

MASTER PROTOCOL DESIGN & IMPLEMENTATION:

Charting Multi-Stakeholder Pathways to Success

Phase 1:
Pre-Planning

Phase 2:
Planning

Phase 3:
Execution



How to use this tool:

Innovative and complex trial designs, such as master protocols, require agile problem-solving approaches that are coordinated across multiple stakeholders. This high-level roadmap highlights common roadblocks that may impede the development of a master protocol study at the pre-planning, planning, or execution phase. Descriptions of critical deliverables and common roadblocks are accompanied by a description of real-world approaches that have been used to guide the successful design and implementation of basket, umbrella, and platform trials. Stakeholders can use this document to foster effective cross-team, cross-institutional problem solving and identify ways to strengthen existing planning and operational processes.

The three phases are laid out as distinct exercises with defined start and stop points. In reality, planning and executing a master protocol is a continuum; the phases were developed to help the reader 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



DESCRIPTION

The preparatory work necessary to:

- Establish the scientific rationale for conducting a master protocol trial
- Develop a business plan that defines the vision for the trial, clarifies the benefits to each stakeholder community, and provides a high-level outline of the full funding model
- Consolidate the partnerships necessary to fund the trial and develop the protocol
- Define the governance structure necessary to execute the trial

CRITICAL DELIVERABLES

DESIGN

- Establish the scientific rationale for using a master protocol study approach
- Detail why a master protocol approach is needed given high-level study aims, disease characteristics, and drug pipeline characteristics
 - High-level study aims may include
 - ◆ Benefits to the patient community
 - Acceptable proportion of patients receiving placebo or standard of care
 - Ability to identify patient subgroups across interventions, with the goal of identifying the most promising interventions for each patient subgroup
 - By running multiple research questions within a master protocol, this increases the opportunities for patients to participate in the clinical trial
 - It may also be important to include a “catch-all” component to the design for those patients who are not eligible to participate in other research arms
 - For example, inclusion of a non-stratified research question into a molecularly stratified umbrella design trial can act as a real incentive for all patients to take part, even if there is not a molecularly stratified research question available for them

- ◆ Study scope
 - “Learn studies”: Proof-of-concept studies that test safety and efficacy of an investigational medical product
 - Seamless Phase 2/3 trial: Integrates learning and confirmatory goals to achieve regulatory approval
- ◆ Primary and secondary endpoints
- ◆ Overall adaptation variables
- **Clarify the disease space**
 - How well is the underlying biology understood?
 - How well is the longitudinal natural history of the disease understood?
 - Do biomarkers enable early decision making?
 - To what extent have the proposed biomarkers demonstrated analytical validity? Does this need to be integrated into the trial design?
 - Will combination therapy be required to achieve the desired clinical response?
- **Clarify drug pipeline characteristics**
 - What research phase will investigational products have to be in to be included in the trial?
 - Do risk-benefit profiles of potential investigational products differ, potentially preventing some products from entering the trial?
 - When must the trial be operationally ready?
 - How many investigational products could be assessed in the trial concurrently?
 - How long is the delay between investigational arms?

OPERATIONS

- **Develop a business plan**
 - Clarify the scientific rationale for utilizing a master protocol approach (see design deliverables)
 - Identify key stakeholder groups (patients, physicians, regulators, sponsors and other potential funders)
 - Identify key champions in key stakeholder groups who can mobilize support for the study
 - Articulate the value proposition for each stakeholder group



- Identify whether international collaborators are needed, and what form of collaboration will be needed
- Agent selection criteria and process
- Site selection criteria and process
- Infrastructure requirements and potential sources
- Create a high-level outline of the investment required by phase—pre-planning, planning, and execution—and potential sources of funding for each phase

MULTI-STAKEHOLDER ENGAGEMENT

• Consolidate partners

- Begin discussions with specific organizations and companies that may play key roles in the project (e.g., funding, drugs, project management, regulatory oversight, patient recruitment, leadership)
- ◆ This will set the stage for detailed contract negotiation during the planning phase

• 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

• Engage regulators

- Develop a strategy to engage regulatory bodies early in the planning process; this strategy should be responsive to key differences between international regulators
- ◆ 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 (e.g., processes for informed consent, compound selection)

KEY ROADBLOCKS

DESIGN

- It is easy to get bogged down and overwhelmed with describing the scientific rationale. At the pre-planning phase it is difficult to know how much detail to provide.
- Scientifically driven experts must undertake a “selling/business development” task that is unfamiliar; success can be defined as securing funding from a decision maker that enables moving to the next step (e.g., more detailed planning, design, or implementation).
- It is important to stress the longevity of the study. Is the commitment of potential partners open-ended, or are these partners committing to agreed timelines with allowance for stop/go decisions as the study progresses?
- 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?

MULTI-STAKEHOLDER ENGAGEMENT AND OPERATIONS

• Partnership consolidation challenges

- Effectively articulating value proposition to multiple competing stakeholders
- Building trust when benefits of collaboration are reaped downstream
- Many potential partners will 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

• Governance structure

- Many governance structures can be successful, but key partners may have strong, possibly competing views about the optimal design and operational approach



- **Regulatory engagement**

- Non-traditional drug developers (e.g., patient groups, non-profits, academic groups) 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

PROBLEM-SOLVING APPROACHES

Will expand based on findings from the October expert meeting

- 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
- Create a business plan that is responsive to key factors that drive sponsor investment such as budget cycle, operational readiness, and ability to adapt and remain flexible
- 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 2: Planning



DESCRIPTION

Efforts to develop a strategy for study execution:

- Develop protocol
- Engage sponsor
- Address ongoing funding and business development needs
- Do regulatory consultation
- Develop data management system
- Assess sites
- Assess vendors

CRITICAL DELIVERABLES

DESIGN

- Refine study hypothesis and objectives
- Solicit input from all stakeholders to ensure the study design is responsive to their needs and the needs of patient communities
- For studies that use an adaptive trial design, simulation-guided clinical trial design may be required to establish the operating characteristics of the trial, including interim analyses, adaptive randomization, inferential power, subgroups, biomarker assessment, and recruitment
 - This information should be included in the statistical analysis plan
- Develop 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

OPERATIONS

- **Develop clinical trial management 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
- **Develop plan to communicate the results of interim analyses**
 - Decide who will know what and when
 - Protect integrity of intended blinding
 - Enable regulatory interactions, including filing
 - Enable required oversight of sponsor
 - Protect confidential information
 - Comply with privacy requirements
- Develop a publication plan that is acceptable to all stakeholders and lays out what would be required to make authorship or acknowledgment on output
- Define a clear end of trial so that timelines for final reporting (transparency) are understood
- Budget and contracting: clarify data sharing and data ownership
 - Who owns the data, especially data in the placebo arm that is shared across all drugs that are tested?
 - Rights to use or license
 - Implications for investigational medical product and registration of new therapies
 - Patient-centric considerations regarding how sharing data can advance scientific understanding while balancing the need to preserve proprietary information to enable long-term viability
- **Develop a network of sites**
 - Assess fit and feasibility 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
- Assess fit and feasibility of vendors; identify vendor training needs
- Develop governance structure via a Data Monitoring Committee (DMC)
 - Educate DMC members who are new to master protocols

Phase 2: Planning



- ◆ Key considerations for adaptive platform trial
 - Educate DMC members on their role in relation to interim analyses
 - DMC members may need to have flexible availability to meet the timely demands of an adaptive trial
- Establish criteria and centralized process for investigational medical product selection

MULTI-STAKEHOLDER ENGAGEMENT AND EDUCATION

- **Regulatory engagement**
 - Engage the FDA early and frequently
 - Clarify differences in global regulatory approaches
 - ◆ Identify available guidance to help identify what these differences may be
- **IRB engagement and education**
 - Determine if a central IRB is preferred
 - If an IRB is new to master protocols, early engagement, discussion, and education are warranted
- **Sponsor engagement**
 - Involve sponsors in the decision making with respect to protocol design and governance to ensure eventual adoption
- **Patient engagement**
 - Secure patient buy-in and engage them early in the planning process
 - ◆ This can be accomplished by working through advocacy organizations, which often have deep connections with patients and families

KEY ROADBLOCKS

DESIGN

- 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 are therefore difficult to adequately detail in the protocol

OPERATIONS

- 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
- Identifying vendors (e.g., central laboratories, pharmacies, readers, biomarker and PK analyses) with appropriate experience with master protocols is difficult
 - Key considerations for adaptive platform trials
 - ◆ The perpetual nature of the adaptive platform can make it difficult to get accurate quotes
 - ◆ Ability to process samples in a timeline (sometimes real-time) manner versus batching samples
- Identifying a CRO with sufficient experience addressing unique design and operational challenges related to master protocol studies
- Funding can often be an impediment as the eventual cost of the trial is substantial; a plan with a budget to take the project through to execution is essential to understanding the budget timing and amounts

MULTI-STAKEHOLDER ENGAGEMENT

- **Sponsor engagement challenges**
 - Due to the longer time horizon of master protocol studies, it can be difficult to maintain long-term vision given turnover and leadership change in sponsor organizations over time
 - 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

PROBLEM-SOLVING APPROACHES

Will expand based on findings from the October expert meeting

Phase 3: Execution



DESCRIPTION

Implementation of the study protocol

CRITICAL DELIVERABLES

DESIGN

- Update weighted randomization probabilities based on accrued trial data (for trials that use response-driven adaptive randomization)
- Conduct additional simulations to support decision making based on accrual patterns and treatment availability
- Monitor the accrual rates, biomarker or subgroup prevalence, and other statistical assumptions including evaluability of patients

OPERATIONS

- Maintain consistency between substudies
- Ensure appropriate tracking and communication between the different databases utilized for the trial
- Track and constantly maintain data availability and quality to facilitate speed of data analysis
- DMC must balance fidelity to the original design while continuing to assess the scientific and ethical appropriateness of that design
- Continue ongoing education and training of sites on the infrastructure and data collection requirements of the trial

MULTI-STAKEHOLDER ENGAGEMENT AND EDUCATION

- Continue to maintain and cultivate relationships with broad stakeholder groups
- Articulate the value proposition of the trial to new potential partners and sponsors

KEY ROADBLOCKS

DESIGN

- Changes in standard of care
- Changes in laboratory assays

OPERATIONS

- Changes in standard of care

MULTI-STAKEHOLDER ENGAGEMENT AND EDUCATION

- 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

PROBLEM-SOLVING APPROACHES

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