CASE STUDY

Meeting Randomization & Clinical Supply Challenges Head-On

Strategic partnership to pair long-standing clinical research expertise with a best in class RTSM system

Introduction

As studies become more complex, it is increasingly challenging to support randomization strategies and ensure accurate supply of the study drug to avoid stock outs while having sufficient supply to meet the number of enrolled participants at each site.

Situation

Randomization and trial supply management (RTSM) for sophisticated study designs relies on both expertise in the full suite of randomization strategies and an RTSM system that is agile enough to respond to evolving designs and specific study needs.

Requirements for the Third Party RTSM

IDDI had a prioritized list of requirements for the third party RTSM to ensure it would meet the needs of its biostatistics driven approach to RTSM as well as those of its clients.

Requirements	IDDI Business Needs
Web-based enabling service for IDDI to continue designing and implementing studies	Is a key feature for RTSM services
Strong integration capabilities with external systems, such as EDC and drug supply providers	Supports full service delivery to sponsors
Strong implementation of randomization strategies such as minimization	Supports a wide range of study designs
Ability to perform statistical checks	Enables the biostatistics team to monitor and adjust randomization as needed
Flexible design	Accommodates mid study design changes, due to either unexpected developments or protocol changes
Feature rich solution	Includes monitoring of data in real time, comprehensive standardized and ad hoc reporting, accountability features, ability to change randomization such as via silent re-randomization, support for central pharmacies, among others

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IDDI's Biostatistics Driven RTSM Service

In IDDI's standard approach to its RTSM service, IDDI's team of experienced biostatisticians contribute at three key points during a study:

Study design

- Define the randomization method in the protocol
- Define the stratification factors in the protocol with a medical expert
- Run random simulations to determine the distribution of the subjects per stratification factor

Study setup

- Re-validate the randomization algorithm to verify the randomization follows the protocol
- Validate drug kit allocation to ensure correct allocation based on treatment group and the protocol-define schedule

Study follow-up

- Check the randomization balance is correct
- Check the accuracy of drug kit allocation
- Resolve issues and accommodate mid-study changes, as needed

Solutions

To find an RTMS vendor that could support IDDI's biostatistics driven RTSM services, the company comprehensively evaluated multiple vendors and selected Sitero as the RTSM vendor of choice.

Sitero RTSM provides a single solution combining IRT and TSO, with features that enable:	
Study delivery in weeks, not months	Optimal settings for floor and ceiling values and specification of quantity by kit type
Interoperability with any third party system such as EDC, CTMS, and central pharmacies	Graphical simulation forecasts of enrollment activity, last patient last date, longitudinal study drug demand, supply/demand alignment, and more
Strong implementation of randomization strategies such as minimization	Supports a wide range of study designs
Flexible configurations and customizations that can accommodate a full spectrum of protocol designs, from simple, randomization only studies to complex studies involving dosing, titration, biomarker driven randomization, dynamic minimization, or cohorts	Mid-study changes accomplished via configurable capabilities, in days, not weeks
Forecasting and optimization to manage the supply chain	Temperature excursion tracking
Time series analyses and simulation and re-simulation based on actual randomization and enrollment	Reporting using standard reports or by designing new reports Direct-to-participant drug supply

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The partnership between IDDI and Sitero enables the IDDI RTSM and statistical services teams to address randomization and drug supply challenges like these real-world examples.

Example 1: Modifying the randomization algorithm

- In a Phase III study evaluating the efficacy and safety of a new therapy for critical limb ischemia, a 2:1 minimization algorithm was used to balance the patients between the active and placebo arms and allowed for mid-study changes.
- Because the therapy was manufactured using the patient's bone marrow, the patient was randomized first, followed by manufacturing of the therapy. Due to issues with the bone marrow extract or manufacturing process, some patients weren't treated. The sponsor wanted to randomize only on treated patients, and the original randomization design included all patients, regardless of treatment status. This created an imbalance in the randomization results.

Because three patients weren't treated, the randomization was imbalanced with 4 in the active arm and 3 in the placebo arm; randomizing participant #9 to the active arm would balance it out.

Subject	Treatment Group	Treatment Status	Initial Design
1	Active	Treated	Included
2	Active	Treated	Included
3	Placebo	Not Treated	Included
4	Active	Not Continued	Included
5	Placebo	Treated	Included
6	Active	Treated	Included
7	Placebo	Not Treated	Included
8	Active	Pending	Included
9	**To be randomized**		**Active favors the balance**

The IDDI team re-designed the algorithm to dynamically exclude untreated and discontinued participants from the randomization, which meant the balance of the trial was no longer influenced by the outcome of the manufacturing of the therapy.

Subject	Treatment Group	Treatment Status	Initial Design	New Design
1	Active	Treated	Included	Included
2	Active	Treated	Included	Included
3	Placebo	Not Treated	Included	Excluded
4	Active	Not Continued	Included	Excluded
5	Placebo	Treated	Included	Included
6	Active	Treated	Included	Included
7	Placebo	Not Treated	Included	Excluded
8	Active	Pending	Included	Included
9	**To be randomized**		**Active favors the balance**	**Placebo favors the balance**

The sponsor was able to improve the accuracy of the trial results.

IDDI helped the sponsor to avoid serious imbalance between the two randomized Sitero RTSM supported dynamic randomization as well as mid-study changes.

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Example 2: Adding a stratification factor mid-study

In another Phase III study, two post-chemotherapy drugs were compared in a relatively large sample of patients with newly diagnosed FLT3-mutated acute myeloid leukemia, with randomization using a 1:1 minimization algorithm based on six stratification factors. **Although the randomization was nicely balanced during the initial review, 10 events occurred in 27 patients with an important biomarker that could potentially impact the outcome. In this subgroup, the treatment allocation was imbalanced.**

- The sponsor wanted to include this additional biomarker as a stratification factor, and the question was whether to replace one or add it as the seventh factor.
- The decision was a joint effort between the sponsor, IDDI biostatistics team, and IDDI RTSM team.
- The IDDI biostatisticians recommended adding a seventh factor, and the RTSM team imported the collected biomarker data for all 187 patients.
- This meant that the updated randomization algorithm could take into account all previous patients during future randomization, eliminating the need to start a new cohort, risking imbalance across the entire sample.

Although identified while the study was already underway, the sponsor was able to introduce an important biomarker into the stratification factors while maintaining the necessary overall balance.

IDDI biostatisticians advised the sponsor to add this important biomarker as a stratification factor. Sitero RTSM allowed mid-study changes to the stratification factors used in the algorithm and the import of additional data for randomization purposes.

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Example 3: Optimizing the drug supply strategy

In a Phase II study assessing the efficacy of the combination of a new drug or placebo and an antibody in patients with advanced triple-negative breast cancer, randomization used a 1:1 minimization algorithm based on two stratification factors and balancing participants between the drug and placebo arms.

As an expensive drug to manufacture, waste was a concern. The initial 5-mg dosage was reduced to 3 mg, and further to 2 mg, if an adverse event occurred, making it difficult to predict the allocation of each dose. An additional complicating factor was the use of central pharmacies for distribution.

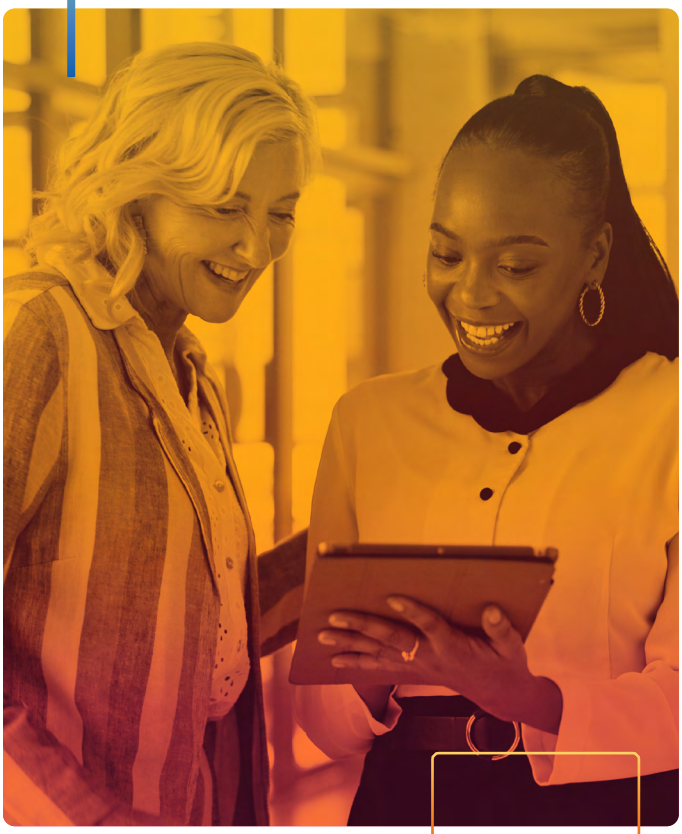
The IDDI RTSM team proposed a predictive drug supply model, with the percentage to allocate for each dose provided by the IDDI biostatistics team.

Initial shipment based on:		Trigger & re-supply based on:
6 kits per central pharmacy's site	**5 mg**	**Number of 5 mg subjects in all central pharmacy's sites** • **Additional % as buffer**
% of 5 mg quantity	**3 mg**	**Number of 5 mg subjects in all central pharmacy's sites** • **% 5-mg subjects** • **Additional % as buffer**
% of 5 mg quantity	**2 mg**	**Number of 3 mg subjects in all central pharmacy's sites** • **% 5 mg subjects** • **Additional % as buffer**

The sponsor was able to use statistical predictions that were updated as necessary to optimize supply based on previous supply records and tendencies.

- **The IDDI RTSM team proposed a predictive drug supply model enabling the sponsor to optimize drug delivery.**
- **Sitero RTSM was capable of handling this dynamic allocation.**

"Addressing unbalanced randomization in real time reduces the impact on the study timeline and costs."



Solving RTSM Challenges

A partnership that solves real-world randomization & drug supply challenges

- Together, IDDI's extensive experience in clinical research and Sitero's robust, flexible RTSM system can support simple to complex randomization and drug supply designs, as well as unforeseen challenges during study conduct.
- Addressing unbalanced randomization in real time reduces the impact on the study timeline and costs.
- Taking the guesswork out of drug demand minimizes both under- and over-supply of study drug at the distribution point, whether that's the site in a traditional in-person study or a central pharmacy in a decentralized trial.

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Learn More About our RTSM Services.

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