Master Protocol Value Proposition Guide

The ability to describe the value proposition of adopting a master protocol study in a specific disease area, early on, is key to a trial's success. Early adopters — patient advocacy groups and other non-traditional trial sponsors — can sometimes struggle to clearly and efficiently articulate the value and feasibility of developing a master protocol study in their disease area of choice to funders, investigational medical product (IMP) developers, and other key stakeholders.

This document outlines key scientific, operational, and funding considerations that can support early adopters' efforts to think through the "why" and "how" of developing a master protocol study. The tool features four critical value domain sections:

1. Patient-centered Design Innovation
2. Operational Feasibility
3. Study Governance and Decision Making
4. Funding Considerations

Specific details, examples, and questions listed in each section are intended to guide early adopter's ability to draft content for pitch decks, business plans, and other communications tools that can help them engage stakeholders in discussion about their innovative trial design.

DESCRIBING VALUE: GUIDING QUESTIONS

Use these questions to kick off early internal discussions about how to describe the value of developing a master protocol study in your disease area of choice. Answering these questions will help you think through whether a master protocol design is appropriate in your disease area. Additional supporting details are provided in the succeeding sections of the document.

Patient-Centered Design Innovation: Demonstrate that the use of a master protocol study design increases patients' access to innovative investigational products and reduces patient burden.

- Questions to consider:
  - Will the design reduce the number of patients deemed to be ineligible? (e.g. potential to randomize patients to a different concurrent or future arm)
  - Will the design decrease the probability of being randomized to a placebo/standard of care and increase the probability of a patient participating in the clinical trial receiving the most promising treatment for their disease?
  - How will innovative design features be used to maximize patient benefit?
  - Does the study have registrational intent?

Operational Feasibility: Describe how a centralized operational infrastructure will facilitate the implementation of an innovative master protocol study design.

- Questions to consider:
  - How will core operational capacitates be built to ensure study feasibility?
    - Patient engagement
    - Regulatory engagement
    - Site network development
    - IRB
- Operational partners network development
  - Who are key stakeholders who need to contribute to the development of the master protocol study?
  - What are key engagement barriers to reaching these stakeholders? (e.g. lack of buy-in to the master protocol concept, relationships, staff expertise and capacity)

Study Governance: Describe the governance structure that will facilitate efficient, centralized decision making.

- Questions to consider:
  - What entity will serve as the study sponsor? (e.g. consortium, patient advocacy organization, academic institution, etc.)
    - What qualifies this entity to fulfill the responsibilities of a study sponsor?
  - What governance groups will facilitate the following:
    - Scientific and medical oversight
    - Statistical input and oversight
    - Data safety and monitoring
    - Data access and publication oversight
    - Legal responsibility
    - Selection criteria for IMPs

F**unding Considerations: Describe the resources that are required to cover the significant upfront planning costs of a master protocol study and ensure the long-term sustainability of the study.**

- Questions to consider:
  - How can you use in-kind resources and expert volunteers to offset early planning costs?
  - What funding strategies will be developed to ensure the long-term viability of the study?
    - Public-private partnership
    - Philanthropic funding
    - Government funding

SECTION 1: PATIENT-CENTERED DESIGN INNOVATION

This section helps early adopters provide a high-level overview of the proposed novel design characteristics of the trial and describe how the novel design characteristics are aligned with the unmet scientific, economic, and patient needs. The list of example features below can be incorporated into a study to respond to unmet patient needs and drive efficiency. Not all of the features need be incorporated into a master protocol study; this should be fit-for-purpose and responsive to specific disease and IMP pipeline characteristics.

Feature	Purpose/Benefit	Resources Needed
Standardized approaches to protocol and document organization and management	Minimize work associated with evolution of the trial, ensure standardization of terminology and common procedures, and avoid duplication	A master protocol describing common elements, supplemented by sub-study protocols
Standardized approaches to clinical trial processes and information management	Workload and operational efficiencies	A highly-centralized operational infrastructure
Shared control arm (placebo or standard of care)	Potentially fewer participants on the control	Simulation capability
Ability to change control as standard of care changes	Flexibility for the study to adapt to a changing treatment environment and not terminate due to enrollment or ethical challenges	Simulation capability
Borrowing information across treatment arms/disease categories	Improved estimation of the treatment effect for the most effective arm(s), and improved expected outcomes of patients included in the trials	Simulation capability; may require Bayesian statistical approach
Response-adaptive randomization (includes adding/dropping arms)	Improves the estimation of the treatment effect for the most effective arm(s) and the expected outcomes of patients included in the trials	Simulation capability
Modeling (e.g. longitudinal modeling, disease progression modeling)	Increases the precision/estimation by using all information/data and the ability to use all early patient information in adaptive decision making	Simulation capability

Feature	Purpose/Benefit	Resources Needed
Incorporation of historical or external controls	Improves the precision of estimates especially in rare disease or limited data settings, reduces the sample size and enables investigation with allocation controls	Access to this information through publications or data from registries that contain natural history data
Enrichment*	Focuses trial resources on the population most likely to benefit from the treatment, and reduces unintended harm	Simulation capability
Pre-specified adaptive decision rules	Ensures the presence of defined operating characteristics and scientific integrity and validity of the clinical trial (if rules are followed); supports regulatory decision making	Statistical analysis plan informed by simulation data, regulatory guidance: ◆ FDA guidance: Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry
Pre-specified final analysis plan	Ensures the presence of defined operating characteristics and scientific integrity and validity of the clinical trial (if rules are followed); supports regulatory decision making	Statistical analysis plan informed by simulation data
Missing data considerations	Ensures pre-specification of interim and final analyses, and helps you understand the strength of the trial evidence	Statistical analysis plan
Oversight and governance	Ensures appropriate disciplined and nimble decision-making regarding trial conduct	Creation of a trial steering committee, arm selection committee, endpoint adjudication committee, sub-study matching committee, communication plan, and DSMB

SECTION 2: OPERATIONAL FEASIBLITY

Section 2A: Building Operational Capacity

The long-term feasibility of using the innovative design features described in Section 1 requires the creation of a robust operational infrastructure. Non-traditional trials may lack the in-house operational expertise and leadership required to successfully design and implement a master protocol study. This section describes common operational capacity building needs that will need to be address early on in the development of the study.

Operational Capacity	Capacity Building Needs	Strategy
Patient Engagement	Provide general education about the scientific rationale and operational feasibility of using the master protocol approach to the patient community	◆ Develop formal mechanisms to engage the patient community in the pre-planning and planning stages of protocol development **(see CTTI's protocol development map)**
Regulatory Engagement	◆ Regulatory agencies will require more interaction earlier in the development of a master protocol study ◆ Formal mechanisms to increase early interaction with international regulators outside of the U.S. may be unclear	◆ Engage the FDA early and often during the pre-planning and planning phases of study development **(see CTTI's FDA engagement tool)** ◆ Host orientation meetings with international regulators who may have limited experience reviewing master protocol studies, so that they are prepared to receive the master protocol
IRBs	◆ Ability to engage more frequently in training due to complex design features of master protocols ◆ Ability to manage the higher volume of amendments that result from adding and dropping arms and the outcome of interim analyses	◆ Engage and educated IRBs about how decisions on the inclusion of new IMPs in the trial will affect overall safety and balance for the trial

Operational Capacity	Capacity Building Needs	Strategy
Operational Partners Network Development	◆ Operational partners will require education about unique operational aspects that characterize master protocol studies ◆ Operational partners should anticipate a greater volume of work and more rapid turnaround times	Develop customized training resources that are responsive to the unique educational and capacity building needs of specific vendors **(See CTTI Operational Partners Assessment Tool)**
Site Network Development	◆ Site network may be underdeveloped in rare disease areas ◆ Sites in common diseases may not have experience working in networks	Engage a diverse group of sites (e.g. geographically dispersed, community-based, and academic sites) that will best facilitate engagement and enrollment with target patient groups

SECTION 2: OPERATIONAL FEASIBLITY

Section 2b: stakeholder engagement considerations

In addition to developing prospective plans to increase operational capacity, early adopters need to build stakeholder engagement strategies that drive buy-in among stakeholders who will need to be active participants in the design and implementation of the study. The table below outlines common barriers to engagement by stakeholder, as well as recommendations to address these challenges.

Stakeholder	Engagement Barrier	Strategy
Patient Advocates	Possible limited experience with master protocol studies	◆ Socialize the master protocol concept within the patient community ◆ After initial education activities, develop formal mechanisms to engage a diverse cross-section of patients and caregivers in protocol development (See CTTI's protocol development guide)
Investigative Site Staff	◆ Design and operationally complexity of master protocol studies may require additional training of site staff ◆ Concern about additional burden due to higher volume of work and faster turnaround times	◆ Provide targeted education to address specific gaps in knowledge about unique design and operational characteristics of master protocols ◆ Acknowledge that a master protocol design may require sites to operate differently – some things may become harder, while others may become easier.
Professional Society Organizations & Other Consortia	Difficulty around consensus building and aligning on governance structure and scientific strategy	◆ Identify key champions within professional society organizations and other consortia who can educate their constituents about the value proposition of using a master protocol study

Stakeholder	Engagement Barrier	Strategy
Regulatory Agencies	◆ Safety concerns (monitoring and reporting safety data) ◆ New design approaches will require more engagement and discussion ◆ Alignment across different country regulatory agencies	Engage regulators early in the pre-planning and planning phases of study development
IMP Developers **Note:** IMP Developers may not be identified in the early pre-planning stages of a master protocol study's development	◆ Time and agility (speed to be able to get things off the ground, and ability to influence that) ◆ Ownership and ability to influence ◆ Experience and resources for smaller companies	◆ Source initial assets from a small group of interested partners participating in brainstorming and design ◆ Use a RFP (request for proposal) approach to elicit interest from all IMP developers that potentially have applicable assets ◆ Proactively manage key concerns, beginning with FAQ • IP / data ownership • Speed compared to other available development pathways
Operational Partners (e.g. central labs, IRBs, site monitoring)	What criteria will be used to determine if existing or new operational partners have the technical expertise needed to fulfill their operational function within the study? **Note:** Even if an operational partner has used the study before	◆ See specific vendor considerations and capacity building/training needs in **Operational Partners Assessment Tool**

SECTION 3: CENTRALIZED GOVERNANCE AND DECISION MAKING

The design and operational complexity of master protocol studies require a unique, robust governance structure that facilitates centralized decision making. Key elements of a master protocol governance structure include sponsorship, governance groups, and IMP selection.

Sponsorship
Normally, in a typical clinical trial the sponsor is either the investigational medical product (IMP) developer (holder of the IND in US) or an investigator (in an investigator-initiated study); however, a platform trial often seeks to include assets from multiple IMP developers in the trial, requiring organizations that serve as the study sponsor of maps may not be familiar with the regulatory requirements guiding the development of medical products and must become familiar and be able to meet those requirements if their studies have registrational intent.

Examples of adaptive platform sponsorship:

- I-SPY: QuantumLeap Healthcare Collaborative, a 501C(3) charitable organization (https://clinicaltrials.gov/ct2/show/NCT01042379)
- DIAN-TU: Washington University School of Medicine (https://clinicaltrials.gov/ct2/show/NCT01760005)
- Duchenne Platform Trial: I-ACT for Children, independent non-profit organization [in planning: Led by Parents Project Muscular Dystrophy (PPMD)] https://www.parentprojectmd.org/recap-of-ppmds-duchenne-platform-trial-community-meeting/

Governance Groups
A formal governance structure is required to clarify how key decisions will be made and to enable effective collaboration. Possible governance groups to engage in governance structure are listed in the table below, along with potential group names.

Group Function	Potential Group Name
A small decision making group that is responsible for ensuring the integrity and long-term viability of the platform trial	Steering Committee
A group of diverse relevant stakeholders (especially including patients and patient advocates)	External Advisory Board
A diverse group that can recommend potential IMPs	Investigational Agent Selection Committee

Group Function	Potential Group Name
A diverse group of investigators and others that determines policy, approves access to data and publication of results, and communicates data to relevant stakeholders	Data Access and Publication Committee
A group of representatives from each site that ensures ongoing involvement and awareness off trial evolution	Investigator's Working Group
A diverse group of advocates who are involved in planning all aspects of the patient experience and play a key role in developing patient recruitment and retention strategy, developing patient educational material, and reviewing informed consent documents	Patient Advocacy Working Group
A group of representatives from each site	Coordinators Working Group
Consider this group if the trial has a large biomarker component or is adapting trial conduct based upon biomarker results	Biomarker Working Group
See CTTI Data Monitoring Committees Recommendations	Data Monitoring Committee

IMP Selection

The questions below can be used as a guide to formulate key principles for prioritizing IMPs to be included in the trial. Focus on the questions that are most relevant to the disease and pipeline of a trial, and uniquely applicable to the master protocol approach.

- How strong is the early evidence for the likely efficacy of this IMP?
- How strong is the early evidence for the safety of this IMP?
- Is this IMP a "first in class?"
- Have other IMPs in this class been studied within this master protocol?
- Has the manufacturer of this IMP already tested an IMP tested under this master protocol? How easy has it been to work with them?
- How enthusiastic is the manufacturer of this IMP to have their IMP tested under this master protocol? Do they bring unique value added to the table?

SECTION 4: FUNDING CONSIDERATIONS

An important part of engaging stakeholders who can provide funding for a master protocol to provide a high-level outline of the investment required during each phase of the study. Master protocol early adopters should make sure their potential funders are aware of the innovative funding strategy and resources required for long-term sustainability of a master protocol.

The chart below describes a list of resources that are needed at the pre-planning, planning, and execution stages of a master protocol study development. Following is another chart outlining potential funding sources, with examples, for master protocol studies.

Resources Needed	Pre-Planning	Planning	Study Execution
Proposal Leader: lead partnership management' develop business plan and high-level project plan including key milestones and timeline; secure resources/funding; integrate stakeholder perspectives; identify gaps; and augment expertise as required	✔	✔	✔
Statistical expertise: identify critical questions to inform master protocol design; complete statistical simulations; develop statistical analysis plan (at high level in partnership with clinical investigators); and provide insight into key regulatory considerations for master protocols	✔	✔	✔
Representation from (~2-5) IMP Developers (usually clinical): provide insight into unmet needs to be addressed by clinical development; provide insight into development requirements of pipeline assets, contrite to clinical trial design; and champion concept and funding within companies contributing assets	✔	✔	
Representation from the patient community: provide feedback on study schedule, endpoints, patient burden, and patient interest	✔	✔	✔
Business Development: ensure that the value proposition and financing model is compelling for contributors	✔	✔	
Regulatory: develop and operationalize strategy for engagement/meetings with regulators	✔	✔	✔
Grant Writing: secure funding for next stage and create budgets based on forecasted per-patient recruitment, engagement, and treatment costs	✔	✔	
Business Development: sourcing funding and building a pipeline of IMPs	✔	✔	

Resources Needed	Pre-Planning	Planning	Study Execution
Contract Development: operational partners, sites, and IMP developers	✔	✔	✔
Medical Writing	✔	✔	✔
Data Maintenance			✔
DSMB			✔
Per Patient Recruitment and Engagement Costs			✔
Per Patient Treatment Costs			✔
Publications and presentation support			✔

Potential Funding Sources

The chart below provides examples of different funding sources that can be used to support pre-planning, planning and study execution.

Potential Funding Sources	Example
Private Philanthropy: Grants and individual charitable donations	Healey ALS Adaptive Platform Study: Funded in part by a large donation from Sean M. Healey and philanthropic organizations
Government	The NIH has sponsored a number of master protocol studies including, but not limited to, NCI-MATCH and ALCHEMIST
Public-Private Partnership	European Prevention of Alzheimer's Dementia (EPAD): public–private consortium funded by the Innovative Medicines Initiative (IMI)
User Fees (IMP Developer)	IMP developers pay to for their arm of the trial. Strategy typically used later in the planning stages and for study execution