

# 5 Points of Operational Readiness

When Onboarding a New Treatment into IRT for Master Protocols

Written by Shelby Roberts

## Master protocols are ushering in a new era in clinical trials and with it they are bringing innovations to the way clinical trials are typically run.

One of the salient innovations a Master Protocol brings is the ability to add new treatments during the trial. Historically, in conventional trials, all included treatments are defined in the Protocol up front. In Master Protocols, the known treatments are defined upfront, but new additional treatments may be defined later in addendums, appendices, or other accompaniments to the Master Protocol. To make this new type of clinical trial possible, there are myriad people, processes, and technologies that must all come together.

Interactive Response Technology (IRT) is at the center of the e-clinical ecosystem, providing randomization and drug supply to all types of trials. In Master Protocols, IRT also has the ability to seamlessly integrate new treatment additions as they are identified. In this article, Almac is sharing operational readiness factors for the clinical team to consider for successful implementation of new treatments in IRT. Our considerable experience has shown that evaluating these 5 points of operational readiness are fundamental to enable the speed of Master Protocols while minimizing hiccups in its practical implementation.

### Master protocol



#### Designed with:

- Multiple substudies / subgroup populations / subprotocols
- One or more treatments
- One or more disease subtypes



#### Typically require:

- Adaptations to occur on a multi-dimensional level
- Ability to manage substudies / subgroups independently



#### Benefits:

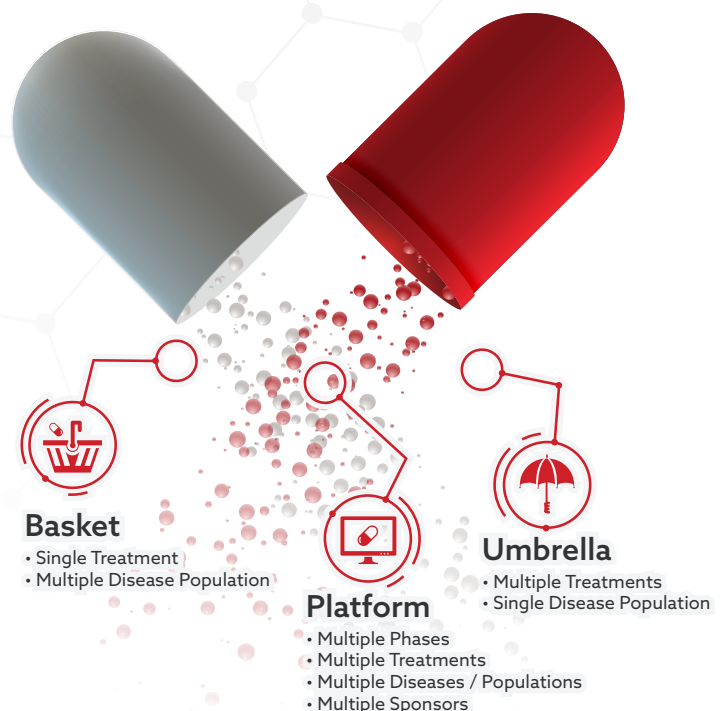
- Increased flexibility and efficiency in drug development
- Shared control arm
- Use of centralized data capture systems
- Patient-centric

### Master protocols terminology

A Master Protocol is defined by FDA as “a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes (FDA, 2018).” There are three main types of Master Protocols (Basket, Umbrella, and Platform, see figure below, (FDA,2018)).

Basket trials focus on a single treatment in multiple disease populations, and typically do not require the addition of new treatment arms. Umbrella trials consist of multiple treatments being studied across a single disease population. Platform trials study multiple treatments across multiple disease populations. Onboarding new treatments are most common for Umbrella and Platform trials.

Regardless, when making considerations for onboarding new treatments, the approach is generalizable. Therefore, this paper will focus on the overall approach and will not break it down by specific type.



## The Big Picture Question:

1

***Is the existing IRT infrastructure ready to receive the new treatment?***

Before onboarding a new treatment, the first step is to assess the existing IRT technology infrastructure. For example, the Master Protocol may have been built with all substudies in a single database or the Master and each Substudy may have been set up as separate entities. Depending on the original design, the biostatistics teams should confirm if the new treatment can be included within the existing structure of the randomization (e.g., treatment management configuration, cohorts, strata, substudies, eligibility requirements, etc.).

The clinical operational and clinical supplies teams should confirm if the new treatment can use existing visit schedules, dispensing calculations, and protocol enforcement rules. These are extremely important considerations that are deserving of their own papers, and these discussions should not be discounted. The purpose here is to examine the logistical concerns once those determinations have been made. If the answer to the Big Picture Question is “no”, and the new treatment has needs beyond the existing IRT infrastructure, then there will have to be an evaluation to work out those IRT infrastructure needs. To move on to the next question, it’s assumed that either the IRT infrastructure is sufficient or is being amended appropriately.



## Logistics Questions:

2

***Is your team trained and ready to apply the real-time adaptations for the new treatment in the IRT?***

In perpetual trials, training and retraining is also a perpetual need. Staff will change, and newcomers will need to understand how the IRT was designed for flexibility. Configuring the real-time adaptations could have a major impact, like setting a block size/treatment ratio and enabling or disabling treatments for various patient cohorts or subgroups. Successful training programs include elements that are less obvious, such as how to ensure any caps are entered correctly or how to optimize the settings when very few sites have received IRB approval for the new treatment.

**Understanding and planning for the human element of administering these high-impact changes is fundamental to successful implementation in the IRT.** Personnel responsible for applying the real-time adaptations configuration settings will likely feel more comfortable if there are quick reference cards and training materials available to refresh their understanding of the impact of the changes they are about to make.

In your study team, there are likely several individuals that could administer the high-impact real-time adaptations in the IRT. There may be an in-house or outsourced biostatistician, and / or clinical operations personnel who will apply the IRT configuration settings to match the ever-evolving protocol.

Designating who is responsible for configuring real time adaptations requires consideration of the context of the adaptations and content included within the feature. For instance, an unblinded user may be required if there is unblinding information displayed on the feature such as total randomized to each treatment. If the inputs impact randomization (e.g., ratio weights, block size, treatment assignment probabilities), the required user is likely a biostatistician or would need to collaborate with a biostatistician. If there are components that impact creation of new kit types (e.g., contents, dosing schedule), then those inputs are likely best suited for a supply manager role.

While decision-making may be collaborative, it is very common for the IRT to require an individual, not a group, to complete the necessary tasks in the system. **Having clear designations for who is accountable for updating the IRT with the real-time adaptations configuration settings will ensure timely implementation.** Having back up staff identified for any time the accountable individual is unavailable is also recommended to optimize operational readiness.

### 3

#### **Are you ready for UAT responsibilities that accompany the new treatment?**

If the IRT includes flexibility for the randomization scheme and / or ability to add new kit types, the UAT scope may be very light or maybe not needed at all. However, if flexibility was not built into the IRT design, or there are additional requirements for the specific treatment, you may need to coordinate a more extensive UAT.

Depending on the scope of the amendment for the new treatment, you may need stakeholders from Clinical Operations, Biostatistics, or other areas to effectively perform UAT. There may be multiple vendors involved, such as a CRO or a statistical services vendor. **Ensuring that the appropriate roles from the appropriate disciplines or vendors are trained and available to complete any necessary testing will be key to meeting your timeline for the new treatment.**



### 4

#### **Are you ready to implement your supply strategy for the new treatment?**

A new treatment arm typically implies new types of drug product. It's possible to avert this need if the new treatment arm is a new combination of existing compounds or product already in the study. However, if there are truly new types of drug product needed, the IRT will need to be updated to include this information in order to complete shipping and product assignment functions. If the new type of drug product is uniquely numbered, it will require creation of a new kit list which will need to be imported into the IRT as well. The lead time to produce/package/-ship any new drug product types will also need to be accounted for in the overall timeline.

To ensure the IRT runs smoothly, it's important to identify the person(s) who will determine the strategy for supplying and resupplying the drug product for the new treatment arm. Creating new or updating existing supply shipping parameters, considering initial order quantities, trigger and resupply quantities, visit projections, as well as the temperature sensitivity and shipping compatibility with existing drug product, will all need assessment.

Coordinating who will be responsible for supply release to the IRT vendor at the appropriate time is also an important element for seamless implementation. The entity providing the new kit list for uniquely numbered supply, or release for non-numbered supply may not be the same entity that has provided them for existing treatments.

**Ensuring the relevant partners know their responsibilities and due dates is critical to meeting your overall timeline.**

### 5

#### **Are your sites ready for the new treatment?**

Typically, sites require new Institutional Review Board (IRB) approval for each new treatment that is added to the Master Protocol. If this is necessary and built within the IRT, defining which role will approve sites in the IRT for the new treatment will be important. Staff in those roles will need a clear understanding of what approval means. For example, whether that approval applies to the ability to receive new drug supply for the treatment or the ability to randomize to the new treatment, or both. The approving role will need to be alerted that the IRT is ready for them to complete this task.

Site readiness is also contingent on drug supply being available at the site. When the IRT manages drug supply as well as patient randomization, the amount of time needed to get the drug supply to sites needs to be factored into the overall timeline. Whether orders are triggered in the IRT from a previous activity like site approval or there are manual triggers of drug ordering, it's a key activity for the operational readiness plan. The real world availability of the drug supply at the site needs to match the IRT capability to assign the new treatment.

## Conclusion

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Real-time adaptations capabilities within IRT are key enablers to the onboarding of new treatment arms in a master protocol. Operational readiness for this critical point in the study can be achieved by ongoing team training, shared understanding of the IRT infrastructure and coordination of stakeholder activities for UAT, site onboarding and supply management. These considerations do not cover every possible scenario for perpetual study designs introducing new treatments, but does give a framework for key decision making to speed and ensure success of new treatment adoption. Working with a trusted and experienced IRT partner who can help ensure broad evaluation is the best way to ensure your Master Protocol is ready to successfully onboard a new treatment.

### References:

FDA (2018), Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics (Draft), available at <https://www.fda.gov/media/120721/download>



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### About the Author

As Business Process Leader at Almac Clinical Technologies, Shelby leads the Adaptive Trial Design Center of Excellence responsible for design and implementation of IRT technology for Master Protocols and Complex Innovative Designs.

Shelby has over 19 years of IRT experience in Quality Assurance & Regulatory, Development and Operations. Shelby holds a Bachelor of Arts in Economics from Rider University and is a certified Lean Six Sigma Black Belt.

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