4G CLINICAL

Best Practices for Sponsor RTSM Strategy

Guidelines for Study Start-Up, Maintenance and Close-Out

Knowledge Sharing Series

Best Practices for Sponsor RTSM Strategy

Guidelines for Study Start-Up, Maintenance and Close-Out

This white paper represents a compilation of industry best practices for designing, implementing and leveraging randomization and trial supply management (RTSM) software in clinical trials. In recognition that most sponsor organizations have internal SOPs for clinical software, the purpose of this paper is to provide general recommendations and discussion points when using RTSM software. These recommendations and points are extrapolated from historical experiences with RTSM (IRT, IVRS) at various size sponsor, CRO,

Introduction

The Need for RTSM Best Practices Development

The RTSM system has critical functions including dispensing drugs and randomizing patients, along with direct patient impact. As clinical trials are becoming more complex, the reliance on these systems, to function as intended is growing and is becoming more top of mind to regulators. However, when it comes to the management of these systems there is a wide range of processes utilized by sponsors and a lack of industry standard. While many organizations have RTSM standards in place, their management varies widely depending on several factors, including:

- **Internal RTSM knowledge and experience**
- **Trial scope, complexity, and standardization potential**
- **Organizational structure**
  SiSize and functional ownership of RTSM (e.g., clinical, supply, data management)
- **Existing clinical systems and/or clinical data strategy**
- **Collaboration with external partners**
  Fully outsourced, SaaS/Tech transfer,

The goal of this white paper is not to establish an industry standard, but rather to present best practices that can be applied regardless of the factors mentioned above. There are demonstrable benefits to defining a RTSM strategy surrounding best practices for quality and compliance, RTSM system design/specification process, user acceptance testing (UAT), system change management and study close-out. Guidelines around RTSM project management, supply chain and data management strategies are also discussed.

Getting Started
Scope of Work and Vendor Qualification

Determine Scope of Work – What Does the RTSM Need to Do?

In parallel with drafting the study protocol, the operations group should begin thinking about what they need the RTSM system to do. This step is commonly skipped if the study managers have little or no expertise with the RTSM. ***Now is the time to start drafting the specifications.***

Fundamentally, the core functions of the RTSM are randomization and trial supply management. From the study manager's point of view, the RTSM is responsible for enrollment, patient tracking, medication dispensation, cohort management, site activation, enrollment and maintaining the study blind. From the supply manager's point of view, the RTSM is responsible for inventory management, drug accountability, and reconciliation.

Since RTSM systems have evolved, trial sponsors can now easily collect data elements that aren't necessary in the RTSM but 'nice to have.' Collecting data elements that are not required for RTSM like inclusion/exclusion criteria or discontinuation reasons may contribute to capturing information in multiple places such as Electronic Data Capture (EDC), and Clinical Trial Management System (CTMS), resulting in a potential misalignment in data across systems. To that point, what clinical systems or supply systems must the RTSM integrate with? Which brings us to the next step. What is the overall data strategy?

Not discussing this upfront can lead to a data problem whereby your data management group needs to reconcile all trial data against duplicate sources.

Keep It simple.

> ***"Collecting data elements that aren't required for the RTSM may contribute to capturing data in multiple places (EDC/CTMS) resulting in a potential misalignment in data across systems."***

Karen Ellis
Sr. Director, Product Development at Infinity Pharmaceuticals

Getting Started
Scope of Work and Vendor Qualification

Create a Data Strategy – Inputs, Outputs and Systems Integrations

A key to success is beginning with the end in mind and working backwards. What study data will be needed from the RTSM once the study is completed? By whom and for what purpose? Who should have access to the information? What reports do you need? What is your audit preparedness strategy? What data will you need on an ongoing basis to support interim analyses? Daily study oversight? The answers to these questions inform your RTSM reporting requirements.

Work backwards.

Align on Initial Supply Strategy

Before designing the RTSM, there are several core supply decisions that need to be made. How will supply release information be entered in the RTSM; lot management features or a data integration? Resupply parameters? Answers to these questions directly impact the RTSM design and can be very challenging to add to the system after the fact, depending on the flexibility of your RTSM.

The next step is to assess how much drug is required to support your clinical trial and what the forecasting strategy should be. An important consideration at this step is to ensure that if a study drug forecasting tool is required to support the study or program, that the drug forecasting tool chosen is built directly in the RTSM or has robust integration capabilities.

In addition to ensuring proper system connectivity, it is also important to leverage the RTSM vendor expertise designing and optimizing the supply strategy for your study.

Tips

The closer your supply planning system is to your operational supply system (i.e. having the forecasting tool built directly into the RTSM), the more accurate your forecasting will be.

Consider developing a small dedicated team for those tools to build a solid knowledge base and knowledge transfer between programs.

Getting Started
Scope of Work and Vendor Qualification

Qualify Your Vendors

The bio/pharmaceutical industry is a heavily regulated industry. RTSM systems must be validated for their intended use according to an established protocol. Any changes to the system must be validated and the results documented. While vendors must build and validate the system, sponsors must be able to show proper oversight and quality controls over their clinical trial operations. Here are some key tips to ensure quality and compliance:

- Familiarize yourself with both good clinical practice (GCP) and Good Manufacturing Practices (GMP) regulations and the impact of the ICH E6 addendum on RTSM systems
- Conduct a computer systems validation (CSV) audit of your vendor; The recommendation is to complete this prior to study start. If that is not possible, your vendor should be on your QA team's audit list
- Audit your vendor's change management procedures and conduct ongoing audits of current projects
- Understand where the data is stored, what measures are in place for disaster recovery and processes to ensure full traceability

Tip

Communicate system and standards expectations with your vendors early in the specification process to avoid unnecessary features in the RTSM system. This ensures that the focus remains on critical functionalities specific to your needs, preventing duplication across other systems.

Study Start Up
Including RTSM in Study Planning

The RTSM development steps should be incorporated in the study start-up plan, including reviewing study requirements/specifications, training materials and participating in UAT.

Assemble a RTSM Project Team

It is critical to assemble a team including the clinical operations lead, clinical supply lead, and statistician to review the specifications. If possible, it is also recommended to include a data management lead (for data collection needs) and a CRO (for site-facing input). The team should demo the RTSM to ensure everyone is familiar with the inputs and outputs of the system.

Designate an Internal RTSM Subject Matter Expert (SME)

In many sponsor organizations, there may not be a clear strategy for the RTSM after the system goes live. In addition, as many clinical trial teams change the RTSM, knowledge may be lost through transition. To combat this, an internal RTSM SME should be designated as part of the study startup plan. This person can also focus on standardizing systems across studies and programs where applicable.

Internal SMEs should be accountable for:

- Alignment on scope of work and strategy for study maintenance and close-out
- Involving all functions in specification review, UAT and deployment
- Liaising as the single point of contact between sponsor and vendor
- Managing system issues and study changes as they arise

"In my experience, identifying an RTSM SME has brought us value by supporting standardization across program and study systems, enabling a reduction in system-build-lead time and overall system costs."

— **Karen Ellis**,
Sr. Director, Product Development at Infinity Pharmaceuticals

Study Start Up
Including RTSM in Study Planning

A few best practices for the RTSM SME include:

1. **Ensure the standards document outlines key elements that are consistent:**

   - Reviewers and approvers of each document should be associated with RTSM/IRT management.
   - System user types are outlined by department with a description, key system functions/modules and which user roles should have access.
   - Key data elements such as site and subject numbering guidelines are included.
   - Guides for web reports and notifications system are available.

2. **Create the standards document in collaboration between Clinical Operations and Supply Operations, with input from other key departments, i.e., data management, safety.**

Simplify the Specification Process for Your Study Team

The traditional system design process is both cumbersome and complex. It begins with drafting a lengthy user requirements specification (URS) document based on the final protocol, clinical study team members are then required to review and approve this complex technical information, which they may not fully understand. Once the URS is approved, the vendor builds the system, and the sponsor reviews it for the first-time during user acceptance testing (UAT). This approach often results in numerous findings during UAT, necessitating further system modifications before it can go live.

However, with advancements in IRT technologies, more flexible and agile software development methodologies, combined with natural language processing (NLP), are transforming this traditional process. Study teams no longer need to approve extensive URS documents they might not fully grasp; instead, they evaluate and approve the actual system. A fully deployable system is delivered before the specifications are signed, sometimes even in a demo state before the initial specification is seen. With each iteration of the system, quality improves, and the sponsor gains increased confidence that the system meets the needs of their trial.

User Acceptance Testing
(UAT)

While the vendor is responsible to ensure the system is properly validated to perform the necessary requirements, sponsors need to accept the system for use. This process, called UAT, involves having the trial sponsor interact with the system and signing-off that it works as intended—or is fit-for-purpose.

The process for UAT varies widely across the industry. Some organizations don't conduct UAT at all while others have teams of people writing scripts and essentially revalidating the system after the vendor does.

Understand What Level of UAT is Necessary

UAT should not be an exercise to find bugs and fix quality issues. The goal of UAT is to accept the system as fit-for-purpose. Major findings should be a red flag to overall quality issues. The process can be utilized to bring additional needs that the sponsor may not have thought of to the forefront.

> ***"To ensure your user acceptance testing is executed as efficiently as possible, I'd recommend having your RTSM SME preschedule testing to ensure the tester has a dedicated chunk of time to spend in the system testing."***

— **Karen Ellis**
Sr. Director, Product Development
at Infinity Pharmaceuticals

User Acceptance Testing
(UAT)

Actual RTSM Users Should Participate in UAT

The RTSM SME drives the UAT process. But who should be involved in UAT? The same principles used to align on the level of UAT apply when determining the number of individuals which should be involved in testing the system. There needs to be a balance. At minimum, the following roles should be involved in UAT:

- The sponsor RTSM project team that helped define the requirements of the system. They are best suited to determine whether the requirements documented are represented accurately in the system.

- Actual system end-users, including the study team, sites and CROs. This is the one that may be skipped during UAT, but it is critical at this stage. The requirements as implemented by the RTSM project team can be reflected in the system, but if the system action is not user-friendly you don't want to wait until system go-live to find that out.

> ***"A UAT strategy should always focus on the high-risk areas of the system which could impact patient safety. Functionality which impacts randomization, dosing calculations, dispensation, and blinding should be comprehensively tested. ."***

— **Carla Reis**
Vice President. Enterprise Operations, 4G Clinical.

Study Maintenance

Managing Protocol Amendments + System

Understand the Process for RTSM Changes to Set Expectations Early

The ability to make changes to the RTSM system after it goes live is of great importance. It is essential to comprehend the process and limitations associated with making modifications to the RTSM system to accurately assess their impact on your study. In the bio/pharmaceutical industry, changes are unavoidable, necessitating the incorporation of flexibility into the system architecture from the outset. By anticipating potential changes and designing the RTSM with possible protocol amendments in mind, one can better navigate evolving study requirements and ensure seamless progress.

Conduct a Protocol Amendment Impact Assessment

If you are finding that minor changes to the RTSM are taking 2–6 weeks to complete, major changes like protocol amendments can feel like a brand-new system build. This can be very disruptive to your study.

Change orders due to amendments may be required to adjust the RTSM functionality; protocol design changes impacting inclusion criteria, dosing and visit schedules are two common examples of protocol amendments that require a system change. Change orders of this nature can historically can take weeks to be reflected in an RTSM system if they go through a waterfall approach of requirements, design, testing, development and validation. These changes can take 6 weeks or longer. In addition to further delaying a study, change orders are costly.

Tip

Simplicity in design is the easiest way to support future changes within your RTSM that reduces risk and scope.

Study Maintenance

Managing Protocol Amendments + System

Your protocol amendment impact assessment should include the following steps:

1 **Quantify the Impact of Historical Changes on Your Study Timelines and Budget:**

Chances are you have had minor changes in a study before a major one has/will happen. What was your experience?

Did the small changes take longer than you expected? What was the incremental cost? What was the impact on your study team, your end-users? Was there a process in which all stakeholders were notified and steps taken to handle delays? Use this experience to assess what could be done differently the next time you have changes arise – especially larger protocol amendments. This also goes back to understanding the flexibility of the RTSM to make changes – this will help make sure you have the best plan in place or at minimum to set expectations internally.

2 **Prepare for Amendments Before They Happen:**

You should familiarize yourself with the most common protocol amendments and where the risks may lie within your study. There should be a process in place, led by the RTSM SME, to assess the impact and communicate to internal stakeholders.

Tip

When designing an IRT solution for your study, it is important to consider end user usability to ease adoption by all parties (internal and external). If the solution is difficult for end users to utilize within their day to day work, the IRT becomes a hinderance and not support for operations of managing the clinical trial.

Study Maintenance
Managing Protocol Amendments + System

Ensure Full Traceability of Data

The RTSM was historically considered to be a transactional system. With the evolution of RTSM functionality and expanding supply related features, RTSM systems are often considered a system containing source of truth data, not just a copy. It contains important supply information which may be required during an audit, as well as stores critical information in the case of a recall. As a result, the importance of RTSM has become even more elevated in the eyes of regulators.

ICH E6 focuses on validated control of clinical systems and data. Authorities want to see all the version changes and understand the impact of any data changes on the trial. In addition to understanding current regulatory requirements, you must build that into the RTSM plan at study start. Again, do not wait until study close to think about what data is needed from the system.

Tip

Familiarize yourself with the recent addendum to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6).

Conclusion

There is no standard RTSM system or process for managing them within the industry. However, given the criticality of these systems to support clinical trials, it is important to share collective Best Practices within the industry. A summary of key Best Practices includes:

- Consider RTSM as a critical element to start-up planning
- Keep the functionality of the system as simple as possible
- Designate an internal RTSM SME to drive strategy and execution from study start through study close
- Don't underestimate the impact the specification and UAT process has on system quality
- Understand the ability of the RTSM to adapt to changing trial needs, both minor and major adjustments
- Familiarize yourself with current regulations and requirements for data management

A Conversation with Karen Ellis

Interview by 4G Clinical

"If you take nothing else from this white paper, the main takeaway should be that you need to consider the full RTSM strategy within the overall clinical study start-up timeline. There is a tendency for teams to put one box in the timeline listing RTSM go-live – this doesn't ensure spec review/ finalization, UAT and training doc development are accounted for and these items are rushed as a result just to meet that one go-live check box. Therefore, it is critical to include all the key milestones of RTSM within the overall study start up timeline."

— **Karen Ellis**
Sr. Director, Product Development
at Infinity Pharmaceuticals

Karen Ellis Karen Ellis is the Senior Director of Product Development and Supply Operations at Infinity Pharmaceuticals, Inc. She is responsible for overseeing the timely preparation and delivery of clinical trial materials for global clinical trials which include activities such as packaging, labelling, distribution, inventory management and comparator sourcing. Karen has worked in the biotech/pharma industry for 17 years. Before joining Infinity 12 years ago, Karen was with Biogen Idec in the Global Operations team focused on clinical and commercial logistics.

Carla Reis serves as Vice President, Enterprise Operations at 4G Clinical. She brings over 20 years of invaluable experience as an operational leader in the development and implementation of RTSM (Randomization and Trial Supply Management) systems within the global pharmaceutical sector. Recognized as a leader within her organization, Carla plays a pivotal role in supporting the establishment of vendor management standards and processes for large accounts. She has helped lead major RTSM process improvement initiatives such as innovative approaches to drug assignment verification and vendor integrations.

About 4G Clinical

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

We reduce the time it takes to commercialise vital medications by delivering validated, easily extendable RTSM capabilities to Pharma and CROs faster than anyone in the world.

4G Clinical is driven by a single purpose: bring crucial medicines to those who need them, faster. 4G Clinical believes that the way to accelerate clinical research is by disrupting the way trials are executed. That's why we have revolutionized RTSM (randomization and trial supply management) and supply forecasting capabilities and services from the ground up. 4G Clinical is committed to helping sponsors and CROs follow the science, wherever it may lead, as quickly and as safely as we can.

While we will not discover the next novel compound in the lab, we are doing our part by leveraging our extensive experience and technological innovations to bring speed and agility to clinical trials.

Prancer RTSM®

Our 100% configurable and agile RTSM is built for the clinical trials of today and tomorrow.

4G's RTSM platform, Prancer RTSM®, utilizes natural language processing alongside integrated clinical supplies forecasting and management functionality to slash development timelines, increase operational efficiencies and offer exceptional quality.

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Contact us today to start a conversation.

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