WHITE PAPER

# Master Protocols in Oncology: A Biostatistics Execution Perspective



PRESENTED BY:

Allucent®
Helping bring new therapies to light

PUBLISHED BY:

FIERCE Biotech

© 2026 Questex Content Marketing. All rights reserved. All registered trademarks are property of their respective owners.

MAY 2026

PRESENTED BY: Allucent | PUBLISHED BY: FIERCE Biotech



# Master Protocols in Oncology: A Biostatistics Execution Perspective

## CONTENTS


Introduction ..... 3

The technical challenges facing biostatisticians ..... 4

Operationalizing complex statistical designs ..... 8

Looking ahead ..... 11

References ..... 11

About ..... 11

## Introduction

Master protocols are a critical shift in drug development, transitioning the industry from traditional, standalone trial designs to integrated, evidence-generating platforms. Adoption of the protocols, including basket, umbrella, and platform trials, is accelerating as sponsors recognize the potential to make R&D faster and more efficient by assessing multiple hypotheses in single studies.

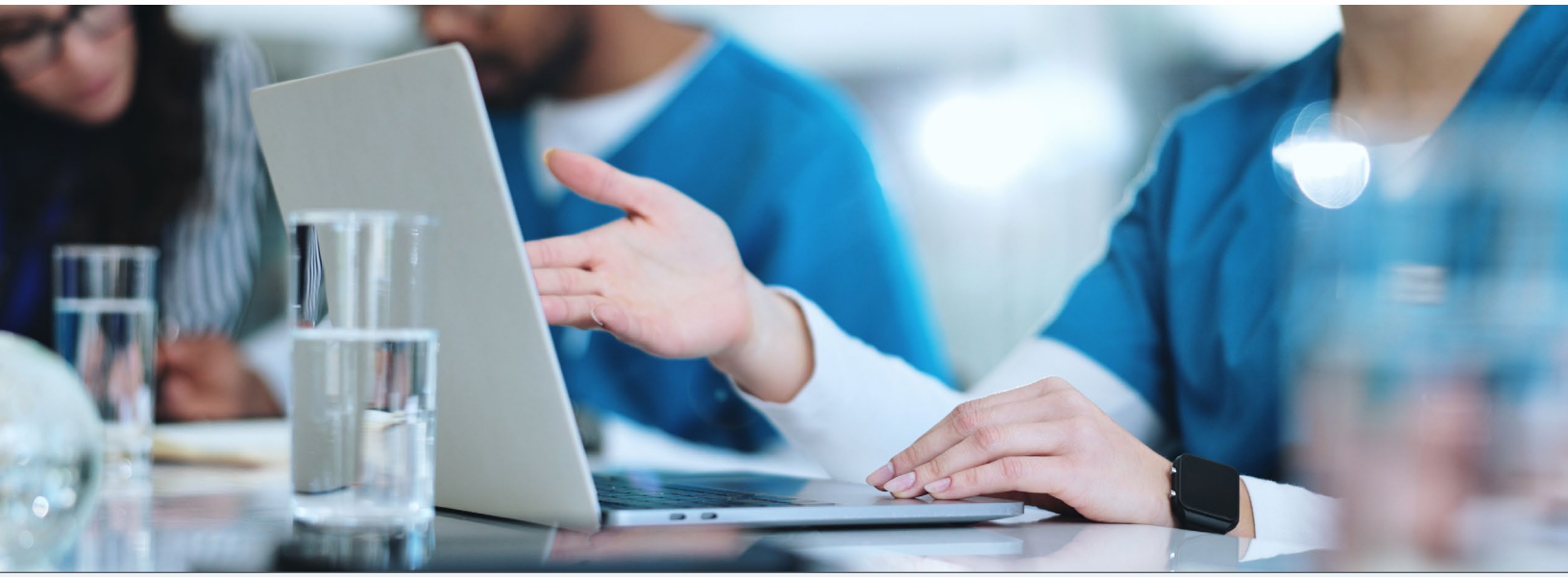
The traditional model of clinical development, in which one drug candidate is tested within one tumor type, is increasingly misaligned with modern cancer care. While the traditional approach worked when oncology R&D was focused on organ-based indications, it is a poor fit for today's biomarker-driven pipelines in the era of precision medicine.

Today, biopharma companies need trial designs capable of screening smaller, highly fragmented patient subpopulations without the redundant time and cost of standalone studies. By leveraging master protocols, sponsors compress development timelines, maximize the clinical utility of scarce patient data, and leverage shared infrastructure. In rare tumor types, master protocols allow researchers to borrow information across cohorts to offset limitations caused by small patient populations.

Sponsors have validated the benefits, with I-SPY 2 demonstrating the ability of platform trials to rapidly select promising regimens for confirmatory phase 3 trials and to accelerate drug development.[1] Other clinical trials including Lung-MAP, NCI-MATCH, and STAMPEDE have provided further validation.[2-4]

However, while such innovative designs are frequently discussed conceptually, less attention is given to the biostatistical considerations needed to execute them successfully in practice. Translating complex, adaptive designs into rigorous statistical practice introduces challenges, causing the promise of master protocols to collide with practical and regulatory barriers.

This white paper explores the gap between theory and execution, examining the implications of using master protocols, how to operationalize complex designs, and practical considerations for biopharma teams.



## The technical challenges facing biostatisticians

To realize the proven benefits of master protocols, sponsors must turn trial design theory into real-world statistical execution. That requires a clear understanding of the key technical challenges associated with the move from traditional trial designs to basket, umbrella, and platform studies.

### Controlling multiplicity across arms

In the context of master protocols, addressing multiplicity is a fundamental requirement for regulatory approval. Health authorities prioritize multiplicity because protocols that evaluate multiple treatments, patient subgroups, or biomarker-driven subtrials raise the risk of type I error inflation. In those scenarios, integrating a robust multiplicity strategy at the initial planning stage is essential to maintaining the integrity of the study's findings.

Multiplicity issues typically emerge in master protocols whenever multiple statistical inferences are made within the same trial framework, when multiple treatment arms, or subgroups, or biomarker-defined cohorts are evaluated within the same overarching framework. Failure to consider these factors can lead to an inflated Type I error rate, a result that is generally unacceptable to regulatory bodies.

Biostatisticians have developed and validated multiple methods for managing multiplicity. When subtrials, such as those in basket or umbrella designs, involve highly heterogeneous groups, each cohort may be treated as a distinct trial. The approach controls multiplicity at the independent subtrial level, rather than across the entire protocol.

Family-wise error rate adjustments are another option. Under that approach, standard statistical adjustments are applied to control the probability of making one or more false-positive discoveries across the "family" of comparisons.

Innovative Bayesian frameworks with extensive pretrial simulations provide other ways to manage multiplicity. By calibrating Bayesian posterior probabilities, researchers can demonstrate how a design behaves under various scenarios, ensuring that Type I error is strictly controlled through computational rigor.

Regardless of the specific trial design, controlling multiplicity is a cornerstone of statistical planning. Demonstrating a clear strategy for managing error inflation is vital for ensuring that the results are scientifically valid and meet the rigorous standards of global health authorities.



Controlling multiplicity is central to master protocol execution. Evaluating multiple treatments, subgroups, and biomarker cohorts increases the risk of false-positive findings, making early statistical planning essential. Sponsors must implement robust error-control strategies to ensure scientific validity, preserve trial integrity, and meet regulatory expectations for reliable, decision-ready evidence.

**Interim analyses and adaptive decisions**

Adaptive decision-making serves as the backbone of master protocol designs. Yet while adaptive decisions are central to realizing the benefits of the model, the approach can present unique challenges. Risks include the potential for interim analyses of drug-specific substudies to reveal comparative efficacy.

There is a common misconception that adaptive interim decision-making can independently resolve every clinical question. As Suman Redhu, Senior Director of Biostatistical Consulting at Allucent, said, "It all depends on what question we are trying to answer, what our hypotheses are, and how many arms we are planning."

While prespecified adaptive rules and stopping boundaries are vital for clarifying and simplifying the trial process, they are not a universal remedy for poorly defined research objectives. To ensure trial success, a robust framework must be prespecified to govern how a trial evolves based on emerging data. This includes defining clear thresholds and stopping boundaries for dropping ineffective treatment arms or expanding promising cohorts.

By implementing sophisticated Bayesian designs, sponsors can utilize posterior probabilities to quantify the likelihood of success or futility. This approach provides Data Monitoring Committees (DMCs) with precise, predefined benchmarks, enabling streamlined and objective decisions regarding the termination or continuation of specific cohorts.

**Managing heterogeneous cohorts and shared controls**

Master protocols can study multiple biomarker-defined subpopulations simultaneously. It is a critical statistical assumption that these diverse groups may not respond to a specific treatment in a uniform manner.

When cohorts are known to be heterogeneous, sponsors must avoid combining data across all groups without adjustment. Applying a single treatment effect estimate to distinct populations can lead to significant bias. The trial must be designed to account for these differences from the outset to ensure the integrity and validity of the results.

There are two primary strategies for managing diverse cohorts within a master protocol. When clinical input suggests high heterogeneity, cohorts should be treated as independent subtrials. In this model, data are not pooled. Instead, hypotheses are tested separately for each biomarker-defined population, and results are submitted to health authorities on a per-cohort basis.



Adaptive decision-making powers master protocols, but flexibility requires discipline. Interim analyses, heterogeneous cohorts, and shared controls introduce complexity that demands prespecified rules and rigorous statistical frameworks. When carefully designed, adaptive approaches enable faster, data-driven decisions while preserving trial integrity and maintaining regulatory confidence.

For designs where some cohorts may share similar treatment effects due to a common molecular alteration or biomarker, a Bayesian hierarchical approach allows for "dynamic borrowing." The model adaptively determines the level of borrowing based on the similarity of observed outcomes across cohorts. If cohorts behave similarly, borrowing increases to improve statistical power. If cohorts diverge, borrowing is restricted or eliminated.

This innovative approach has been successfully implemented in high-profile trials such as I-SPY 2, STAMPEDE, and ROAR.[5] The model leverages shared information while maintaining a safeguard against the influence of non-responding groups, balancing efficiency and rigor.

**Handling shared control arms**

A prevalent misconception in master protocols is that shared control arms are always valid or the best approach. In reality, determining whether to use a shared control requires rigorous upfront evaluation. Sponsors must first ask if a control arm is necessary for the specific clinical question, or if a single-arm design assessing multiple treatments in a basket or umbrella setting would suffice.

Shared control arms are more efficient than individual trials, but also pose statistical challenges. Specifically, sharing a single control group across multiple experimental arms results in correlated treatment comparisons. If biostatisticians do not account for this correlation structure and prespecify the adjustments in the statistical analysis plan, the resulting estimates will be biased.

Managing temporal shifts in a shared control arm is a significant execution challenge for long-running master protocols. Because platform trials can run for years or even decades, with various experimental treatments entering and exiting, the standard of care and patient demographics evolve during the course of the study. Assuming uniformity across time without adjustment can bias the results.



Regulators are aware of this risk. FDA guidance addresses patients who were randomized to the control arm before a specific experimental arm was added to the trial. Generally, the FDA cautions against comparing an experimental treatment to nonconcurrent control data because of the high risk of unmeasured confounding variables introduced by shifting temporal trends.

To mitigate this, biostatisticians must employ rigorous methods to control for time. This often involves joint modeling or time-matched subcohorts that strictly limit comparisons to concurrently randomized patients. While excluding nonconcurrent data might seem to diminish the value of a shared control, advanced statistical modeling ensures the trial retains its statistical power.

When designed and modeled correctly, shared controls remain a highly efficient mechanism, preserving the scientific integrity of the trial while reducing the total number of control patients needed across the platform.

**Bayesian versus frequentist designs**

The acceptability of Bayesian versus frequentist trial designs remains a subject of active debate within the clinical research community. While there is broad industry encouragement to adopt innovative Bayesian methodologies, sponsors often experience hesitation due to potential uncertainties regarding approval probabilities and submission timelines.

Regulatory agencies have different perspectives on these statistical approaches. The FDA has been more flexible in recent years, demonstrating openness to Bayesian designs for signal finding and early-phase exploratory studies. The EMA tends to be more cautious than the FDA, particularly regarding Bayesian hierarchical designs that incorporate data borrowing.



Both agencies maintain a strong preference for frequentist methodologies in confirmatory settings, including treatment arms that graduate from a master protocol into a confirmatory phase. The agencies' caution makes it vital for sponsors to proactively address concerns related to multiplicity, shared control arms, and overall operating characteristics for the study design.

"As long as you address their concerns through simulations and engage with regulators early on, there's strong potential for alignment and consensus," Redhu said.

The regulatory environment is shifting toward greater acceptance of innovative designs. As the clinical community's understanding of these complex models matures, and as more successful case studies emerge, regulatory acceptance of these high-efficiency statistical frameworks could continue to increase.

## Operationalizing complex statistical designs

A primary misconception surrounding master protocols is that their defining challenge lies in complex statistical design. In reality, while a robust and streamlined statistical framework is critical, the most formidable hurdles are typically related to operational infrastructure and governance. Extensive upfront planning and substantial effort are required to mitigate these risks.

These complex designs require substantial, synchronized effort from cross-functional teams long before study initiation. To ensure a master protocol is successful through its execution and interpretation phases, several key strategic, statistical, and operational pillars must be established early.

### Strategic and scientific foundations

The explicit definition of the primary clinical question is the foundation of any master protocol. Sponsors must determine whether the trial will evaluate multiple treatments in a single disease setting, study multiple tumor types with one treatment, or focus on biomarker-defined populations. Establishing the scientific objective guides sponsors to the trial design that will best achieve the goal.

Sponsors should forge connections with collaborators before starting clinical trials. Studies with master protocols, especially trials with platform designs, are often collaborative efforts and may involve academic groups, multiple sponsors, and other stakeholders. A platform trial sponsor may need relationships with companies willing to include their molecules in the study and research sites capable of following the protocol.



Master protocols are often misunderstood as primarily statistical challenges, but the greatest complexity lies in operational execution. Success depends on early governance, cross-functional coordination, and extensive upfront planning. Clear scientific objectives and strong collaborative networks are essential to ensure these sophisticated designs can be implemented.

Launching a platform design without a sustainable treatment pipeline is a risk. Lacking a robust pipeline or, where applicable, strong cross-sponsor collaboration can limit the effectiveness of the design, reducing long-term efficiency gains and potentially delaying timelines.

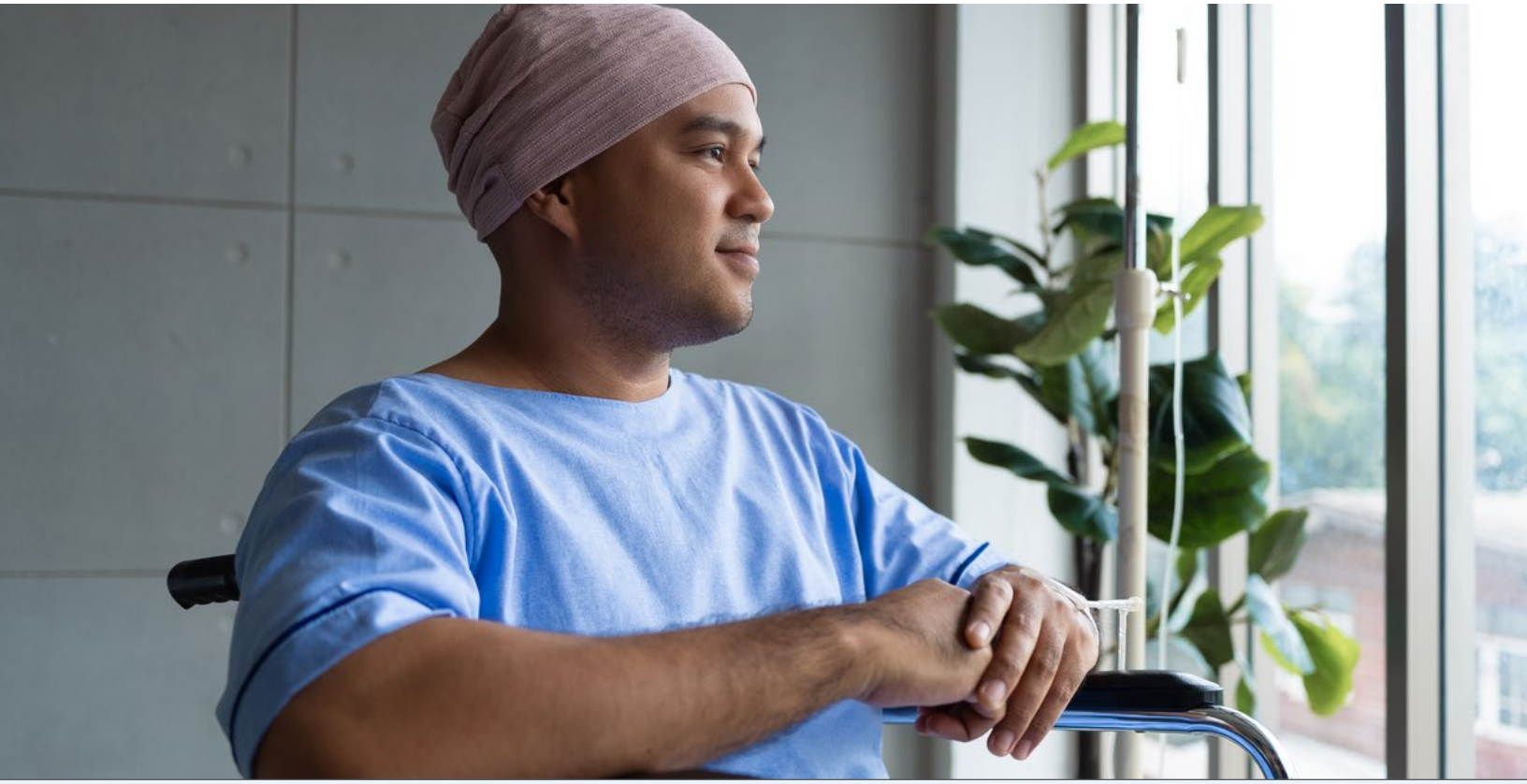
**Statistical framework and regulatory alignment**

A rigorous statistical framework is essential to govern the trial's adaptability. This requires clearly defining the parameters for adaptive randomization, patient enrollment, and adaptive decision-making. Trial planners must rigidly prespecify statistical thresholds, stopping boundaries, and rules for the sequential entry or dropping of study arms over the trial's duration.

It is vital to run extensive simulations of the trial's operating characteristics to understand how the design performs under various assumptions. Such simulations underpin proactive, early alignment with regulatory health authorities. Achieving regulatory consensus upfront ensures agencies' expectations are met, thereby mitigating the risk of structural challenges or late-stage protocol amendments.

Sponsors may be tempted to apply highly complex, innovative methodologies, such as intricate Bayesian borrowing or hierarchical designs, simply because the platform allows them. However, Redhu said sponsors "should avoid overcomplicated designs that are really difficult for your DMCs or regulatory authorities to interpret."

Excessive complexity can create significant downstream challenges. Statistical designs must remain optimal and closely aligned with the specific clinical question, actively avoiding unnecessary complications that obscure interpretability.



**Operational agility**

Developing a highly flexible operational structure is as important as statistical rigor. To successfully execute a master protocol in oncology, clinical teams must implement systems capable of rapid, real-time biomarker and driver mutation testing to assign patients to the appropriate study arm.

Because study arms are continually being added and removed, drug supply must be flexible to avoid costly delays. Sponsors need Interactive Response Technology systems that support adaptive randomization, as well as a centralized data management architecture capable of managing complex flows of data from different sources, assessments, and biomarker-based subgroups.

**Robust governance and oversight**

Inadequate governance structures can jeopardize the success of master protocols. Because these trials simultaneously involve multiple treatments, patient subgroups, and biomarkers, they require robust oversight and DMC frameworks. Long-term success depends heavily on seamless, well-planned collaboration across multiple stakeholders, including sponsors, cooperative groups, and health authorities.

The FDA recommends sponsors appoint an independent, external DMC to oversee accumulating safety and efficacy data. Depending on the trial design, sponsors may also establish an endpoint assessment or adjudication committee. The importance of DMCs to the success of master protocols makes the composition of the committee a key consideration.

“DMC members need intense, specialized training before a study starts to ensure they understand the trial’s outputs, interim decision processes, and statistical stopping boundaries,” Redhu said.

When evaluating multiple treatments, potentially across multiple sponsors, maintaining strategic and operational alignment among all participating organizations is essential for ensuring the trial’s long-term continuity and scientific integrity.



## Looking ahead

The evolution of the oncology R&D pipeline makes it essential for sponsors to consider master protocols when designing clinical trials. Cancer care has changed dramatically in recent years, moving from an organ-focused model to a biomarker-driven, precision medicine approach where treatments are tailored to specific molecular characteristics rather than tumor histology. Consequently, clinical trial designs are undergoing a parallel evolution to support the efficient development of today's oncology treatments.

Deep, rigorous planning is a key enabler of the new model. By considering the biostatistical strategy early, sponsors can address the technical challenges, secure alignment with regulatory agencies, and operationalize trial designs that facilitate efficient development of life-changing cancer medicines. ■

## References


1. Wang, H. & Yee, D. I-SPY 2: a Neoadjuvant Adaptive Clinical Trial Designed to Improve Outcomes in High-Risk Breast Cancer. Current breast cancer reports 11, 303 (2019).
2. Lung Cancer Precision Medicine Trials. https://www.cancer.gov/news-events/cancer-currents-blog/2015/lung-cancer-landscape (2015).
3. O'Dwyer, P. J. et al. The NCI-MATCH trial: lessons for precision oncology. Nature Medicine 29, 1349–1357 (2023).
4. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT00268476.
5. Subbiah, V. et al. Dabrafenib plus trametinib in BRAFV600E-mutated rare cancers: the phase 2 ROAR trial. Nat Med 29, 1103–1112 (2023).



Allucent®

Today, Allucent delivers innovative strategies and robust solutions based on over 30 years of background in regulatory trends, therapeutic experience, and operational expertise. We share small and mid-sized companies' deep commitment to supporting breakthrough science by partnering with them to navigate the complexities of delivering novel treatments to patients.

With offices across North America, Europe, and the Middle East, Allucent has experience conducting trials in more than 70 countries, focusing on some of the most complex development areas. Globally, Allucent has worked on more than 825 clinical trials, with oncology representing the majority.

LEARN MORE