CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

MASTER PROTOCOL DESIGN & IMPLEMENTATION:

Charting Multi-Stakeholder Pathways to Success

Phase 1: Pre-Planning | **Phase 2:** Planning | **Phase 3:** Execution

Complex innovative trial designs, such as master protocols, have innovative and complex trial designs that require strong communication and flexible problem-solving approaches across multiple stakeholders. This high-level roadmap outlines critical deliverables, common roadblocks, and real-world solutions for design and implementation of basket, umbrella, and platform trials. Early adopters of master protocols – including sponsors, nonprofits, and academic groups – can use the roadmap to foster effective cross-team, cross-institutional problem solving and identify ways to strengthen existing planning and operational processes for a master protocol study.

The three stages – pre-planning, planning, and execution – are laid out as distinct stages. In reality, planning and executing a master protocol is a continuum; the stages were developed to help the user understand the flow. Each master protocol initiative will unfold at its own pace depending on the uniqueness of the disease and maturity of drug development in that space.

Phase 1: Pre-Planning

During the pre-planning stage, the study sponsor establishes high-level study objectives and secures buy-in to utilizing the master protocol approach from a broad cross-section of stakeholders.

Design

Action	Key Elements	Potential Roadblocks	Solutions
Establish the scientific rationale ◆ Establish the scientific rationale ◆ Clarify the disease space ◆ Clarify drug pipeline characteristics	Clearly articulate how using master protocol approach will respond to unmet patient needs **Clarify the disease space:** ◆ How well is the underlying disease biology understood? ◆ How well is the longitudinal natural history of the disease understood? ◆ How will biomarkers enable decision making? ◆ To what extent have the proposed biomarkers demonstrated analytical validity? **Clarify drug pipeline characteristics:** ◆ What is the current availability of drugs to treat the disease? What IMP developers own these drugs? ◆ What investigational drugs are currently being evaluated to treat the disease? ◆ Do risk-benefit profiles of potential investigational products differ, potentially preventing some products from entering the trial? ◆ How many investigational products could be assessed in the trial concurrently?	◆ Getting bogged down and overwhelmed with describing the scientific rationale ◆ Knowing how much detail to provide ◆ The chicken and the egg dilemma: Do you identify partners who have interventions that will be ready to enter and design with and for them, or design the best trial and then find partners? The preferred order will likely depend on your goal ◆ Lack of clarity on the duration of the study and the commitment for collaboration (open-ended, agreed timelines, etc.) ◆ Having to undertake unfamiliar "selling/business development" tasks	◆ Focus on the scientific problem you're solving and why a master protocol is required to maximize benefits to patients. ◆ **Use CTTI's Value Proposition Guide** to articulate the scientific rational and feasibility of using the master protocol approach ◆ Use CTTI's **Master Protocol Content Development Guide** to engage a broad range of stakeholder to develop and refine high-level study objectives and operational characteristics of the master protocol study ◆ **Use CTTI's Statistical Simulation Tool** to understand how statistical simulation can be used in the pre-planning and planning stages to define trial characteristics and build consensus on the design approach

Phase 1: Pre-Planning

Multi-Stakeholder Engagement & Operations

Action	Key Elements	Potential Roadblocks	Solutions
Develop a business plan	◆ Executive summary that articulates the value proposition ◆ High-level design overview ◆ Operational infrastructure development and capacity building ◆ Stakeholder engagement strategy ◆ Governance and decision making ◆ Funding and budgeting	◆ Many organizations may express interest, but prefer not to make commitments until other partners are in place and more details are established ◆ Most organizations and companies have complex management structures and decision-making processes that are not always transparent	◆ Use **CTTI's Value Proposition Guide** to understand design, operational, and funding considerations to include in a written business plan ◆ Cultivate and mobilize a coalition of partners who work well together and are willing to experiment and innovate to facilitate the development of a master protocol study ◆ Focus on the patient; align stakeholders around how best to address patient needs ◆ Explore if there can be incentives for early "investors" without discouraging later entrants ◆ Ensure the business plan is responsive to key factors that drive sponsor investment such as budget cycle, operational readiness, and ability to adapt and remain flexible
Outline governance structure	◆ Executive oversight and decision making for investments ◆ Scientific and medical oversight, including compound selection ◆ Statistical input and oversight ◆ Operational oversight ◆ Data safety and monitoring ◆ Data access and publication oversight	◆ Many governance structures are successful, but key partners may have strong, possibly competing views about the optimal design and operational approach ◆ Some individuals have difficulty accepting change and will resist efforts to move beyond traditional clinical trial designs	◆ Reference **CTTI's Value Proposition Guide** for an overview of key elements of a governance structure ◆ Incorporate external and internal stakeholders in developing the governance plan ◆ Ensure the governance plan is comprehensive but not complex or burdensome ◆ Ensure clarity of decision rights for more critical decisions (e.g., budget, compound selection, safety, data sharing)

Phase 1: Pre-Planning

Action	Key Elements	Potential Roadblocks	Solutions
Develop a strategy to engage regulatory bodies early in the planning process	◆ This strategy should be responsive to key differences between international regulators ◆ Regulatory requirements for master protocols intended for registration are more rigorous than those intended for exploratory or "learning" purposes—the method and timing of engagement should vary based upon study intent	◆ Non-traditional drug developers may have limited regulatory experience, requiring either sourcing of regulatory affairs expertise or partnering with other organizations that have more regulatory affairs experience ◆ International regulatory bodies' approaches to master protocol studies may differ or lack transparency, creating ambiguity ◆ There may be differences of perspective across international regulators regarding ● Risk-benefit profile of candidate compounds for the trial ● Ability of the regulator to provide appropriate oversight if the trial does not have a "fixed" design ● Design aspect, which may pose ethical questions	◆ Use **CTTI's FDA Engagement Tool** to engage the FDA early and often during the pre-planning and planning phases of study development

Phase 2: Planning

During the planning stage, the study sponsor develops and designs regulatory, operational, and governance strategy for study execution.

Design

Action	Key Elements
Refine study hypothesis and objectives	Solicit input from all stakeholders to ensure the study design is responsive to their needs
For studies that use an adaptive trial design, statistical simulation is needed to establish the operating characteristics of the trial, including interim analyses, adaptive randomization, inferential power, subgroups, biomarker assessment, and recruitment	◆ Statistical simulations can support the development of a plan for pre-planned adaptations and refine processes for key decisions, including adding new investigational medical products or new treatment arms as the trial progresses ◆ Findings from statistical simulations should be included in the statistical analysis plan (SAP)
Develop a study synopsis and schedule of assessments	◆ These documents can be used as tools to drive engagement and alignment across stakeholders about key design and operational aspects of the study

Potential Roadblocks	Solutions
◆ Reaching consensus on key design requirements requires significant time and engagement of multiple stakeholders ● Alignment on key assumptions ● Evaluation of design features tested in statistical simulations ● Ability to respond to and resolve competing pressures (e.g., time, budget, risk) ◆ Potential future amendments can be difficult to identify early on and, therefore, are difficult to adequately detail in the protocol	◆ Use **CTTI's Protocol Development Guide** to review key stakeholders that should be included in the review of the study design ◆ Use **CTTI Statistical Simulation** tool to better understand how to leverage the findings of statistical simulations to engage patients, IMP developers, funding agencies, regulators, IRBs, and sites

Phase 2: Planning

Operations & Stakeholder Engagement

Action	Key Elements
Identify a network of operational partners that can fulfill key operational functions within the study	Develop a formal request for proposals (RFP) process to build a network of operational partners that can respond to the complex needs of a master protocol study
Build electronic data capture systems that are flexible and integrated	◆ Build flexibility and integration into Web-Based Randomization System (WBRS), which can guide integration of drug inventory management, site payment and tracking, and clinical monitoring systems ◆ Establish implementation logistics of the statistical analysis plan ◆ Prepare for ongoing data cleaning needs to accommodate frequent and timely pre-planned interim analyses
Build a site network that can meet the demands of a master protocol study	◆ Assess fit and feasibly of study sites; a master protocol often differs from a traditional study in terms of the expected long-term commitment and progressive building of capability to serve a patient population ◆ Identify unique training needs that selected sites may have to meet demands of a novel, complex trial design
Build a governance structure that can facilitate centralized decision making	Continue to clarify the following: ◆ Executive oversight and decision making for investments ◆ Scientific and medical oversight, including the selection of investigational medical products (IMPs) ◆ Statistical input and oversight ◆ Operational oversight ◆ Data safety and monitoring
Ensure that the study team is adequately staffed, trained, and supported	Cultivating a well-trained and well-supported study team is especially important given the greater volume and complexity of work that characterizes a master protocol study

Phase 2: Planning

Action	Key Elements
Clarify data sharing and data ownership	Consider the following: ◆ Who owns the data, especially if data in the placebo arm that is shared across all IMPs that are tested? ◆ What data will be provided to other partners? What comparisons can be made across multiple drugs that are tested, either directly or indirectly? ◆ What are the rights to use or license? ◆ What are the implications for investigational medical product and registration of new therapies? ◆ How and when will individual and overall findings will be communicated to study participants? To the scientific community?
Develop a plan to communicate the results of interim analyses	◆ Decide who will know what and when, including site personnel, study participants, and the broader public and patient community ◆ Protect the integrity of intended blinding ◆ Enable regulatory interactions, including filing ◆ Enable required oversight of sponsor ◆ Protect confidential information ◆ Comply with privacy requirements
Continue to engage regulatory bodies in the review of the study as needed	Incorporate feedback in preparation for submission

Phase 2: Planning

Potential Roadblocks	Solutions
◆ The number of operational partners who have experience conducting a master protocol study is limited ◆ Identifying a CRO with sufficient experience addressing unique design and operational challenges related to master protocol studies ◆ Funding can often be an impediment given the high cost of the trial; a plan with a budget to take the project through to execution is essential to understanding the budget timing and amounts ◆ Establishing a network of qualified sites can be difficult, and additional sites may be needed because of the larger number of patients entering the trial ● Perception of regulatory uncertainty creates concerns for feasibility and timeliness ● Securing buy-in may be dependent on a sponsor having an intervention ready to enter the trial	◆ Use **CTTIs Operational Partner Assessment Tool** to identify factors that can be used to engage operational partners ◆ Use CTTI's **FDA Engagement Tool** to identify formal mechanisms that allows for ◆ Use CTTI's **Protocol Development Guide** to review a real world example of the cross-functional review of the written protocol and sub-protocol documents.

Phase 3: Execution

During the execution stage, the study sponsor implements and, as needed, modifies the study protocol.

Design Modification

Action	Potential Roadblocks	Solutions
Balance the need for consistency and centralization with need for flexibility—this is critical for the study's ability to continue to respond and be relevant to changing clinical and scientific landscapes	◆ Data availability; balancing need for speed with need for quality ◆ Information firewalls: who knows what when? ◆ Limited flexibility within SOPs; produces structural and procedural barriers to supporting the successful execution of a master protocol trial ◆ Delays associated with approvals and amendments ◆ Need for continual stream of funding to support the long-term sustainability of the study	◆ Develop formal mechanisms that facilitate communication and escalation pathway across all stakeholders to facilitate necessary study modifications and streamline decision making ◆ Use CTTI's Master Protocol Value Proposition Guide to review key considerations for articulating the value proposition of the trial to new potential partners and IMP developers
Continually reassess and maintain IT system to ensure function, reliability, security, and scalability		
Ensure appropriate tracking and communication between the different databases		
Track and constantly maintain data availability and quality to facilitate speed of data analysis		
Regularly report summary data to study team, stakeholders, and external groups, including regulators		
Monitor and manage the study team's time carefully—ensure the study team is adequately staffed, trained, and supported for the complex and higher volume of work		
Appropriate oversight of patient safety is paramount, either through a DMC and/or other appropriate mechanisms		
Continue ongoing education and training of sites on the infrastructure and data collection requirements of the trial		
Manage drug supply		
Continue to maintain and cultivate relationships with broad stakeholder groups		