4G CLINICAL

Master Protocol Studies

Technology Considerations for the 'Never-Ending' Clinical Trial

Knowledge Sharing Series

Master Protocol Studies
Overview

The underlying goal of using master protocols is to increase efficiency and expedite drug development for critical unmet need. Now that the FDA is encouraging creativity in trial designs, it is important for all stakeholders (sponsors, CROs, vendors, etc.) to adapt processes to follow the science and ultimately bring medicines to patients, faster. This white paper addresses the complexities that come with these trial designs, and how technology – specifically randomization and trial supply management (RTSM) solutions – are critical to run flexible, robust and quality driven trials.

Regulatory Guidance

In an effort to accelerate the path to approval for therapies of unmet need, regulatory agencies have begun providing guidance around modernising clinical trials.

In August 2016, the EMA published the **"Guidance for companies considering the adaptive pathways approach."** This guidance enables organizations who are investigating medicines where traditional trials would be inefficient, to explore more creative protocol designs including iterative development.

In September 2018, the FDA released a draft guidance entitled, **"Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics."** This guidance provides recommendations regarding the design and conduct of clinical trials developing cancer treatments. It outlines methods to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same overall trial structure (master protocols) in adult and pediatric cancers.

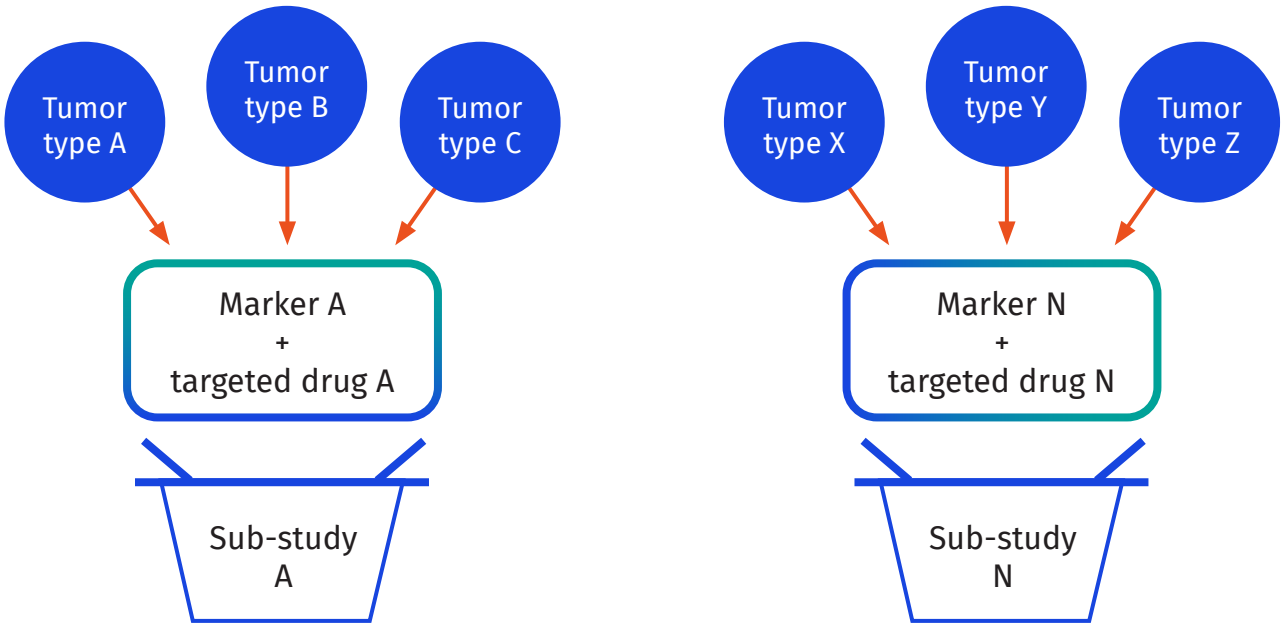
What are Master Protocols, exactly?

As defined by the FDA, a master protocol is "a protocol designed with multiple sub-studies which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure." Simply put, a master protocol acts like a map showing many routes to get to a destination where the sponsors don't know in which direction their study will evolve, until the trial is under way.

There are two types of trial designs that fall under Master Protocols: **Basket Trials and Umbrella Trials.**

Basket Trial

A **basket trial** involves a single investigational drug or drug combination that is studied across multiple cancer populations defined by disease stage, histology, number of prior therapies, genetic or other biomarkers, or demographic characteristics. It is usually designed as a single-arm, activity-estimating trial with overall response rate as the primary endpoint. A strong response signal seen in a sub-study may allow for expansion to generate data that could potentially support a marketing approval. These trials may also include expansion cohorts.

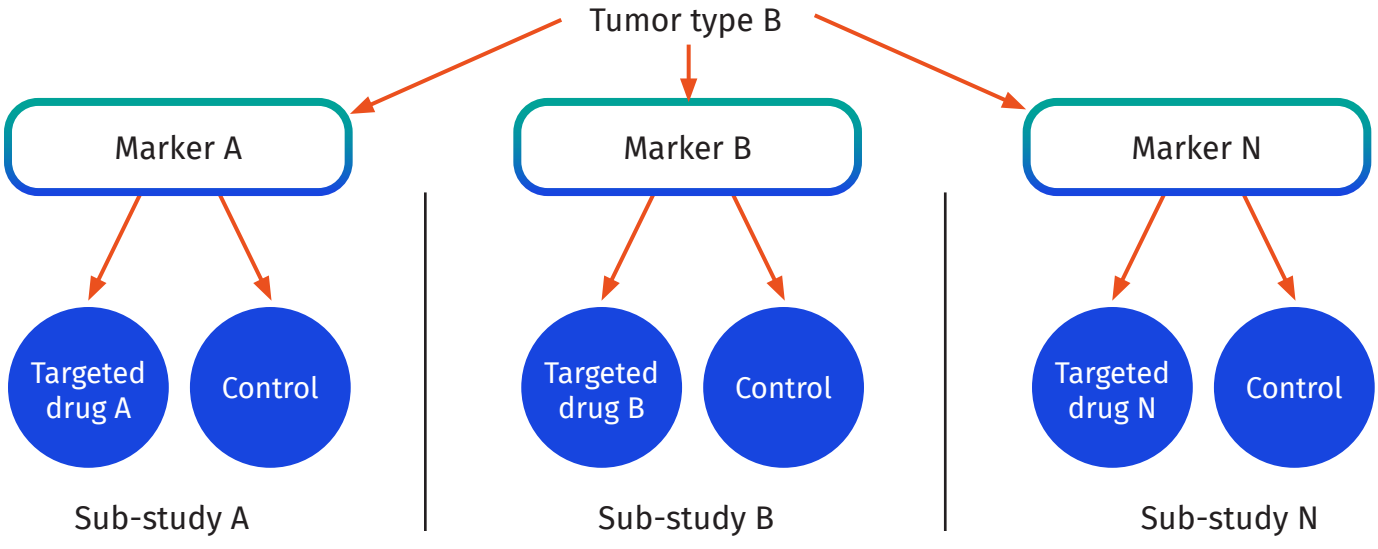


Umbrella Trials

An **umbrella trial** is designed to evaluate multiple investigational drugs administered as single drugs or as combination drugs in a single disease population. Sub-studies can include dose-finding components to identify safe doses of an investigational drug combination before proceeding with an activity-estimating component. These trials are generally designed with multiple arms where patients of the same histology or other unifying characteristics enrolled into different arms and multiple investigational agents are evaluated in a single protocol. The "umbrella" is a broad disease sub-type with several treatment options under development.

Protocols may even combine the two, for example by starting with a dose escalation using multiple combination therapies (more of an umbrella) accepting any type of solid tumor and then refining their recommended phase two dose in more specific tumor types (more like a basket).

In all types of master protocol, a common element is that the sponsor will not know what is going to be effective. If the protocol is written to allow changes to either the disease sub-types included or to the treatments explored the protocol can be labeled as a Platform trial. These changes are usually rolled out via protocol amendments. By keeping the options open, sponsors can follow any positive signals and refine the treatment as data is collected over the course of the study.



The **Problem**

There is an understanding that master protocol studies will look dramatically different in few years (i.e., 20+ new cohorts, etc.). These trials need to be designed in a way that can support multiple protocols, amendments, patient populations and supply chains, all while maintaining quality and patient safety.

Once the study is live, clinical operations professionals continuously respond to new trial data and amend the trial based on results. Each amendment can be incredibly time consuming, costly and complex. On average, amendments take 180+ days to process and can cost upwards of $250,000 – $450,000 over the life of a study.[1]

Master protocols and their subsequent amendments can also have a ripple effect on supply chains, quality, inspection readiness, validation, regression testing and timelines.

Addressing the Complexity of Master Protocols

What is needed to disrupt this process and help streamline the execution of master protocol studies? While there are many aspects of a master protocol that can be streamlined, the focus on this white paper is on the use of technology, specifically Randomization and Trial Supply Management (RTSM).

Back when the gold standard was to have one randomization and a fixed dispensing schedule it was fairly simple to program new code for each new study and work within a repeatable framework. To this day, many studies still rely on traditional, custom-coded and partially configurable systems for randomising patients, dispensing drug and site resupply (RTSM). These types of systems were built before the industry started moving towards the use of master protocols and are not equipped with the technology to support multiple protocols, amendments and supply strategies within the same study.

1. (Getz KA, Wenger J, Campo RA, Seguine ES, Kaitin KI. Assessing the impact of protocol design changes on clinical trial performance. Am J Ther 2008;15(5):450-7 doi\ Analysis of the protocol design process. Clinical Research Roundtable Symposia; April 18, 2007; 2007; Boston, MA.

The Case for Modern Technology in **Master Protocol Studies**

Even if an RTSM is designed to handle multiple paths, there are almost always unforeseen changes to the protocol that require amendments. Traditional custom-coded systems treat these amendments as new study builds and therefore the process to modify the system is incredibly lengthy, costly and challenging. Partially-configurable systems still require some level of custom coding, leaving sponsors to choose between working within the limitations of the preset system configurations, or introducing delays while custom code is developed.

Once the study is built, all possible dispensing options must be tested to confirm that the right treatment is dispensed to the right patient at the right time – this is absolutely critical for patient safety. Almost as importantly, every user experience must be tested for exposure to unblinded information in order to protect the integrity of the study and the results from it. The more complex the logic, the more thorough this validation must be. In custom-coded and partially configurable RTSM systems, the more amendments that are made, the more times this process needs to be repeated.

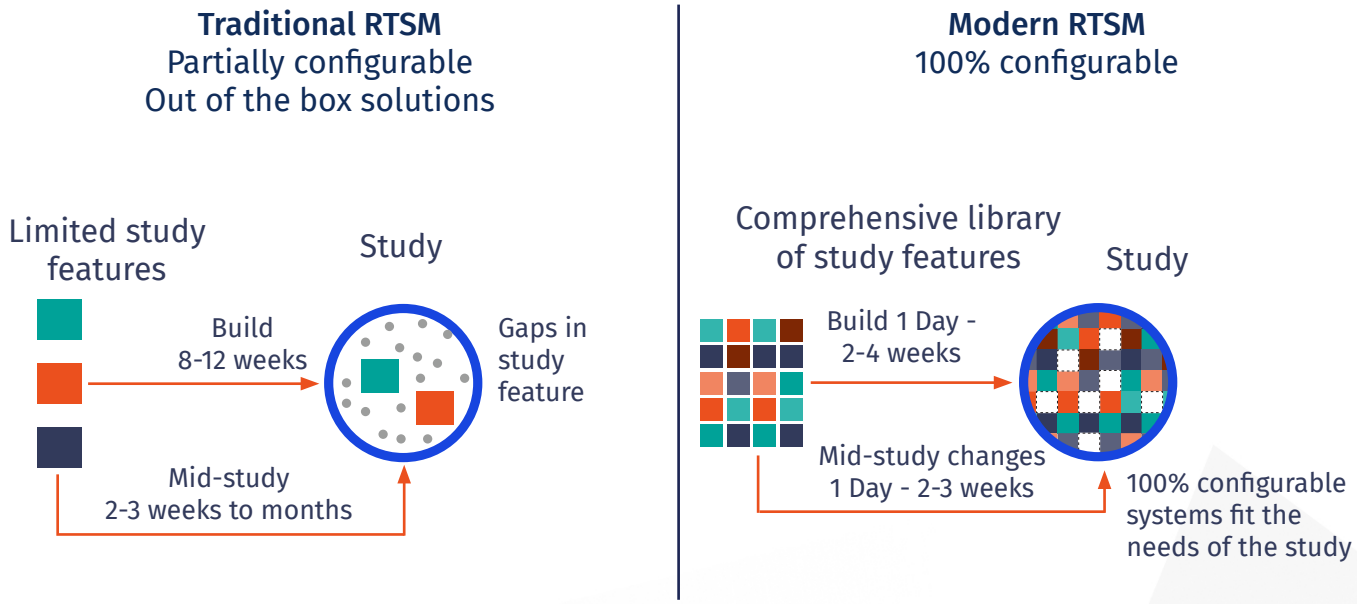
In a way, traditional RTSMs approach these system builds and validation processes as multiple, separate RTSMs for a single study. This is not sustainable as more and more trials move to these designs. Sponsors should not settle for the delays and limitations of a “multiple RTSM in one” approach, but rather seek one RTSM that was built to enable flexibility to follow the science (no matter how many amendments or supply changes are needed) with robust quality and audit trail reporting.

The Case for Modern Technology in **Master Protocol Studies**

*The answer is **modern RTSM systems.***

Modern, fully-configurable RTSM system offer robust configuration options that can support the level of complexity a master protocol demands, and are critical to reduce the operational and administrative burden for these studies.

Traditional vs. Modern RTSM



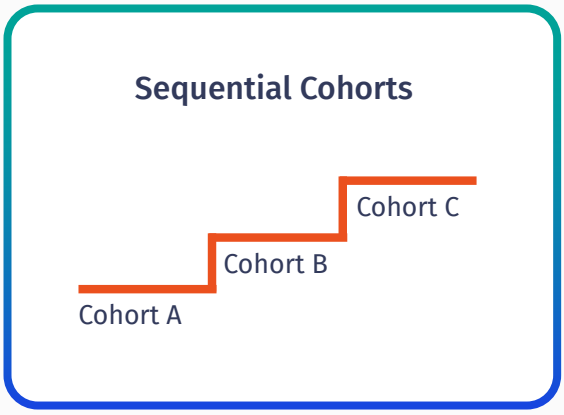
Why Modern,
100% Configurable RTSM

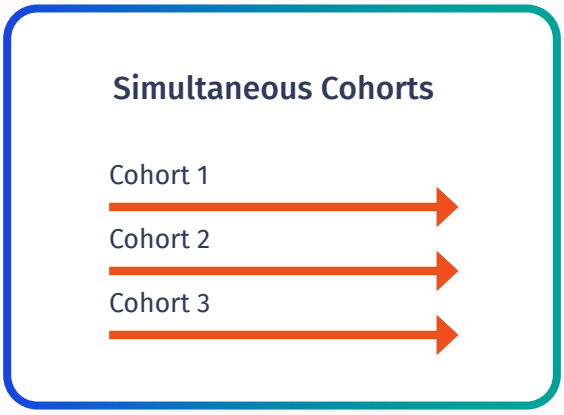
Master protocols are critically dependent on configurable and flexible randomization and trial supply management (RTSM) systems. Not only can you build in flexibility from the onset, but mid-study changes and amendments can become faster and more efficient while offering robust quality.

The following delves into more detail about configuration features to look for when launching a master protocol study:

Robust Cohort Management

Robust cohort management functionality allows sponsors to support increasingly complex protocols while adapting to new information. Each sub-study can be contained as a series of cohorts that can be dedicated to specific combinations or dose levels of therapy needed for basket studies or disease sub-types for umbrella studies. Each cohort enrolls patients that may have different dosing requirements, distinct dispensing schedules, and varied enrollment caps.





Why Modern, **100% Configurable RTSM**

The ability for the sponsor to make changes as the study progresses without having to contact and wait for the vendor is critical.

Some capabilities to consider:

For dose escalation cohorts it may be preferable to maintain tight control over which patients qualify for which cohorts, and have a medical monitor assign the cohort per patient after confirming eligibility. Once a study expands it may be impractical to do so, and cohort assignment may occur just before the first dosing and be performed by site users. The sponsor is able to leverage both options within the same study.

- **Increase enrollment caps as studies progress to tightly control how much data is collected**
  Cohorts may begin with sentinel patients to confirm safety and then expand to include a few more patients, or may need additional patients to determine if a dose limiting toxicity indicates the maximum tolerated dose. The sponsor is able to adjust these caps as those decisions are made, without delay.

- **Choose to reserve slots for specific patients or specific sites.**
  Rather than having a medical monitor assign cohorts, the sponsor is able to allow sites to do so and still maintain tight control. By reserving a slot in a cohort, the sponsor can respect any communication with sites about patients in screening while allowing competitive enrollment for additional remaining slots.

- **Define the dosing scheme and/or dose level.**
  Once recommended dose levels are determined the sponsor can set new cohorts to that level to continue research into the combination or disease sub type that is seeing the most efficacy. Additionally, the sponsor can set dosing schemes to ensure others at a lower dose titrate up without having to contact the vendor.

These are just a few of the many decisions a flexible RTSM and innovative cohort management functionality allows sponsors to make regarding their study. Being able to implement these changes themselves rather than going through the traditional change order process saves time and resources while allowing them to focus on the clinical trial.

Why Modern, **100% Configurable RTSM**

Protocol Versioning

Protocol amendments cannot be applied to all sites at exactly the same time. Each site has to perform its own approval process in order to begin working under the new protocol version. Often this results in multiple protocol versions being used at the same time, so it is critical to know what protocol version each site is operating under. A modern RTSM allows the sponsor to define this per site.

What does this mean? As each site begins working under a new protocol version, the sponsor can assign the correct version to the site. Each protocol version can be connected to a different visit schedule, different dosing schedule, specific cohorts - whatever the protocol change requires. Per site, any new patient registered will fall under the new protocol version with whatever that entails.

Impact Assessments – *Supply Complexity Resulting from Changes*

There are complications of adding cohorts beyond the challenge of adding a new subset of patients to research. It is important not to underestimate the added complexity that comes with it. For example, adding a cohort could mean increased burden on recruitment and retention leading to new sites in new locations.

With a modern RTSM changes to the supply chain are expected, and the sponsor is empowered to make adjustments without needing to reach out to the RTSM vendor.

- **Lot management:**
  Perhaps a new label is needed for a new country but you need to use the lots already assigned to the study. The ability to sublot within the RTSM helps manage the re-label effort to specific regions.

- **Add countries:**
  If new countries are needed, with a modern system the sponsor can add them themselves. If a new depot is needed that may require intervention from the RTSM vendor to update drug distribution integrations, but the sponsor can begin setting up sites in the new country themselves.

- **Cohort-specific resupply:**
  Each cohort may have different supply projections. A dynamic RTSM can see which cohorts are open and project demand that is specific to the current status of the study.

As with any change, there needs to be an impact assessment and discussion across the organisation before any system changes are implemented. The RTSM should enable quick execution of study changes once the sponsor has determined the best path forward.

Why Modern,
100% Configurable RTSM

Testing and Audit Trail

One of the major headaches that comes with amendments from a systems perspective can be regression testing. With traditional RTSMs, where each amendment is treated as a new study build, there is added complexity, cost, internal resources and added time associated. It has also been noted some sponsors are seeing additional inspections focus on these amendments of master protocol studies.

A configurable system can streamline the validation process, but when inspected the same rules must apply as with any software system. Any changes to the production environment have to have a clear story to tell, from the approval of requirements to testing and getting approval to make the change in production. The quality story increases in importance with each new change introduced. The more changes are needed the more important this quality story will be. When qualifying vendors, ensure that the SOPs controlling this process are clear and that a robust internal audit system is in place to ensure they are being followed. If it isn't documented, it didn't happen.

Where the sponsor is empowered to make changes themselves auditors will look at the audit trail to see the story of how a study has evolved. Modern RTSMs have full transparency into changes with a robust audit trail that is easily queried. In particular, the sponsor can see an audit trail of the cohort management, to see who updated a cohort to increase caps or reserve slots per site and when they made each update.

Conclusion

Master protocols can become incredibly complex as sponsors are following ***where the science leads.***

Traditional RTSM systems were not built to support the level of flexibility and agility needed from a technology standpoint.

Therefore, ***a robust, modern, 100% configurable RTSM is critical*** *to enable the goals of these studies –* ***increasing overall study efficiency*** *and expediting drug development.*

Meet Kathleen Greenough

About the Author

Kathleen Greenough, Director of Client Solutions at 4G Clinical, has 16 years of experience in life sciences spanning Clinical Operations, Finance, and IT. Her wide range of solutions implementation expertise includes RTSM, CTMS, trial costing tools, OLAP financial suites and patient enrollment planning.

Kathleen has also spent many years as a Clinical Financial Planner and Analyst at a major biotech in Cambridge, MA, gaining a broad and deep understanding of the challenges inherent in Clinical Development. Specializing in software adoption and a frequent speaker at industry conferences, Kathleen is most in her element when working within a user community to facilitate solutions that are insightful and truly helpful.

Curious to hear more?
Explore our Resource Center

Still have questions?
Contact us today to start a conversation.

About 4G Clinical

4G Clinical is a leader in randomisation and trial supply management (RTSM) for the global life sciences industry, offering the only fully cloud-based, 100% configurable and flexible solution utilising natural language processing (NLP) and integrated supply forecasting.

Our expert staff possesses a combination of humility, confidence, curiosity and commitment to getting things done. Most importantly, everyone at 4G Clinical is passionate about our mission of bringing crucial medicines to those who need them, faster.

4G Clinical, a leader in randomssation and trial supply management for the global life sciences industry, is headquartered in the U.S., within the Boston Biotech corridor in Wellesley, Massachusetts, alongside a West Coast office in Portland, Oregon. The company also has offices in Europe: Amsterdam, Basel, Brussels, Dublin, Nottingham, and Rheinbach, as well as Tokyo and Tel Aviv. To find out more about 4G Clinical's expertise and advisory services to bio/pharmaceutical companies and contract research organisations, visit **www.4gclinical.com**

About 4G's Clinical Supply Forecasting

Supply planners no longer have to build excel sheets or have the knowledge base to decode complex algorithms to inform supply decisions.

4G's clinical supply forecasting solution enables you to make decisions based on business need rather than relying on complex calculations. As the world's first integrated RTSM and clinical supply forecasting solution, supply planners employ real-time visibility and leverage scenario planning to control supply decisions.

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

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