Master Protocols: Operations Partner Assessment

WHAT IS AN "OPERATIONS PARTNER"?

Throughout CTTI's Master Protocol work, "operational partner" is used in place of "vendor" to underscore the critical contributions organizations (such as CRO's central labs, etc.) make to planning and problem-solving during the development and execution of a master protocol study.

Building a robust operations partner network – including, but not limited to, CROs, electronic data capture systems, and central labs – is critical to a successful master protocol. It is important to find engaged, flexible operations partners (preferably with experience in master protocols) who are willing to constantly adjust to change as the master protocol study evolves. This tool helps sponsors and operations partners to best prepare for executing core operations functions within the trial.

Unique Considerations for Selecting an Operations Partner

- Master protocol studies iteratively cycle across the pre-planning, planning, and execution stages, as data accrues and arms are added and dropped to the study.
  - Operations partners require training and education on the operations implications of the innovative design features of master protocol studies.
  - Variability in workflow and budgeting requires operations partners to nimbly scale-up and scale-down their services to adjust to changing needs within the study.
- Operations partners need a high level of flexibility and engagement to be successful.
  - Standard business practices may need adjustment to better respond to the complex, changing needs of the master protocol study.
  - Flexibility is required to handle what may be a greater volume of work overall

OPERATIONS PARTNER: SAFETY MANAGEMENT (DSMB AND MEDICAL MONITOR)		
Role	**Assessment Considerations**	**Training & Capacity Needs**
◆ Each investigational medical product (IMP) evaluated within the master protocol study has a unique safety profile, requiring the medical monitor and data safety monitoring board (DSMB) members to devote significantly more time to the trial ◆ Industry partners may require final call on determination of serious adverse events (SAEs) that require expedited reporting (SUSARs), so a unique relationship with the Medical Monitor (MM) is needed ◆ The DSMB may need to include multiple specialties depending on the side effect profile of each IMP ◆ A clear communication process is needed to support certain adaptive features of the study, such as early stopping for futility or efficacy	◆ Ability to manage the high volume of safety reporting ◆ Ability to track and assess the reference safety documents for IMPs that are active in the study ◆ Broad experience and ability to consult on an ad hoc basis with additional experts	◆ If multiple industry partners are engaged in the study, the MM needs to be trained by each industry partner on the IMPs ◆ The MM may need to collaborate with MMs employed by industry partners contributing medical products to the study discuss specific cases

OPERATIONS PARTNER: ELECTRONIC DATA CAPTURE AND DATA MANAGEMENT SYSTEMS		
Role	**Assessment Considerations**	**Training & Capacity Needs**
◆ The electronic data capture (EDC) system and data management operations partners must understand the unique data collected for each drug tested (inclusion/exclusion criteria, adverse events of special interest, additional safety monitoring procedures, etc.), and how they will impact special considerations for randomization and drug supply ◆ Account for the changes that will be made to sub-protocols appendices as multiple arms are added and dropped over the life of the study ◆ Facilitate a large volume of data cleaning and be able to support interim analyses. Build requirements should include a careful balance of planning for future adaptations while avoiding unnecessary rigidity in the face of current unknowns.	**For a study that uses one unified database:** ◆ Ability to capture data for multiple IMPs within the same database, with appropriate firewalls and reporting capabilities so that both master protocol and sub-protocol specific reports can be generated **For a study that uses multiple databases:** ◆ Ability to report across databases efficiently ◆ Ability to analyze data at a program level ◆ Ability to deliver on data requests quickly to facilitate frequent interim analyses	A user-friendly database interface for site coordinators to clearly understand where to input information for which sub-protocol

OPERATIONS PARTNER: WEB-BASED RANDOMIZATION SYSTEM[1]

Role	Assessment Considerations	Training & Capacity Needs
◆ The web-based randomization system (WBRS) plays a vital role in study success, as it uniquely sits within a clinical study's EDC and database infrastructure. ◆ Allows seamless adaptations to randomization, on demand, without interrupting randomization functionality ◆ Evaluates the protocol from the operations and the biostatistics perspectives and assists the client in determining potential adaptations to include in the initial build of the WBRS ◆ Carefully balances planning for future adaptations, while avoiding unnecessary rigidity in the face of current unknowns ◆ Proposes innovative software design options that address the needs for advanced statistical models for randomization, and also provides for the seamless integration with other operations partners stakeholders in kit packaging, labs/diagnostics, EDC, and other clinical systems as the protocol's adaptations evolve	◆ Has biostatistics staff dedicated to making complex randomization designs ◆ Demonstrates expertise in master protocol designs and offer consultancy and guidance on WBRS implementation ◆ Has relationships with other operations partners in the e-clinical ecosystem and understands the critical connections enabled through systems integration as part of a team of partners to the master protocol sponsors ◆ Employs employ site and patient-centric response systems, including the availability of a global technical support service desk 24/7/365	◆ The WBRS provider will need to be involved from the outset of protocol design and study planning; this will allow for effective collaboration with biostatistics and other stakeholders ◆ Sponsors should provide workflows on how, when, and in what sequence, clinical decisions are made on how they expect to on-board new treatments or sub-protocols. These workflows will ensure a seamless and effective WBRS design that supports clinical decision making

[1] The WBRS is a key part of the EDC and Data Management Systems. Additional information was included to guide the selection of a WBRS given the critical role the WBRS plays in building an integrated EDC and data management system.

OPERATIONS PARTNER: CLINICAL EVENTS CLASSIFICATION		
Role	**Assessment Considerations**	**Training & Capacity Needs**
◆ Each IMP tested might have different needs for monitoring based on its safety profile	◆ Need to have broad capabilities to accommodate the safety profiles of multiple IMPs	◆ Ability to adapt to rapid turnaround times based on IMP-specific needs; some regimens may require STAT central reads

OPERATIONS PARTNER: CENTRAL LAB Read a real-world example from the Healey ALS study for additional central lab considerations.		
Role	**Assessment Considerations**	**Training & Capacity Needs**
◆ Processing samples for PK/PD biomarkers differently adds to the complexity to the study ◆ A central lab must adapt each time a new IMP is added, and be able to re-supply sites with lab kits perpetually ◆ Anticipate an ever-changing set of IMPs and arms.	◆ Flexibility within the central lab database for changes as new study arms are dropped or added ◆ Ability to think creatively about how the lab kits are being constructed to efficiently manage the greater volume of lab kits that are sent to sites ◆ Ability to manage the high volume of work and rapid turnaround times ◆ Critical lab values, and type of labs drawn at each visit based on regimen specific needs	The central lab will need to develop creative strategies to manage an increased volume of work and collaborate closely with sites to streamline lab-related operations processes

OPERATIONS PARTNER: INSTITUTIONAL REVIEW BOARD

Role	Assessment Considerations	Training & Capacity Needs
◆ Single intuitional review boards (sIRBs) need to understand how the inclusion of new IMPs will affect overall safety and balance of the overall trial ◆ Not all master protocol studies require the use of a sIRB. However, using a sIRB can help centralize and streamline IRB work	◆ Ability to engage more frequently in training ◆ Ability to manage a higher volume of amendments that result from adding and dropping arms, and the outcome of interim analyses ◆ See **CTTI's sIRB recommendations and tools** for additional considerations	The sIRB requires training on the statistical components of the trial to better understand how innovative design features may impact risk profiles and the balance within the study

OPERATIONS PARTNER: SITE MONITORING

Role	Assessment Considerations	Training & Capacity Needs
◆ Regimens may be testing drugs from different companies, thus, appropriate firewalls are needed ◆ The site monitoring plan may include co-monitoring with industry monitoring ◆ Because interim analyses are required in platform trials, subsets of data will have to be frequently and closely monitored	◆ Staff availability to conduct a monitoring plan that might support certain adaptive features of the trial such as interim analysis ◆ Availability to constantly retrain sites as arms are added or dropped.	Frequent and carefully timed monitoring is critical to support interim analyses

OPERATIONS PARTNER: INSTITUTIONAL REVIEW BOARD

Role	Assessment Considerations	Training & Capacity Needs
◆ Most likely used only if the sponsor is a patient advocacy or other non-profit work ◆ The contract research organization (CRO) will need to have the bandwidth and flexibility to support a continuously evolving trial ◆ Take an active and sustained role in managing the team of secondary suppliers in order to effectively quarterback these unique master protocol projects ◆ Set priorities across the different operations partners and stakeholders ◆ Constructively include all stakeholders and facilitate communication so that critical path decisions are made	◆ Previous experience working on a master protocol study ◆ Cost-effectiveness of the partnership • Are there cost concessions that the CRO might make because they want to be part of a novel IMP development program?	◆ Capacity in all operations functional areas of the trial ◆ In the event of changes in project management staff, need to be able to coordinate all operations partners and stakeholders with unique master protocol roles

Real World Example: Central Labs and Specialty Labs

Study: HEALEY ALS Platform Trial
Challenge: Central Lab and Specialty Lab Selection and Contracting

Central labs can be used to streamline coordination and communication with sites and specialty labs in master protocol studies. In the HEALEY ALS Platform Trial, as with other drug agnostic adaptive platform studies, the selection and contracting process with central labs commenced before the selection of investigational medical products (IMPs). Therefore, identification of sample type, storage requirements, and processing turnaround time was ongoing at the time of operations partner selection.

Beyond the use of a central lab, the HEALEY operation's team had to select and contract with specialty labs to analyze pharmacokinetic/pharmacodynamic and biomarker labs associated with specific IMPs. Collaborating with specialty labs introduces additional and contractual complexities as they often require greater communication and coordination efforts than traditional randomized control trials (RCTs). Contractually, the sponsor will have to ensure that the analysis conducted by specialty labs does not jeopardize the blinding of the study or introduce additional privacy and data sharing concerns.

PROBLEM-SOLVING APPROACH & SUCCESS FACTORS:

- **Ensure that the central lab and specialty labs understand that the scope and complexity of the work will evolve over time as new IMPs are added to the study.** Engage central labs and specialty labs in ongoing discussions at a granular level about the types of labs that need to be done in association with each IMP as it is introduced to the study. Central labs and specialty labs will need to understand and anticipate the need for contractual amendments as IMPs are added to the study over time.
- **Develop an approach to contracting to address data sharing and privacy concerns between the central lab, specialty lab, and industry partners.** Expect this approach to be more complex than contractual agreements with labs and industry partners in RCTs.
- **Anticipate and prepare to address challenges related to staff turnover.** Staff turnover within the study sponsor and labs is expected. An archive of communication and training materials can streamline the training of new staff.