

Meeting Randomization and Supply Challenges in an Innovative Dermatology Study

A multi-national pharmaceutical company was looking to improve speed and efficiency across its clinical trials. While the use of electronic data capture (EDC) had greatly improved their clinical trial operations since its adoption years before, the company now wished to utilize a randomization and trial supply management system (RTSM) in a study that presented several new challenges in this area.

Planning the Study

As a mid-market pharmaceutical company, the firm enjoyed a strong reputation worldwide and a large global market for its products, sold both over-the-counter and via prescription. They planned to undertake a Phase IV study to further determine the effectiveness of one of their recently approved and marketed skin care products.

The study was designed in two parts:

- Part One involved open-label use of the investigational medicinal product (IMP) in subjects who could potentially benefit from its use. Only subjects who experienced a significant improvement in skin condition were brought to the next study
- In Part Two, those subjects experiencing a significant improvement by one of three factors were randomized to receive either placebo control or active treatment. The company expected to enroll a total of 200 patients at 10 geographically scattered sites to meet the statistical power for the study

With a long history of innovative products, the sponsor was not averse to welcoming innovation in its study methods and embraced technology in this area. However, the company recognized a need for caution because of the importance of safely acquiring reliable results; therefore, any new technology adopted would receive scrutiny for quality compared to existing means.

THE CHALLENGE

For a 200-patient Phase II dermatology study to be conducted across 10 US sites, a midmarket pharmaceutical company sought a robust integrated solution for randomization and electronic data capture (EDC). Speed and efficiency were key.

THE SOLUTION

The sponsor selected Medidata Rave RTSM, an innovative randomization and trial supply management (RTSM) system that comes pre-integrated with Medidata Rave EDC, the market-leading solution. Implementation of this unified RTSM/EDC solution easily met aggressive study timelines.

BUSINESS IMPACT

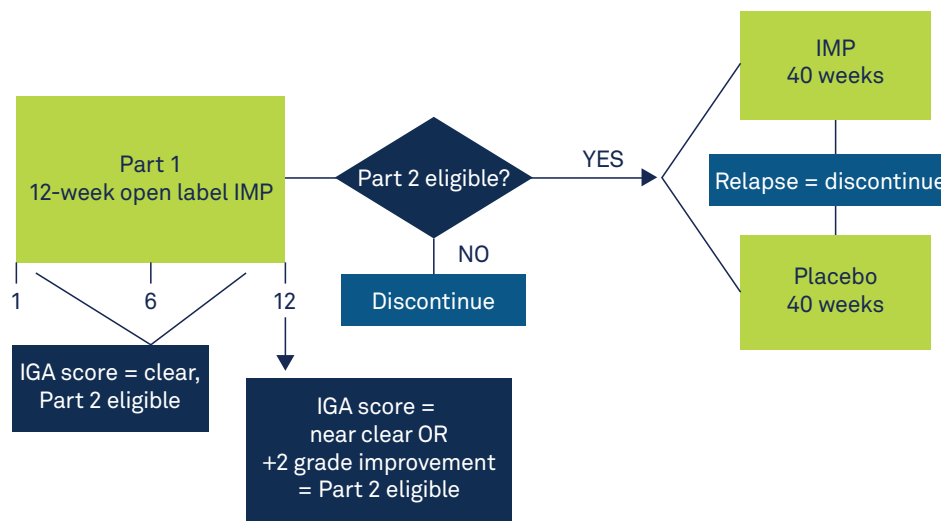
With the solution's intuitive design—including unique simulation tools—and Medidata training, a wide range of users were able to be trained quickly. They configured Rave EDC and Rave RTSM to have sites up and running with minimal effort. Site work was eased by having one intuitive interface for randomization and patient data capture.

Subject Flow in the Study

In Part One, enrolled subjects underwent an open-label 12-week treatment program with the IMP to see if it would improve their skin condition. When any subject received an IGA score of “clear” within this open label period, they were immediately entered into the double-blind randomized Part Two of the study. At the end of Part One, subjects were again evaluated and those with an IGA score of “near clear” or with a minimum 2 grade improvement were also randomized into Part Two.

Part Two was to determine whether a maintenance regimen using the IMP would be effective over an additional period of 40 weeks. However, the proper execution of Part Two introduced some challenges in both randomization and supply as discussed in the following section.

Figure 1: Subject flow



Challenges with the Study

RANDOMIZATION

Subjects continuing into Part Two of the study were randomized into either placebo control or active IMP. With conventional randomization techniques, the sponsor would be dependent on the completion of software specifications and programs that would run the interactive voice response (IVR) or interactive web response (IWR) system. Additionally, if errors were found in the IVR/IWR programs, a delay in randomization might occur. With only a short start-up period available, a tool facilitating a quick start-up time was preferred. The sponsor also wanted to use a dynamic randomization method and wanted to simulate randomization to ensure acceptable balance prior to study start.

SUPPLY

The sponsor needed to manage supplies for both the open label Part One and double-blind Part Two of the study, ensuring adequate stocks at sites without requiring excessive overage or wastage. The ability to adjust supply plans on an individual site basis would also help combat overstock and wastage at low recruiting sites and allow for the increased IMP requirements at higher recruiting sites. Again, the speed of implementation of supplies management was crucial, and the delays inherent with the setup and validation of traditional IVR/IWR systems were very unattractive.

Innovative RTSM Solution for Better Study Performance

The sponsor had evaluated several RTSM solutions on the market, determining that Medidata Rave RTSM offered key advantages over traditional methods and could meet the unique challenges of the study:

- Rave RTSM was configurable—it could be set up for the study design in days rather than months. With no programming required, there would be no delay in making the randomization and supply capabilities available to the sites and thus would meet the aggressive start-up timelines
- Rave RTSM offered a built-in simulator that could be used to test randomization scenarios in determining potential balance during an actual trial. Simulation would help alleviate any balancing concerns and confirm adequate power of the study
- Rave RTSM supply management capabilities offered both minimum/maximum trigger levels and a predictive mode of determining supply by looking at future dispensing requirements for subjects already randomized, thus minimizing risk of stock-outs at sites while also avoiding over-stock and wastage
- Rave RTSM was integrated with Rave EDC management and reporting so that sites could use the same interface for entering patient data and receiving randomization and dispensation instructions, greatly simplifying training, streamlining study activities and offering real-time response via Rave EDC

Figure 2: Configurable randomization design

The screenshot displays the 'Randomization Design' configuration page in the Medidata Rave interface. The page includes a navigation bar with tabs for 'Randomization Design', 'Simulation Setups', 'Simulation Results', 'Treatment Design', 'Visits', and 'Assign Treatments'. A 'Configuration Report' icon is visible in the top right. The main content area is titled 'Randomization Design' and features a 'Dynamic Allocation' dropdown menu and a 'Save Design' button.

Study Arms

Ratio	Name
1	Arm A
1	Arm B

Randomization Factors

Weight	Factor	Values
1	Site	N/A
1	Stratum	N/A
1	Study	N/A

General

Randomization Second Best Probability (%) ?
15

Strata

Name

Figure 3: Simulation Output

Study Balance	Arm A: 1		Arm B:		Total
Name	Subjects	Imbalance	Subjects	Imbalance	
Medicillin-Jackson (DEV)	101	1.0	99	1.0	200
Site 1	11	0.5	10	0.5	21
Site 10	10	0.5	9	0.5	19
Site 2	10	0.5	9	0.5	19
Site 3	12	0.0	12	0.0	24
Site 4	11	0.0	11	0.0	22
Site 5	11	0.5	10	0.5	21
Site 6	10	0.0	10	0.0	20
Site 7	10	0.5	11	0.5	21
Site 8	7	0.0	7	0.0	14
Site 9	9	0.5	10	0.5	19

Unique Simulation Capability

Rave RTSM’s built-in simulation capability emulates the assignment of subjects in the trial into arms, strata, sites and factors in order to provide a view of how the randomization will be balanced within the selected design. As a result, researchers can adjust the design of the study to minimize imbalance in accordance with study goals. Figure 3 illustrates the simulator’s output, showing the balance achieved across potential sites.

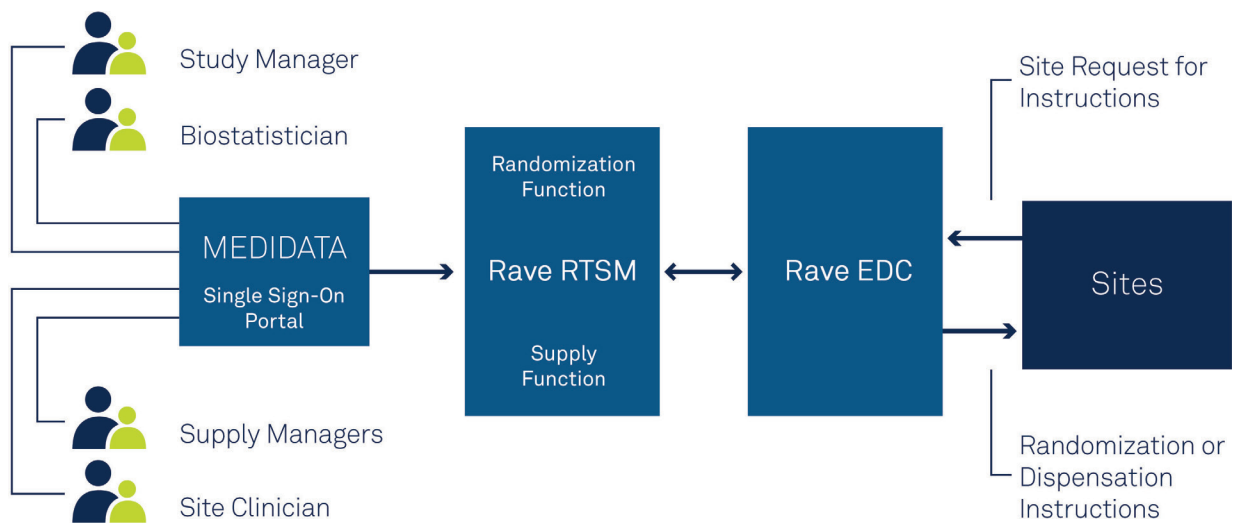
Rave RTSM’s randomization simulator allowed the sponsor to run multiple simulations based on the specified number of sites and subjects in order to show potential imbalances across study factors. The sponsor’s biostatistics team found this to be a particularly useful tool to fine-tune the randomization design of this study.

Selecting a Randomization Method

The study team discussed at length which method of randomization to use: dynamic allocation or the traditional permuted block randomization. The advantages of dynamic allocation in maintaining a continuous state of balance between the two arms throughout the randomization process could mean higher statistical reliability. The configurable second-best probability was also seen as a benefit.

After reviewing their goals and requirements for the study, the team decided that the dynamic allocation method of randomization would best meet their needs.

Figure 4: User environment for medidata balance



System Environment for the Study

Lastly, the team reviewed the environment for the operation of Rave RTSM (Figure 4). They noted that the environment brought the entire study into the control of the sponsor by eliminating the previous dependencies on outside service providers to supply key technical services, such as software programming and maintenance. The sponsor determined that with Rave RTSM they would retain greater control over all aspects of the study, leading to better understanding of the study progress.

Getting Started with Medidata Rave RTSM

Following their selection of Rave RTSM, the next step for the sponsor was to quickly turn their attention to the training needs of their staff to ensure the effective use of the new system.

Balance training was easily and quickly delivered via eLearning modules and allowed the sponsor to specify mandatory training completion prior to gaining access to the study. Individual user training was tracked by user login and could be retaken as needed at any time throughout the study duration.

Conclusion

Following an evaluation of the leading industry solutions, Rave RTSM was deemed the best choice for this midmarket sponsor to get off to a rapid start. At the design stage, the study team found that the entry of trial parameters, such as arms and factors, quickly established the study design. The randomization simulation allowed their biostatistician team to test the required power for the study and identify potential imbalances across study arms.

Easily accessed training helped get the study off on the right track. Moreover, members of the study team observed at the end of training that the integration of Rave EDC and Rave RTSM greatly simplified site tasks and accelerated the flow of trial and patient information, helping to streamline trial activities.

Finally, the pre-validated nature of Rave RTSM helped streamline the user acceptance training (UAT) that was required in conjunction with the Rave EDC electronic case report form UAT. As the live study was conducted, ongoing study support was delivered by Medidata within the existing Rave EDC support infrastructure.

The use of Medidata RTSM exceeded the expectations of the members of the study team and satisfied the specific needs and challenges of this study.