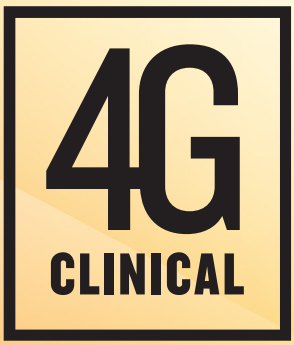

Best Practices

For Randomization and Trial Supply Management (RTSM)

Knowledge Sharing Series

Best Practices for **Randomization and Trial Supply Management (RTSM)**

Guidelines for Sponsor IRT Strategy – *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, extrapolated from historical experiences with RTSM (IRT, IVRS) at various size sponsor, CRO and vendor organizations.

Introduction – *The Need for RTSM Best Practices Development*

The RTSM has critical functions including dispensing drug and randomizing patients, with direct patient impact. As clinical trials are becoming more complex, the reliance on these systems to function as intended is growing in importance 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 no industry standard exists. In many organizations there are RTSM standards, but across organizations they are managed very differently based on a variety of aspects, including:

- **Internal RTSM knowledge and experience**
- **Trial scope and complexity, ability to standardise**
- **Organizational structure**
  Size, function that manages the RTSM (clinical, supply, data management)
- **Existing clinical systems and/or clinical data strategy**
- **Collaboration with external partners**
  Fully outsourced, SaaS/Tech transfer, technology platform differences

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**

Best Practice #1

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.

Recommendation: ***Now is the time to start drafting the specifications.***

Fundamentally, the core functions of the RTSM are randomization and trial supply management. What does that mean? From the study manager's point of view, the RTSM is responsible for patient tracking, medication dispensation, cohort management as well as 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.

As RTSM systems have evolved, trial sponsors can now more easily collect data elements that aren't necessary in 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 (EDC, 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.

Recommendation: ***Keep it simple.***

Best Practice #2

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 analyzes? Daily study oversight? The answers to these questions inform your RTSM reporting requirements.

Getting Started
Scope of Work and Vender Qualification

> *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

Best Practice #3
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 conduct an internal assessment on forecasting capabilities. What forecasting tools are available to support your trial? Is this tool built into the RTSM itself or separate systems?

Tip: ***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.***

In parallel with assessing forecasting tools, you should also understand your current level of internal forecasting expertise. Unfortunately, clinical drug supply managers that only have to forecast a few studies never really get the chance to gain experience in using forecasting tools optimally.

Tip: ***Consider developing a small dedicated user group for those tools to build a solid knowledge base and knowledge transfer between programs.***

Getting Started
Scope of Work and Vender Qualification

Best Practice #4
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 GCP and 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

> By sharing a standards document with the vendor at the beginning of the specification process, it can prevent teams from building unnecessary functionality into the system that is not critical to the purpose of the RTSM system or may be a duplicate across other systems.

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

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.

Best Practice #5

Assemble a RTSM Project Team

It is critical to assemble a team to review the specifications including the clinical operations lead, clinical supply lead and statistician. 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.

Best Practice #6

Designate an Internal RTSM Subject Matter Expert (SME)

In many sponsor organizations, there may not be a clear strategy for the RTSM after system go 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 standardising 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

Study Start-Up — **Including RTSM in Study Planning**

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

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 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
- Guides for web reports and notifications

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

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

Study Start-Up — **Including RTSM in Study Planning**

Best Practice #7
Simplify the Specification Process for Your Study Team

The traditional system design process is cumbersome and complex. A 200+ page specification document is drafted from the final protocol and clinical study team members must review and signoff on complex technical information they may not fully understand. After sign-off, the system is built by the vendor and the sponsor reviews the system for the first time during UAT. This process ultimately leads to increased findings in UAT and further edits to the system before the system can go-live.

As technology evolved, the 4th generation of RTSM using agile software development methodologies and natural language processing (NLP) is being applied to disrupt this process.

Study teams no longer must approve 200+ page specification documents they may not fully understand – they approve the actual system. The fully deployable system is delivered before the specs are even signed, and in some cases, in a demo state before seeing the actual spec for the first time. The quality increases with each iteration of the system, and the sponsor has confidence that the system they are approving meets the needs of their trial.

> *Our iterative build process allows study teams to explore their RTSM design before signing off on the specifications. This has enabled us to iterate alongside our clients, ultimately leading to higher quality systems.*

— **Amy Ripston**
Vice President, Marketing at 4G Clinical

User-Acceptance Testing (UAT)

While the vendor is responsible to ensure the system is properly validated to perform to 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.

Best Practice #8

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 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 to the forefront additional needs that the sponsor may not have thought of prior to seeing the system.

Best Practice #9

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 necessary apply when determining the number of individuals that should be hands on testing the system. There needs to be a balance.

At minimum, the following roles should be involved in UAT:

- The RTSM project team that helped define the requirements of the system. They can determine if the requirements they documented are represented accurately in the system

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

User Acceptance Testing (UAT)

*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.*

*A **well thought out and executed UAT** lends itself to a higher quality product.*

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

Study Maintenance – Managing Protocol Amendments, System

Best Practice #10
Understand What Level of UAT is Necessary

How flexible is the RTSM to make changes post go-live? It is important to understand the process for and limitations to change the RTSM so you can assess the impact on your study.

Tip: ***Ask your vendor if the RTSM is 100% configurable. If it isn't, then enquire what% is customized versus configured.***

Why? With 100% configurable systems, updates and changes are made without disruption to the customer. Partially configurable systems (even 80–90%) can range between 2–6 weeks to implement a small change. Changes are unavoidable in the bio/pharmaceutical industry. You should have a clear understanding how changes impact your study progress from a systems perspective.

Best Practice #11
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.

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

Study Maintanence — Managing Protocol Amendments, System

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.

Best Practice #12

Ensure Full Traceability of Data

RTSM historically was considered to be simply a transactional system. With the evolution of RTSM and expanding supply related features, RTSM systems may be considered the home of source 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.

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).*** 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.

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 include:

- 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 of 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

> "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

A conversation with **Karen Ellis**

Interview by Amy Ripston

Karen Ellis is the Director of 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 11 years. Before joining Infinity six years ago, Karen was with Biogen Idec in the Global Operations team focused on clinical and commercial logistics.

Amy Ripston is the Vice President of Marketing at 4G Clinical. She has 20 years of B2B experience building brands, identifying market trends and creating content, engaging thought leaders and connecting businesses together to solve complex challenges.

In addition to her role at 4G Clinical, Amy serves as the Global Marketing Officer for the Global Clinical Supplies Group (GCSG) where she launched their new brand. Amy is an Official Member of the Forbes Communication Council and contributing writer to Forbes.com.

About 4G Clinical

We reduce the time it takes to commercialize 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.

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

4gclinical.com