

WHITE PAPER

INTRODUCTION TO MODERN RANDOMIZATION AND TRIAL SUPPLY MANAGEMENT SERVICES

Randomization is fundamental to clinical trials—it enables treatment group balance, eliminates selection bias and limits the predictability of treatment allocation. Clinical trial supply management assures that the right medical supplies are delivered to the right patient at the right time, every time.

Over the past 20 years, randomization and trial supply management (RTSM) services have been adopted across clinical trials. Such services affect how quickly a trial can start, how it is conducted and how quickly patients receive medication kits so that safety and efficacy data can be collected as soon as possible.

INTRODUCTION

Randomization in clinical trials prevents bias in selecting which patients receive the investigational product or the placebo/comparator. It helps balance the allocation between patient groups (cohorts) based on predetermined criteria (for example age, sex and smoker/non-smoker). RTSM services use interactive response technology (IRT) to:

- Manage randomization and clinical trial supply chain management including study medication dispensing and inventory
- Monitor real-time recruitment
- Manage emergency “unblinding” or “code breaking”
- Perform calculations to ensure accuracy of dosing

RTSM services can also help solve difficult supply issues including adaptive trial design management, titration regimens or medication pooling across multiple protocols. This white paper explores how an agile, flexible and scalable RTSM service can meet the needs of any clinical trial while increasing speed to first patient in, simplifying technology interactions for study teams and sites, and minimizing risk through expert design, project management and support.

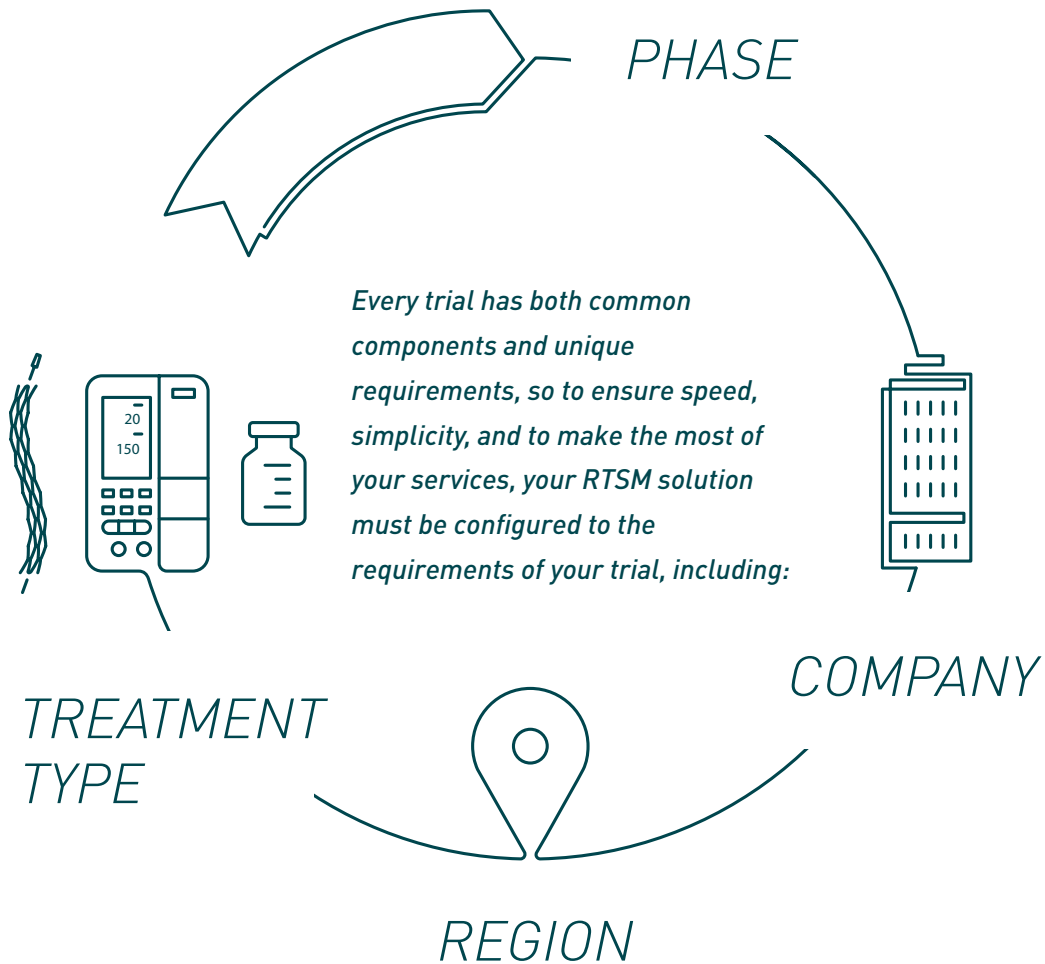
A BRIEF HISTORY OF RTSM

Until the early 1990s, medication randomization and clinical trial supply management was conducted manually. Sites were equipped with binders, sealed envelopes and answering services. Materials were prepared and allocated in advance of the trial. Medical kits were labeled with randomized subject identification numbers. Manual processes limited randomization methods, allowed for little treatment flexibility and, in many cases, resulted in the overstocking of supplies.

In the mid-1990s, early RTSM systems involving simple randomization with emergency unblinding capabilities began replacing paper-based manual solutions. The solutions deployed typically leveraged interactive voice response (IVR) systems, were programmed on a per study basis and were characterized by long set-up times.

By the 2000s, vendors began offering systems that used interactive web response (IWR) in addition to IVR. Capabilities expanded to include options such as dynamic randomizations and advanced logistics controls. As experience with RTSM systems grew, the software solutions were customized to increase their flexibility and accommodate the proliferation of sponsors’ or clinical research organizations’ (CROs’) requirements. Although usability improved and set-up times decreased, customizations based on company or study-specific requirements still required a significant time investment to review, update and validate the systems.

RTSM FOR EVERY TRIAL



EVERY TRIAL IS DIFFERENT

To be successful, today's RTSM services must be easily configurable based on study-specific needs including those pertaining to the development phase of the trial and the region(s) in which the trial is performed. Specific phase and regional needs include:

- Early Phase
 - Meeting short-study start-up timelines by implementing complex study designs quickly
 - Adapting the study design rapidly as new information is learned
- Phase II/III
 - Managing supply complexities
 - Scaling to meet the needs of the most complex studies
- Peri-/Post-Approval
 - Managing large volumes of sites and patients
 - Addressing global sites with potentially limited experience of clinical studies and non-English-speaking staff
- Asia/Pacific
 - Working with local services in the local language

THE RISE OF THE MODERN RTSM SERVICE

A new breed of RTSM services leverages cloud-based software-as-a-service (SaaS) solutions that can be configured rather than programmed to meet the specific needs of a study. These solutions provide a web interface (IWR) and voice back-up (IVR). They are easy to integrate with the client's chosen electronic data capture (EDC) system or other eClinical applications. Because the general workflow of RTSM activities remains common across multiple studies, modern RTSM services enable simple configuration to comply with company standards or unique protocol requirements.

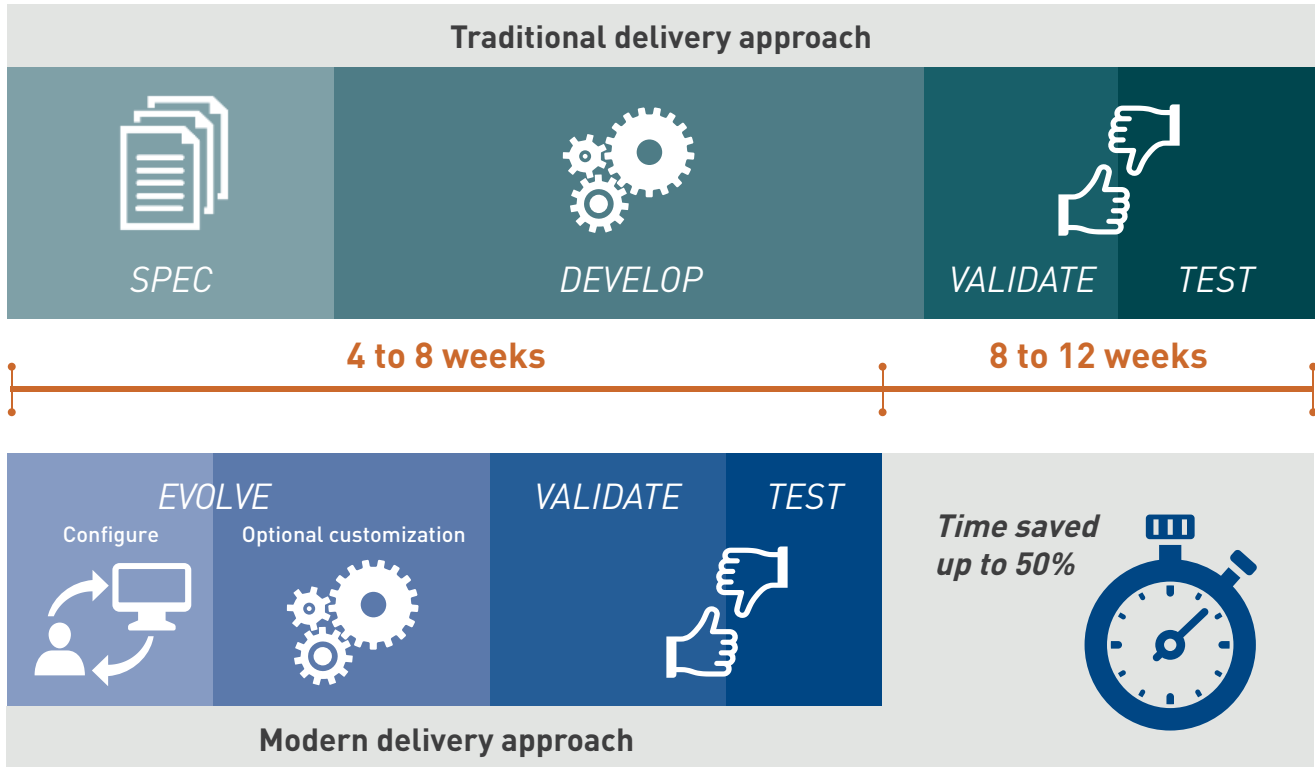
Companies that have extensive experience developing RTSM services reuse randomization methodologies and algorithms that have been validated, deployed and optimized previously to create dependable, configurable systems that can be quickly adapted to any clinical trial regardless of the company, phase, region or therapeutic area being studied.

The randomization capabilities have been combined with supply management functions that enable the efficient restocking of sites and depots throughout the supply chain and consulting services from study design (including randomization algorithms and clinical trial supply chain strategies) to technical and clinical support throughout the duration of the trial. Usually, the modern RTSM service is managed by an experienced project management team.

Given that trial complexity continues to increase as more sophisticated treatments are developed, novel ways of measuring efficacy emerge, and trials evolve into adaptive and direct-to-patient studies, the ability to deploy flexible, scalable RTSM services has increased in importance. The modern approach makes it easier and faster to address the full range of clinical trials, from simple to complex, from early to late phase and from North America to Asia-Pacific.

These modern RTSM services enable a faster and simpler study design, build, and test process. A client's study can be deployed iteratively using demonstrable versions of the system, enabling the client's study team to understand what has been implemented and allowing the services team to rapidly create the next update. Systems can typically be delivered in four to eight weeks, depending on the specific study requirements. Last-minute changes, both pre- and post-go-live, can be implemented quickly without disrupting the live system.

COMPARING 'TRADITIONAL' AND MODERN IRT DELIVERY PROCESSES



COMPONENTS OF A SUCCESSFUL RTSM SYSTEM

Randomization services include:

- Selection of the right algorithm for the study from a comprehensive spectrum of validated randomization methods
- Centralized emergency code breaking via web and phone (IWR and IVR)
- Simulations and consulting to optimize the randomization methods
- Randomization methodologies for adaptive trial designs

Trial supply management services include:

- Automated site and depot medication inventory control
- Real-time reporting of patient progress, medication assignments and supply location and status
- Unique supply algorithms to optimize efficient use of available supplies
- Expiration date management and relabeling at depots and sites
- Pack-type substitution and multi-pack box handling within shipments
- Supplies management for adaptive trial designs

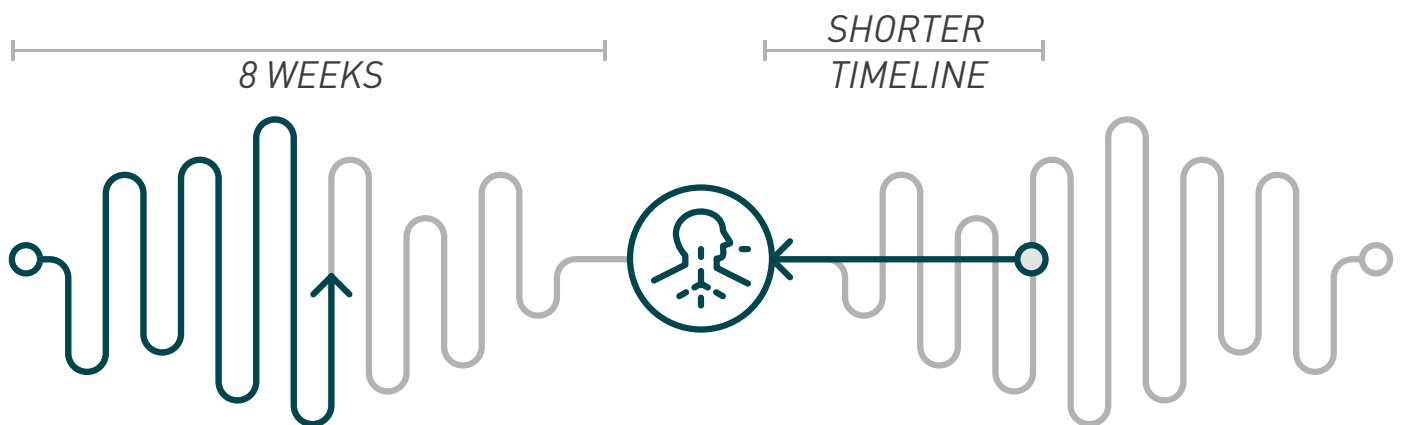
Study teams and site can easily and quickly access administrative and management functions and data including:

- Supply administration to provide clinical teams with the ability to control and manage their trial inventory
- Site management to allow study personnel to view site-level and patient status in real-time
- Site inventory management to allow site users to easily view the status of their on-site supplies

WHY RTSM REALLY STANDS FOR SPEED, SIMPLICITY AND SERVICES

To balance treatment groups, eliminate selection bias and, limit the predictability of treatment allocations while accurately managing supplies, a robust, timely, cost-effective RTSM solution must provide speed, simplicity and services to meet the needs of the trial. Here's how it is done.

WHY SPEED?



Most eClinical systems take at least 8 weeks to set up.

Lowering that start-up time gets you to “first patient in” faster and shortens the overall study timeline for quicker results.

SPEED—GET TO FIRST PATIENT IN AND MAKE IN-FLIGHT CHANGES FASTER

By deploying an RTSM service faster, a sponsor or CRO can reach the first patient in milestone quicker and accelerate the study's overall timeline.

Instead of collecting requirements at an initial kick-off meeting and returning weeks later with the final version

of the system, a modern RTSM service provider can take the basic requirements to create a demonstrable version of the system ready for the kick-off. This process makes it easier for the client to understand what has been implemented and provide robust feedback.

The service provider, in turn, can move toward a final product much faster. In addition, given the flexibility of the configurable system, changes can be made quickly

both pre- or post-go-live without significantly disrupting the study start date or progress of the live trial.

Compared to the eight to twelve weeks systems previously required to go live, the modern RTSM system can be delivered in four to eight weeks, depending on the specific study requirements. Any variations in this timeline typically are due to the creation of novel protocol parameters or custom integrations with proprietary eClinical systems.

The client will typically need reduced time, fewer resources, and less expertise to perform design reviews (finding flaws in the old-style requirements documents is time-consuming and requires a greater understanding of the service provider's design approach). And user acceptance testing is likely to run more smoothly because there should be far fewer surprises at this final test stage because the client has system visibility and has been providing feedback to the service provider throughout the delivery process.

By accelerating the deployment of the RTSM service, clients benefit from:

- Faster system design review with less expertise required to understand the design
- Accelerated study start-up and first patient in

- Decreased costs associated with user acceptance testing
- Reduced study delays

SIMPLICITY—FOCUS ON THE SCIENCE

RTSM services should be designed to simplify all technology interactions, from initial contact through end of study. The system design approach described above simplifies the system review and test process for the client. In the live system, it is important that the access to data and actions needed by study teams and sites is as intuitive as possible to speed and simplify the ability to ensure the right medication kit is available to the right patient at the right time.

In late phase (IIIb/IV) studies the number of sites and subjects increase, and general practitioners and nurses are the primary contacts for the study patients. These physicians and nurses typically have limited experience with clinical trials and systems and need to find that learning to use the RTSM systems and incorporating them into their day-to-day routines is easy.

By simplifying the design and deployment of the RTSM service, clients and their sites benefit from:

→ WHY SIMPLICITY?¹



22%

Of 81 pharmaceutical participants recently polled said their sites find individual systems difficult to use.

- Easier access to the system to input data
- Decreased labor intensity at depots for supply chain management and at sites for patient and supplies administration.
- Easier communications with depots regarding lost or damaged medical kits or a need to reorder supplies

Finally, by making the RTSM system easy and intuitive, studies can avoid protocol violations associated with “stock out”—sites not being able to provide a medication kit to patients on their scheduled visits.

SERVICES—MINIMIZE RISKS ASSOCIATED WITH RANDOMIZATION AND SUPPLY CHAIN MANAGEMENT

Throughout this paper you will have noticed the use of the term “RTSM service.” Yes, this service is enabled by technology, but technology alone is not enough to provide a first-class RTSM capability.

The RTSM services that utilize the technology are a significant value-add, from the selection and creation of the most effective randomization algorithm and clinical trial supply chain methodology, to the design of the system and technical and clinical operational support of the study. All the technology implementation and use are managed

WHY SERVICES?²



By 2016

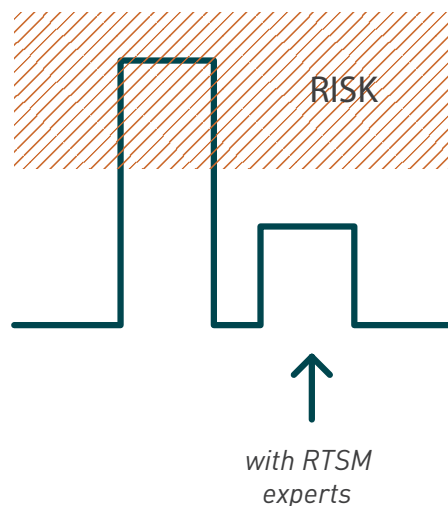
80%

of pharmaceutical companies surveyed will use an off-the-shelf/outsourced IRT application versus an in-house solution



44%

will flow somewhat or substantially more business to integrated service companies versus dedicated IRT suppliers



Ensuring that complex work goes to the right RTSM experts is important to minimize risk because the cost of a mistake in RTSM is high.

Mistakes can cause trials to be scrapped and restarted—at a cost of millions or even billions of dollars.

by a team that helps ensure that RTSM processes are performed with high quality and minimal risk. In fact, when a service provider delivers RTSM service, the provider typically takes responsibility for risk mitigation.

When the RTSM service provider has been audited regularly and successfully and has a global in-house 24/7/365 help desk for technical and clinical support, then clients can be assured the system is reliable and will not be a point of failure. Instead, it will efficiently serve its

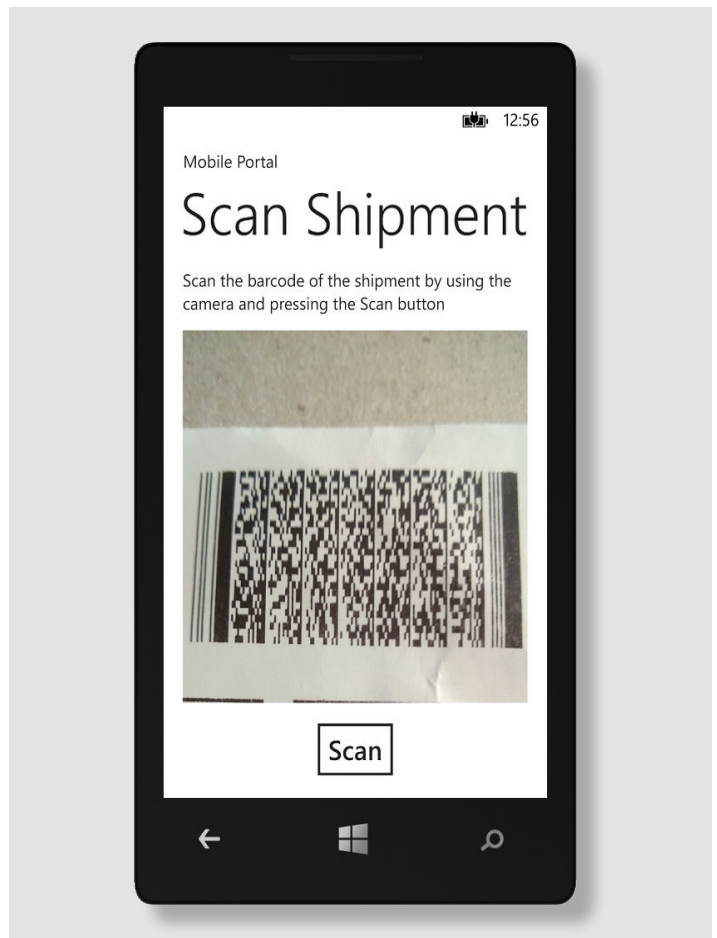
primary function to ensure the right medication kit is dispensed to the right patient, on time, every time.

Clients also benefit from RTSM services that are part of a complete, integrated clinical trial supply chain management service that facilitates logistics management, from supplies planning through packaging and labeling to distribution and final reconciliation.

THE FUTURE OF CLINICAL TRIALS AND RTSM SERVICES

Mobile technology and its pervasiveness is a key trend that will continue to affect clinical trials and RTSM services. Mobile apps are being developed to support the tracking and tracing of all clinical trials supplies. Barcodes or eLabels (RFID chips, for example), can be scanned at the manufacturer, distribution, depot, or site or, in the case of direct-to-patient studies, in a patient's home.

The use of eLabels could be extended to check patient compliance in opening the medication kit or taking the medication by detecting a break in the seal on the packaging or even the ingestion of a chip embedded in the medication.



GPS systems will further enhance the tracking process by providing continuous information on the location of shipments, including temperature information, enabling greater security of the supply chain and providing distributors the ability to diagnose any source of temperature deviation during transportation or storage.

Apps are being developed to translate and regionalize labels in global trials and help guide depots or sites with relabeling of packaging to meet local requirements or updating expiry dates.

All of this remotely collected data would be fed back into the RTSM system to provide a control center dashboard for the clinical trial supply chain.

For clients, the benefits include increased clinical trial supply chain transparency, an increased facility to expand trials regionally, increased insight into patient behaviors and the assurance that patients are receiving the right medication at the right time.

CONCLUSION

RTSM services have kept pace as new technologies emerged over the past 20 years. Today's leading RTSM providers deliver expert services to speed and simplify clinical trials, while minimizing risk.

By using proven and validated randomization methodologies and algorithms, modern RTSM services create dependable, configurable systems that can be quickly adapted to any clinical trial regardless of the company, phase, region or therapeutic area being studied.

Utilizing a faster and simpler study design, build, and test process, RTSM services can typically deliver a system in four to eight weeks. The system can be easily modified as needed either before or during the trial, without disrupting its progress.

Simplifying the user interface is a key to successful deployment of the system at sites around the world, regardless of the user's language or level of experience with clinical trials and technology. User-friendly RTSM services enable investigators and their staff to control supplies at their sites and depots to track and manage supplies, and to ensure that patients get the supplies they need, when they need them.

The expertise that designs, develops and manages the RTSM system for clients is as important as the technologies that power it. A project management team backed by a qualified provider with global capabilities and experience provides assurance to the sponsor or CRO that the RTSM service will support the success of the clinical trial.

FOR MORE INFORMATION

To discuss your organization's requirements and learn more about RTSM services from PAREXEL, contact us at info@PAREXEL.com or visit www.PAREXEL.com/rtsm.

REFERENCES:

- 1 PAREXEL Online Poll, www.parexel.com/eClinicalSolution/data, June 2014
- 2 IRT Market Dynamics and Service Provider Benchmarking, www.ISRreports.com, October 2014

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JOURNEY TAKES YOU,
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