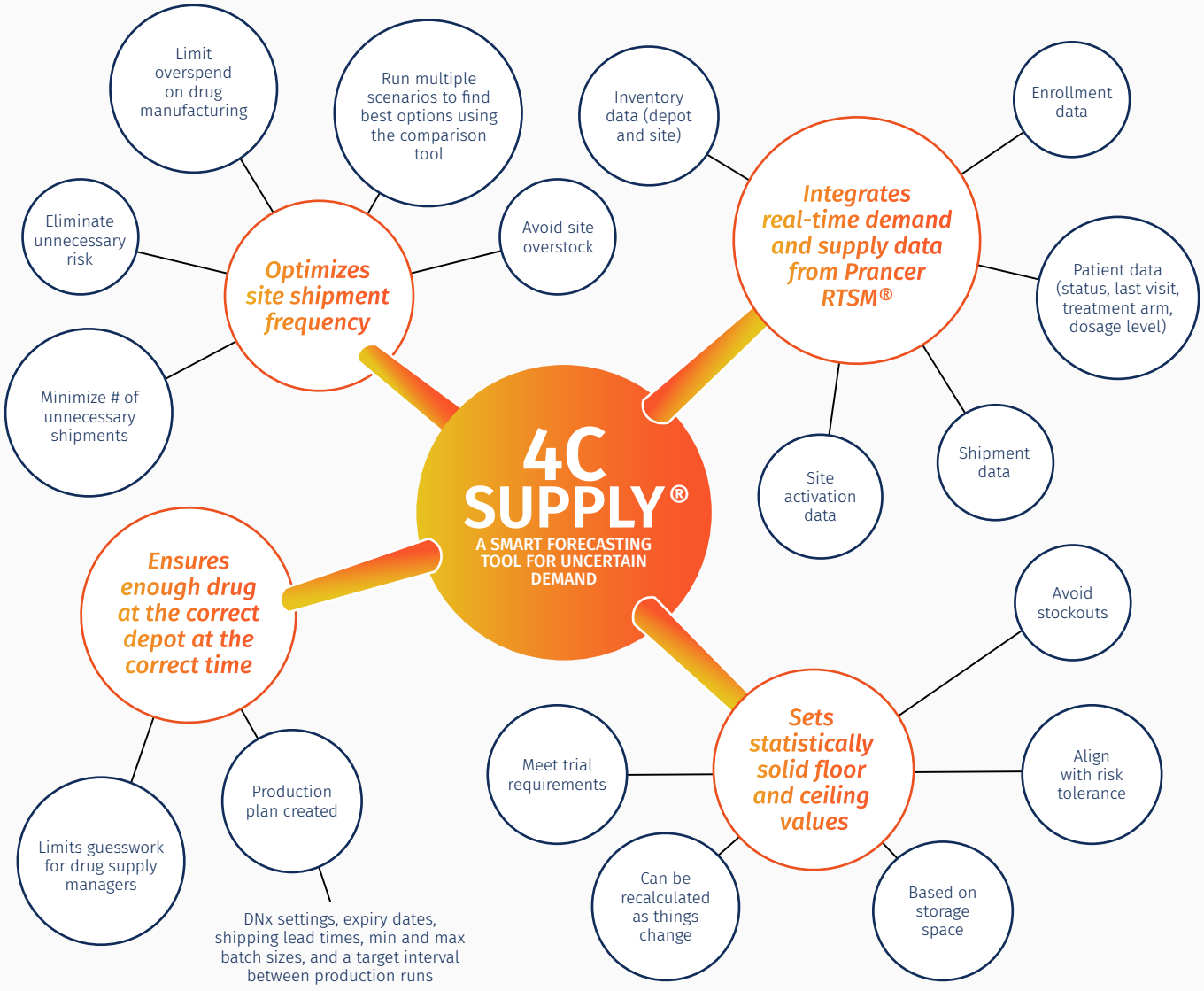
Prancer RTSM® data as the basis for the clinical forecast



From the moment when the first patient is screened, the RTSM system is the most comprehensive and up-to-date source of trial supply data. Therefore, integration of the RTSM actuals to a long-term forecasting solution, such as 4C Supply®, is critical for the process of reviewing and revising the drug supply production and distribution plan.

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Prancer RTSM® data as the basis for the clinical forecast

As each RTSM system build is unique, integration of the RTSM database contents to a long-term forecasting solution can be challenging.
This is particularly the case if the RTSM system and the long-term forecasting solution are from different vendors, which can add differences in integration technologies and communication gaps into the equation.

Prancer RTSM® and 4C Supply® are unique in this regard because they are provided by a single vendor, built on a common platform and utilize a common integration technology. In studies which use Prancer RTSM® and 4C Supply®, the integration from Prancer RTSM® to 4C Supply can be implemented rapidly and at no charge, rather than a long process requiring clear communication across multiple parties and incurring substantial costs.

Once set up, RTSM database extracts are generated daily, allowing 4C Supply® forecasts to be run using 'fresh' RTSM data at any time. This makes it quick and easy to verify whether the current drug supply production and distribution plan is adapted to the latest developments in the trial. If needed, updates are quick and easy as well.

Using the 4G Clinical products increases confidence and lowers risk.

On balance, the combination of Prancer RTSM® and 4C Supply® has the unique potential of making it easy to consistently maintain oversight over the clinical supply chain, from the Primary Depot to the Regional Depots, even down to the sites and the patients.

By using the 4G Clinical software solutions, drug supply managers gain confidence in the clinical supply chain even as unexpected paths come to light. Each of the risks that inevitably come along with every clinical trial can be managed more effectively.

Clinical operations and drug supply managers can use these tools to help better communicate the intentions and outcomes of supply decisions across the clinical trial.

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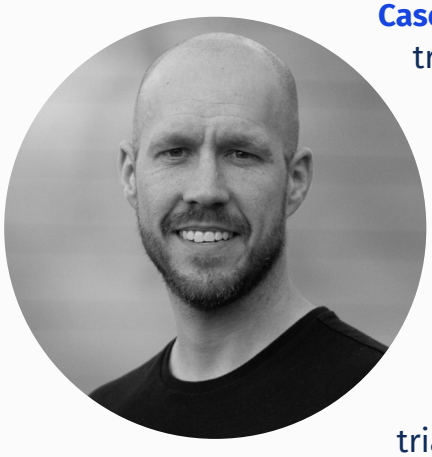
Meet the **Authors**



Casey Ferrier brings 15+ years of experience in the clinical trial supply industry to 4G Clinical. He has implemented and led supply chain strategies to deliver solutions that support packaging, distribution, and logistics requirements for clinical trials for Pharma, Biotech, and CRO organizations. Casey also spent four years with a clinical supply chain services provider managing the supply chain team and driving the product roadw map to focus the development of the clinical supply forecasting solution on targeting problem areas in clinical trials and enabling users to solve challenges in their supply chain.

Benjamin Etschmann has spent more than 10 years in clinical trial supply management in various roles, including operational trial supply logistics management and trial supply setup management. However, his primary focus has been in IVRS/IRT/RTSM management and demand forecasting using dedicated stochastic simulation tools. In his current role, he consults clients and internal teams on probabilistic site and depot demand forecasting in IVRS/IRT/RTSM.

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Bringing crucial medicines to
those who need them, ***faster.***

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