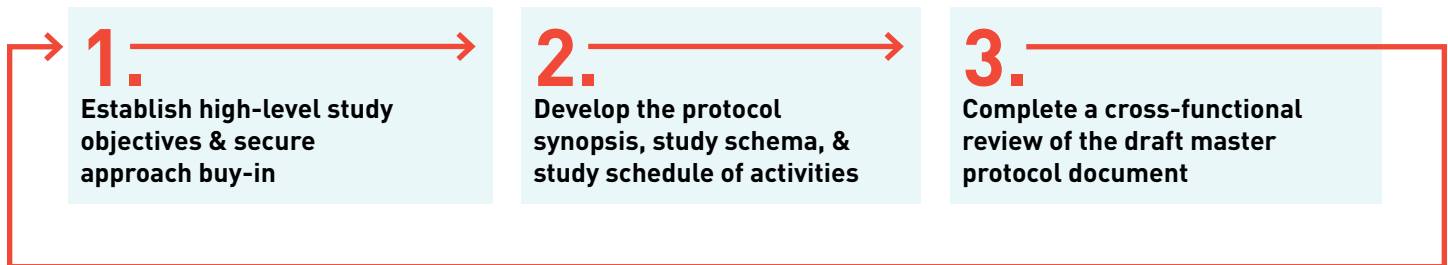


Master Protocol Content Development Guide

Developing the written content of a master protocol and sub-protocols (protocols that guide the design and conduct of specific arms of the study) requires upfront multi-stakeholder collaboration. Reaching consensus among these diverse groups during the following three pre-planning and planning stages is critical to success:



HOW TO USE THIS TOOL?

- ◆ Use this step-by-step tool to develop an engagement strategy for engaging all relevant stakeholders early in the protocol development process (for additional stakeholder engagement considerations, see CTTI's Value Proposition Guide).
- ◆ Make specific requests for feedback and information from stakeholder groups to avoid unnecessary protocol amendments after study launch.

UNIQUE CONSENSUS-BUILDING CONSIDERATIONS FOR DEVELOPING A MASTER PROTOCOL

- ◆ **More time and resources are required.** Master protocols require intensive upfront planning because they need to accommodate a variety of initial and subsequent sub-studies. Each stakeholder group has unique educational and capacity-building needs to efficiently participate in protocol development.
- ◆ **More stakeholders are needed to participate in the content development process.**
- ◆ Operational partners that are traditionally approached during the execution phase in a static trial could be a stakeholder that you engage during planning for a master protocol. Grounding your trial in a **Quality by Design (QbD)** approach – one that is grounded in engaging all relevant stakeholders in the study development process early on – is especially needed for master protocols.
- ◆ **Consensus-building deliverables are iterative and cyclical across the lifecycle of a study.** Stakeholders are required to engage in iterative consensus-building activities for each new investigational medical product (IMP) added to the study. Therefore, the protocol development is not a single process; instead, it's a set of overlapping processes that unfold over time and require unique, consistent stakeholder engagement to overcome design and operational challenges.
- ◆ **Greater efficiency can be achieved.** Although development can be iterative and cyclical, greater efficiency is gained over time because a high-quality, well-vetted master protocol document allows for flexibility in the sub-protocols as data accrues to the study and the disease landscape evolves.
- ◆ **Maintaining the content in the core master protocol document should be a principal objective.** While amendments to sub-protocols are necessary to maintain innovation and efficiency within a master protocol study, amendments to the core master protocol are disruptive and should be minimized.

Sponsor: In context of this tool, “sponsor” refers to the organization that is ultimately responsible for the initiation and management of the study. Master protocol studies are often initiated and managed by a non-commercial entity such as a non-profit patient group or academic institution

Consensus: The process of achieving broad alignment on key design and operational elements in the protocol across stakeholders. The study sponsor is ultimately accountable for the final master protocol and sub-protocols.



STAGE 1: ESTABLISH HIGH-LEVEL STUDY OBJECTIVES & SECURE APPROACH BUY-IN

Goals

- ◆ Articulate high-level study objectives and scientific rationale to diverse stakeholder groups.
- ◆ Educate stakeholders about how the master protocol approach differs from traditional RCTs and why it is fit-for-purpose (for how to effectively articulate the value proposition of the master protocol approach, see CTTI's Value Proposition Guide)

Unique Challenges & Opportunities

- ◆ Master protocol studies using an umbrella and platform trial design are often disease-centered studies. Therefore, the high-level study objectives of master protocol studies are often developed before IMPs have been identified. This lack of clarity about the IMPs may seem overly vague to some stakeholders, making it difficult for some stakeholders to get engaged in protocol development process at this early stage.
- ◆ Operational partners need to be engaged early on to begin thinking through core operational aspects of the trial, especially as it relates to the use of technology to maintain the master protocol, as well as to reduce patient and site burden.

Steps to Success

- ◆ As in all clinical trials, it is critical to engage all stakeholders in the earliest stages of a master protocol study's development to ensure buy-in to the design approach and to get early feedback on strategies.
- ◆ Accurately identify the stakeholders that need to be engaged in the protocol development process from the outset (see sample list below).
- ◆ Educate all stakeholders on the unique features of master protocol design approach being used and relevant operational and statistical efficiencies.
- ◆ Remember that few groups have experience designing and implementing master protocol studies; take significant care to educate stakeholders about advantages and potential challenges of adopting a master protocol approach.
- ◆ Build a strong engagement strategy that proactively addresses barriers to achieving buy-in that are unique to each stakeholder group that will be engaged in protocol development.
- ◆ Ensure that there is strong engagement with the patient community, who will help advocate for the adoption of the master protocol approach across other stakeholder.
- ◆ Review existing datasets and recommend statistical methodology.

Stakeholder	Role and/or Contribution
Patients	Provide feedback on high-level study objectives
IMP Developers (those who are contributing IMPs to the trial)	Provide feedback on high-level study objectives and clearly communicate what expectations would need to be met to engage in a formal, contractual partnership
Biostatisticians	Review existing datasets, recommend statistical methodology, educate all stakeholders on unique design features that will be used in the trial to maximize statistical efficiency (e.g. shared placebo or SOC control data across arms)
Regulatory Affairs	Request meetings with relevant regulatory agencies to request early feedback on high-level study objectives and IND submission strategy; as needed, orient to the long-term project scope so they can receive the protocol for review
Regulatory Agencies	Provide high-level feedback on study objectives and design
Researchers	Contribute to the high-level study objectives and ensure that the study design and endpoints are scientifically and clinically relevant
Clinical Operations	Understand high-level objectives and design of the study, provide any initial feedback on the operational feasibility of the study
Medical Writers	Early on, gain a deep understanding of the clinical development program and what each stakeholder needs, and keep archives of meeting notes and documents throughout the protocol development process.
Clinical Data Management	Provide early feedback on potential data management systems that the study will need

STAGE 2: PROTOCOL SYNOPSIS, STUDY SCHEMA, & HIGH-LEVEL STUDY SCHEDULE OF ASSESSMENTS

Once you've achieved high level consensus and gained buy-in regarding the use of a master protocol, the next step is to develop critical documents for your master protocol: the protocol synopsis, the accompanying study schema, and a high-level study schedule of assessments. Again, consensus is important to achieve for the success of the master protocol – all stakeholders must review these documents, ideally through joint meetings during which all parties can directly engage and discuss critical considerations.

Goals

- ◆ Develop the protocol synopsis – the higher-level, abridged version of the protocol – and the accompanying study schema and high-level schedule of assessments
- ◆ Gather and incorporate input from each stakeholder group, and revise as needed

Unique Challenges & Opportunities

- ◆ Due to the innovative design of master protocol studies, these documents will require more detail and may be more complex to review. Detail is essential because master protocols studies are characterized by greater design flexibility and complexity.
- ◆ Elements of the study schedule are likely to remain constant across the master protocol and sub-protocols. This will allow sub-protocols to enter and exit the trial more seamlessly over time and will also avoid unnecessary amendments.
- ◆ Amendments to the sub-protocols will occur and are necessary to ensure the study can allow for IMPs to be dropped and added to the study over time, preserving the study's ability to remain responsive to evolving disease landscapes. However, again, do not amend the core master protocol document (see stage 1).

Steps to Success

- ◆ Engage with all stakeholders who are critical to this stage (see sample list below).
- ◆ Develop draft documents using information gathered from stage 1.
- ◆ Accurately capture the findings from joint meetings with stakeholders in the study protocol synopsis, schema, and schedule of events.
- ◆ The protocol synopsis will also be used by operational leads to trigger a number of parallel activities to prepare for study execution such as site selection, operational partner selection, and safety monitoring.

Stakeholder group*	Role and/or Contribution
Patients	Review the study design; evaluate inclusion and exclusion criteria, ensure that end-points that are meaningful to patients, and the patient burden is low (Also see CTTI's Patient Group Engagement work)
IMP developers (those who are donating IMPs to the trial)	Stay informed and participate in the study (Note: at this stage this commitment may still be pre-contractual).
Biostatisticians	Develop power calculations, sample size, and other key elements of the statistical analysis plan (SAP)
Regulatory Affairs	Formalize regulatory engagement strategy and provide an informed perspective on what's approvable in different regions of the world
Regulatory Agencies	Engage as necessary with specific questions and information about the evolving study design
Researchers	Develop protocol synopsis outline and engage in ongoing efforts to preserve the clinical and scientific relevance of the study objectives and design approach
Clinical Trial Operations	<ul style="list-style-type: none"> ◆ Provide feedback on core operational aspects of the trial and overall operational feasibility; use the protocol synopsis to trigger the start of parallel operational processes such as site and operational partner network development ◆ Use the study protocol synopsis, schema, and schedule of activities to engage supply chain planners to project supply chain planning needs and engage appropriate operational partners
Medical Writers	Stay informed and participate in the study, as they will be accountable for the initial draft of the protocol and sub-protocols
Data Manager/ Data Programmer	Provide detailed feedback on what a unified data collection approach could look like, considering database interoperability and data collection needs
Safety/Pharmacovigilance	Participate in discussions about data safety monitoring board (DSMB) set-up and membership
CRO	Use the protocol synopsis to develop a more complete list of the specific CRO services that will be required for the study
Contract & Budgets	Formalize contractual partnerships with industry partners, sites, and operational partners, and provide a more complete overview of study costs
Single IRB	Work with the sponsor to understand how innovative design features may impact risk profiles and the balance within the study



STAGE 3: CROSS-FUNCTIONAL REVIEW OF THE WRITTEN MASTER PROTOCOL AND SUB-PROTOCOL DOCUMENTS

Once the master protocol and the sub-protocol documents have been drafted, each stakeholder will review them. This is an iterative process that will likely require multiple reviews from each groups once edits and changes have been incorporated.

Goals

- ◆ For each stakeholder to select key reviewers to provide feedback on the draft protocol.
- ◆ When the content of the protocol is finalized, the operational team will develop a robust operational and governance infrastructure to implement the study.

Unique Challenges & Opportunities

- ◆ All reviewers will have the opportunity to review and provide feedback on the master protocol document, but IMP developers may only have access to the final sub-protocols that correspond to the IMP they contributed to the trial.
- ◆ Any significant changes to the document at this stage could necessitate returning to consensus-building stages 1 and 2.

Steps to Success

- ◆ Ensure the correct reviewers are selected from each functional group.
- ◆ Facilitate opportunities for formal face-to-face interactions with reviewers from all stakeholder groups to streamline the review process.
- ◆ Formalize early on what review processes will look like for sub-protocols to seamlessly add and drop study arms as data accrues to the study over time.



Real World Example: Cross-Functional Protocol Review in the HEALEY ALS Adaptive Platform Trial

THE APPROACH

The cross-functional review of the final master protocol document and sub-protocol documents look different across studies. The HEALEY ALS Platform Trial developed a three-tiered approach that included key stakeholder perspectives from the following areas of expertise: budgets and contracts, database development, data monitoring, clinical operations, regulatory affairs, disease key opinion leaders (KOLs), biostatisticians, and statisticians.

TIER 1: THE LEADERSHIP TEAM

The leadership team consisted of disease KOLs, biostatisticians with experience in the field of ALS, statisticians from Berry Consultants to provide Bayesian statistical expertise, and the director of research operations. The leadership team identified and prioritized major design and operational issues that needed to be addressed by specific functional groups, and included a therapy evaluation committee that guided the selection of investigational medical products (IMPs) that would be evaluated in the trial. These high-level leadership conversations were used to organize and assign the various aspects of the cross-functional review process.

TIER 2: WEEKLY DESIGN AND OPERATIONAL MEETINGS

Weekly design and operational meetings were used to discuss details of the priorities set by the leadership team. Key design elements were discussed in weekly design meetings and the operational meetings focused on the overall study implications of those design decisions. Members of this team discussed platform level topics that required input from regulators, then planned, requested, and conducted meetings with FDA, which guided the development of the master protocol and regimen specific appendices.

Project managers identified the sequential order of specific action items that needed to be completed across functional teams. The project managers provided a key bridging role across functional groups that were engaged in different meetings at different times during the pre-planning and planning phases of the study.



TIER 3: FOCUSED MEETINGS FOR INDIVIDUAL IMPS

The Healey team worked closely with each industry partner who's IMP would be added to the master protocol. Weekly meetings were held to review the fundamental design elements of the master protocol, recommended analysis components, and determine if any additional entry criteria or safety monitoring procedures are required based on the safety profile of the IMP. The team then developed a regimen specific appendix that provided all details about the IMP to be tested and any specific modifications required. Once completed, all appropriate documents were submitted as an amendment to the master protocol, prior to moving forward with operational aspects.

KEY SUCCESS FACTORS:

- ◆ A focused group of key decision-makers needs to provide a framework for the cross-functional review process. The HEALEY team described the development of their master protocol, using the cross-functional review process, as building a house. The master protocol served as the structural foundation for the house, and each IMP tested was an "addition" to the house by engaging functional teams that have a deep understanding of the foundation.
- ◆ Strong leadership and project management processes were required to facilitate cross-functional dialogue and set goals for each of the cross-functional meetings. This allowed key issues to be explored iteratively while maintaining momentum needed to achieve key action items.