Budget Guide for Clinical Research

Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit research and educational organization, is sponsoring a Clinical Development Plan for MDMA-assisted psychotherapy for treatment of Posttraumatic Stress Disorder (PTSD) that is currently beginning Phase 3. This is the final regulatory stage prior to filing a Food and Drug Administration (FDA) New Drug Application (NDA) seeking approval for prescription sales. MAPS created the MAPS Public Benefit Corporation (MPBC), a wholly owned taxable for-profit subsidiary, to sell MDMA by prescription after NDA approval (for more information, see MAPS Bulletin, Spring 2015,25:1, p.4-5). MPBC also designs and conducts clinical trials within the Clinical Development Program, maintains the quality of study conduct through ongoing monitoring of data and participates in writing study publications. MPBC contracts with independent entities who represent Clinical Sites to accomplish these goals. Collectively, MAPS and MPBC share the regulatory responsibilities of pharmaceutical sponsorship.

Purpose

The purpose of this document is for MPBC to provide MAPS with a dynamic model of MPBC costs associated with properly conducting Phase 3 MDMA/PTSD research studies of various methodological designs at multiple locations around the world. Included is information on a variety of direct costs, indirect costs, determination of staff efforts, and contractual costs.

Definitions

Direct Costs: Costs that support a project or program including personnel, equipment, supplies, subject treatment costs and, if applicable, subcontract costs. Some direct costs for supplies will be paid for by the Sponsor centrally and provided to the sites.

External Costs: Costs associated with the conduct of research activities for study implementation at the Project Level and by Clinical Sites.

Indirect Costs: Costs that are not directly accountable to a cost object (e.g. project, facility, function, or product), associated with the general operation and the conduct of research activities like facilities and administrative costs; calculated by applying a specified rate to the Direct Costs.

Internal Costs: Costs MPBC incurs from the conduct of research activities delegated from MAPS to MPBC. Clinical Site costs to run the study are not a part of these costs.

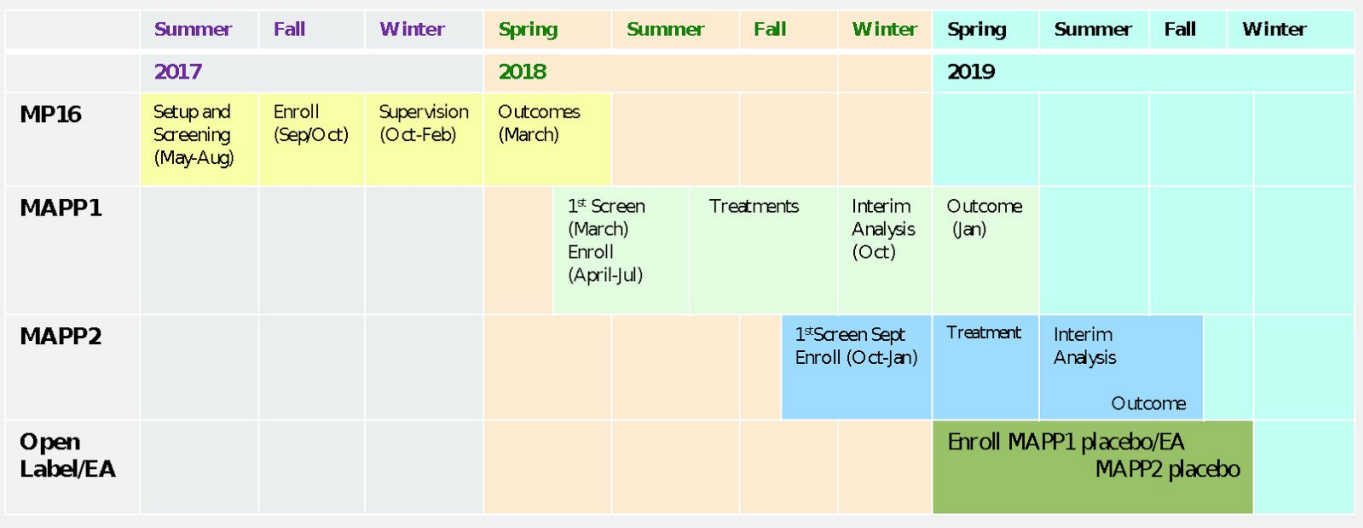
Total Site Costs: Total Clinical Site costs, both direct and indirect, to carry out a project or activity. The sponsor costs to run and support the study are not a part of this total.

Procedure

Determining staffing needs and other costs is a cooperative process between MPBC and the Clinical Site.

The staff and amount of time budgeted per study will vary depending on the study phase and timeline, i.e. specific tasks may vary by project. MPBC will provide MAPS with timelines and a customized budget template based on study needs and information obtained from the Clinical Site. Participation in Phase 3 studies (MAPP1, MAPP2, and Open Label/Expanded Access (EA)) as a Clinical Site requires each new male/female co-therapist team to first treat one patient with therapeutic supervision in the MAPS-sponsored open label Phase 2 study (MP16,) to provide a training opportunity and to gather safety data.

Figure 1: The timeline of U.S. Phase 3 and associated studies is presented in the figure below.



In general,

- The Start-up Period involves final protocol approval; identifying staff and training; site set up
- The Active Period for study implementation involves primarily study subject recruitment, study management, intervention implementation, data collection, data entry, data cleaning, Data Monitoring Committee (DMC) reporting and interim data analyses as required by the study (performed by MPBC)
- The Close-out Period involves cleaning of final data for statistical analyses by MPBC and long term follow up calls, abstract and manuscript preparation
- The Open Label Period will be a separate extension protocol (MAPPE1), after database lock of the Phase 3 study, creating an opportunity for all placebo subjects to receive MDMA-assisted psychotherapy following the schedule in the Phase 3 design. Treatment costs are included under each respective study budget under the Open Label/Stage 2 site costs.

- The Long-term Follow-up Period will be a separate extension protocol (MAPPE2) this involves a single follow up visit by telemedicine at 1 year after the last experimental session for all subjects.

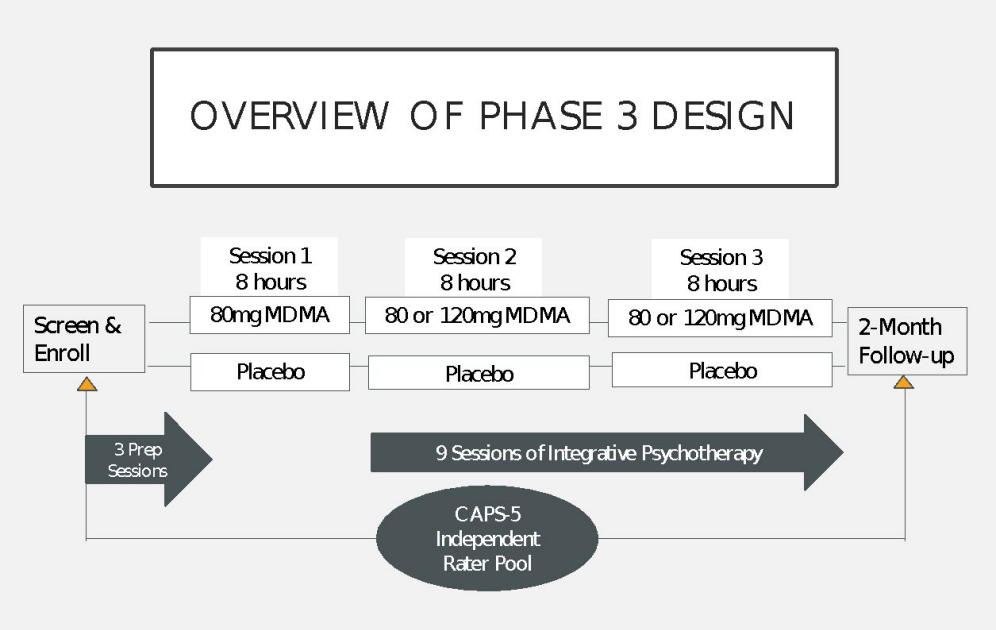


Figure 2: During the Active Period of each study, every trial participant completes the following treatment course of MDMA-assisted psychotherapy presented in the figure below.

Components of the Study Budget

The following is a description of the types of costs that are included in the study budgets.

Table 1: Overview of distribution of tasks by budget component within each Phase 3 study budget model are presented in the table below. For more details, see the Appendix.

Overview of Distribution of Activities	**MPBC** **Internal Cost or Project-Level External Cost**	**Site-Level** **External Cost**
Study Design	Provide	Review
Study Set-Up	Provide	Review
Drugs & Study Materials	Provide	Review
Drug Management	Provide templates	Manage
Study Management	Collaborative Oversight	Provide
Project Management	Provide	
Safety	Review & Advise	Collect

Clinical Data Management	Monitor & Advise	Collect
Biostatistics & Regulatory Reports	Provide	

Direct Costs incurred to conduct the research will include Internal and External Costs:

Internal Costs

Personnel effort (salary and fringe): All internal personnel efforts are described as percent efforts of Full Time Equivalents (FTE). Costs are calculated as a combination of salary and fringe, with annual 4% raises to account for inflation and accumulated experience of internal staff. When converting percent effort in a year to hours, multiply by 2080. For example, 10% effort is 208 hours in a year, 20% effort is 416 hours in a year and so on. It is anticipated that certain periods of costs (e.g. Start-up and Close-out costs) incurred by MPBC will be shifted between study budgets due to overlapping timelines. Start-up Period internal personnel costs are within the MAPP1 study budget. Active Period internal personnel costs are spread across the MP16 supervision study, MAPP1 and MAPP2 Phase 3 study budgets. Close-out Period costs for MP16 will be absorbed by the MAPP1 and MAPP2 budgets. Preparation of regulatory submissions in support of the NDA for MAPP1 and MAPP2 will require coordinated internal effort across internal MPBC staff and consultant statistician and statistical programmers using SAS.

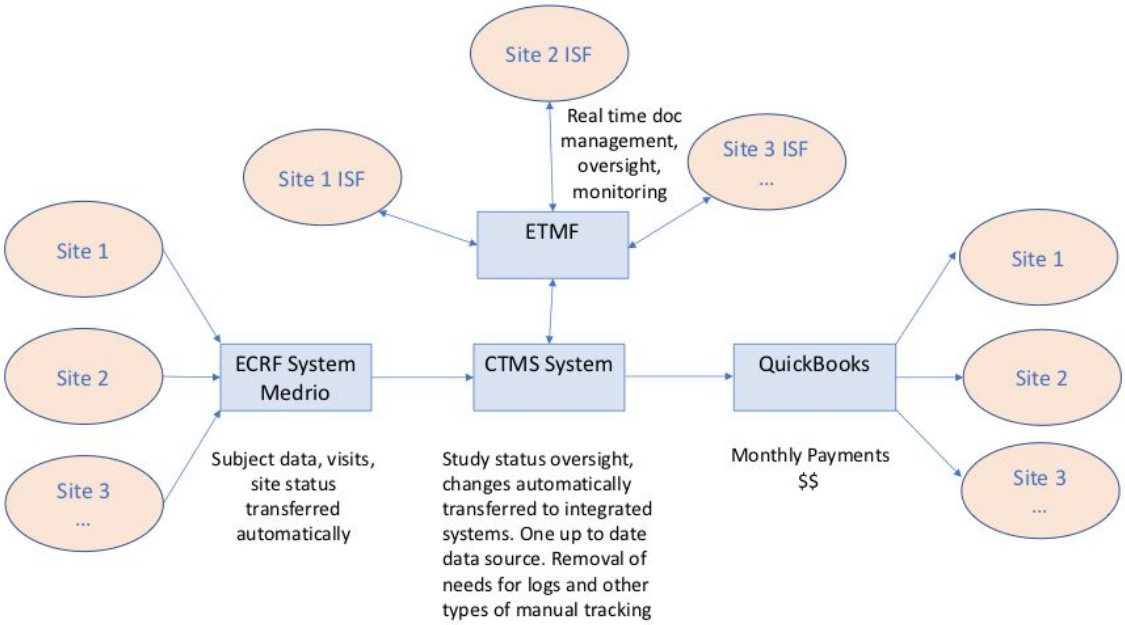
Study Monitoring

On-site and remote monitoring is provided by MPBC personnel. Time and travel costs are included in the Internal Cost budget for MPBC personnel to work with the Clinical Sites at these visits and remotely.

eClinical Software Technologies for Remote Management

The study budgets include web-based FDA-compliant Electronic Case Report Form (eCRF) randomization systems that allocates study subjects randomly to blinded treatment groups. This includes an up-front payment to cover the build, training, and service fees.

Figure 4: Multi-site studies will be managed through integrated eCRF, Clinical Trial Management System (CTMS), Electronic Trial Master File/ Investigator Site File (eTMF/ISF) and Quickbooks systems presented in the figure below, budgeted under the Phase 3 Program and the studies as appropriate.



External Costs

Budgeting Clinical Site staff efforts for various activities depends on the scope of work and complexity of the project which is provided by MPBC. In general, the following personnel are critical to the successful implementation of the study; the Investigator, Sub-Investigators (Therapy Teams), and Study Coordinator. In some studies, staff can assume dual roles or there may be a need for additional roles such as a Study Physician (unless this is covered by the Investigator or Therapy Teams), and possibly a Project Manager if the Investigator will be delegating certain administrative duties. The amount of effort to be budgeted for each person is carefully matched to the responsibilities of the individual and the scope of work of the study, with input on this provided by MBPC. In addition, investigators should be aware of and adhere to any effort guidelines that must be followed. In certain cases, study conduct may take a longer or shorter amount of time, with the understanding that effort estimates and payments are made on an average basis. The sponsor will provide information on estimated percent effort by role as a part of a site budget template. The following is an example of how to calculate FTE's (Full Time Equivalent) for a Study Coordinator:

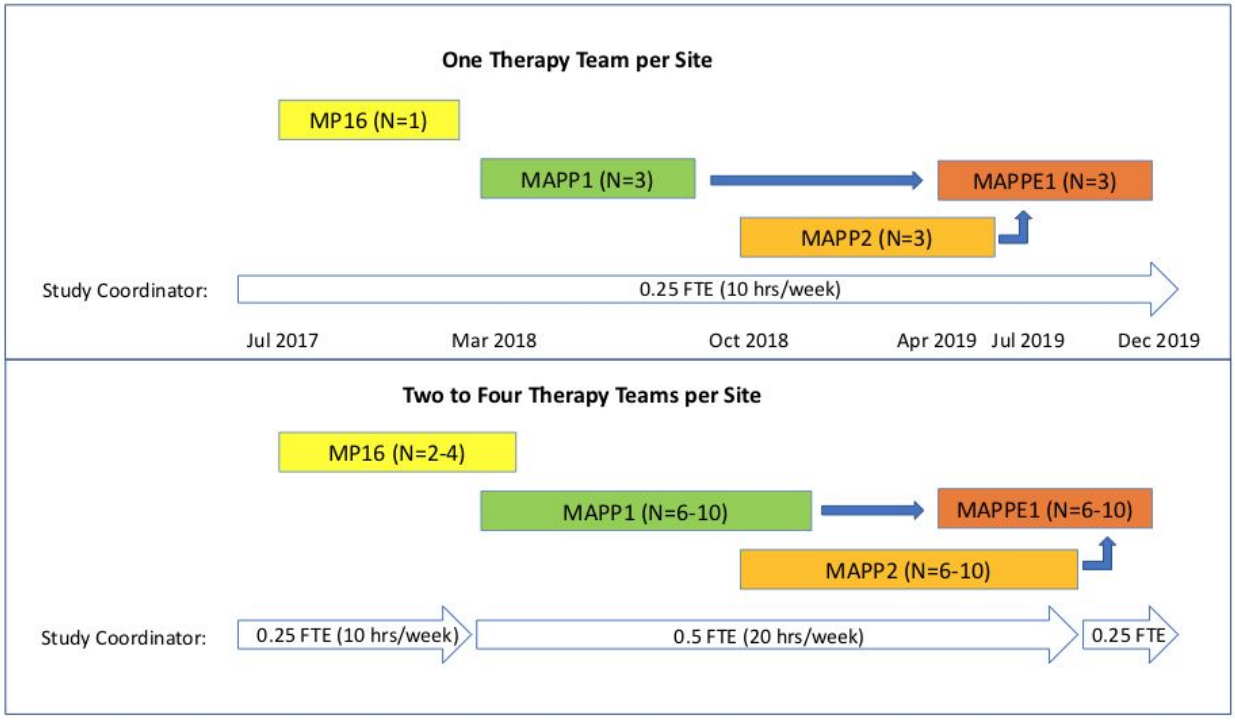
Recruitment phone calls and waitlist maintenance are anticipated to take 18 hours per month over 12 months of enrollment periods across Phase 3 studies for a total of 216 hours. Investigator site file maintenance, biweekly meetings with the sponsor, query resolution, logistical and monitoring visit support are anticipated to take 20 hours per month over 28 months, for a total of 560 hours. Taken together, these duration-based activities are likely to take 776 hours spread over 28 months across the Phase 3 studies. The FTE would then be 776 hours/4853.33 work hours in 28 months = 0.1599, or about

16% FTE for site support activities conducted by the Study Coordinator.

If a Clinical Site with a single Therapy Team anticipates enrolling 10 subjects cumulatively across Phase 3 studies, who will each complete 20 study visits over a 28-month period (200 visits), it is estimated that there will be 6 Case Report Forms (eCRFs) per visit for a total of 120 eCRFs, and it will take 10 minutes on average to data enter each eCRF. Therefore, the Sponsor estimates that the Study Coordinator will need 200 hours of primary data entry effort over the course of the 28 months or 7.1 hours per month on average (120 eCRFs x 10 subjects x 10 minutes = 12,000 minutes / 60 minutes = 200 hours). Phone screening according to an IRB-approved script, scheduling study visits, source record review, self-report measure administration and scoring, and facilitating drug dispensation and returns are anticipated to take 20 hours per subject, for a total of 200 hours spread across 28 months. The FTE for subject-based activities would then be 400 hours/4853.33 hours = 0.0825, or about 8.25% effort over 28 months conducted by the Study Coordinator to support a Clinical Site with one Therapy Team. Together with duration-based activities, the cumulative FTE would be 24.2% effort for the Study Coordinator in this example.

If a Clinical Site with multiple Therapy Teams anticipates enrolling 27 subjects cumulatively across Phase 3 studies, who will each complete 20 study visits over a 28-month period (540 visits), it is estimated that there will be 540 hours of primary data entry effort over the course of the 28 months or 19.3 hours per month on average (120 eCRFs x 27 subjects x 10 minutes = 32,400 minutes / 60 minutes = 540 hours). Phone screening according to an IRB-approved script, scheduling study visits, source record review, self-report measure administration and scoring, and facilitating drug dispensation and returns are anticipated to take 20 hours per subject, for a total of 540 hours spread across 28 months. The FTE for subject-based activities would then be 1080 hours/4853.33 hours = 0.2225, or about 22.25% effort over 28 months conducted by the Study Coordinator to support a Clinical Site with multiple Therapy Teams. Together with duration-based activities, the cumulative FTE would be 38% effort in this example.

Figure 3: Fluctuation in Study Coordinator effort across the Phase 3 and associated studies depending on number of Therapy Teams supported at each Clinical Site are presented in the figure below, with Max FTE for the Study Coordinator roll budgeted for each scenario.



Administrative Supplies and Treatment Room Equipment:

Supplies must have a documented direct benefit to the Phase 3 project. They must also meet MPBC guidelines provided in the Study Reference Manual.

Equipment that is used specifically for the benefit of the project may be budgeted on the project according to MPBC specific guidelines. General equipment such as copiers and computers for use on multiple projects should not be budgeted for a specific project. This type of equipment is reimbursed through the indirect cost rate.

Examples of study-specific supplies or equipment budgeted include audio/video equipment, DEA-compliant drug storage, specific furniture for setting up the treatment room, copyrighted outcome measures, or human specimen related processing and shipping supplies etc.

Study start-up and close-out fees

This is calculated by the Investigator by estimating the amount of resource time needed for up front study preparation and management and closing out the study (non-subject care related activities, including document receipt, budget meeting and review, contract meeting and review, submission administration, etc.). Typically, start-up are approximately $15,600 and close-out costs are $3,12. These costs will have a range that depends on the size of the site, number of therapy teams, number of

subjects/site and if it's an academic or private site.

Therapy Cost

The costs for subject care such as subject travel, subject interviews, and office visits should be included as direct costs in the budget.

Subject Care Costs are provided under Costs by Visit Type in the budget model. These are determined based on validated average time estimates corresponding to each visit type provided by the sponsor.

Lab Tests and Procedures

Lab tests that are budgeted are allowable direct costs as defined by the sponsor guidelines. In most cases these will be charged directly to MBPC which has a central contract with Lab Corp.

Costs Associated with Investigational Drug Management

These costs are part of the Facility Costs line item, and include registration fees for DEA licenses and security alarm service. Institutional sites may also charge drug storage and dispensation fees.

Costs Associated with Facilities and Overnight Stay

These costs are budgeted as direct costs for private practice sites and may be designated as Indirect Costs at institutional Clinical Sites. Associated costs include laundry, possible overnight stay fees or reimbursement for night attendants, and facility fees such as rent, high speed internet service for video uploads, phone service, and cost of administering invoices for study staff prorated based on usage for the sponsored project.

Subject Reimbursements

No subject incentive payments are included to avoid any concern about coercion violating human subject protections. There may be some reimbursements for subject costs for travel, lodging, and parking; especially when it is expected that subjects will be traveling any extended distance for participation in the study. Food will be provided during extended visits.

Project-Level External Costs

Central IRB Review Fee: A central IRB will be used with the fee paid by MPBC.

Insurance coverage: A central third-party insurance policy will be provided by MPBC.

Advertisement and Recruitment: For sites that require additional support to ensure recruitment goals are met, MPBC may provide additional funds as needed.

Indirect Costs incurred to support the research will include:

Clinical Sites and MPBC incur indirect costs as each entity conducts research activities. The MAPS

Board of Directors has a published accepted indirect rate cost of 10% for institutional Clinical Sites. (See link: www.maps.org/donate-redirect/funding-priorities)

Site Indirect Costs:

Indirect costs for Clinical Sites are currently calculated based on 15% of direct Total Site Costs, as this remains to be negotiated with Clinical Sites. This rate should be confirmed with the Clinical Trial Agreement upon completion of negotiations and applied to the study budget.

MBPC Indirect Costs:

Indirect costs for MPBC are currently calculated as 10% of total costs. These funds cover all internal pooled expenses. In addition, intercompany expenses related to support of MPBC by MAPS (Accounting and Finance, Information Technology, Website design and maintenance, Communications, shared rent and utilities as well as other operational costs) are accounted for as part of this calculation.

Clinical Site Personnel and Responsibilities

Each PI should customize this template as appropriate to the work scope of their study and include specific names, titles, and degrees of the staff proposed.

INVESTIGATOR (Tasks be delegated with oversight to Project Manager/Lead Therapist or MD)

- Oversees the scientific and administrative aspects of the study to ensure successful conduct
- Leads the implementation of the study at the site
- Ensures appropriate delegation of responsibilities to qualified designees
- Signs off on enrollment in the trial with input from the Medical Monitor and site team
- May be the controlled substance license holder
- Provides financial oversight of the project
- Provides overall direction and leadership to the project staff
- Assess safety, review subjects' data, participates in the analysis and interpretation of the data
- Prepares manuscripts for publication
- Ensures site communication, leads meetings and conference calls

PROJECT MANAGER (role to be added as needed per site)

- Oversees study implementation, including recruitment, intervention, and data collection and data management activities.
- Conducts training of site staff
- Coordinates project meetings and supervises the tasks of staff involved in the project
- Monitors study progress including recruitment status, subject drop-out or losses, study form completion, and intervention compliance, and performs quality assurance of data collection methods
- Oversees the accuracy and completeness of the data entry and the resolution of data entry errors

THERAPY TEAM (one member maybe the PI or MD for the study)

- Performs Informed Consent interview
- Performs therapy in the clinical trial
- Reviews participant's returned measures
- Accurately completes source documentation
- Receptive to clinical supervision from the therapy training team as the need arises
- A representative should attend team meetings with the sponsor

STUDY PHYSICIAN (May be a PI or Therapist)

- Assess adverse events, vital signs, EKGs
- Perform physical exams
- Prescribe concomitant medications
- Schedule pre-study medication tapering

STUDY COORDINATOR (SC)

- Assists Principal Investigators (PIs) in planning and implementing clinical research studies as assigned. Attends team meetings with their site and the sponsor.
- Performs initial phone screens for recruitment of study participants for enrollment in clinical trials. Assists with obtaining medical records as needed.
- Organizes study procedures and schedules study participants for study visits physical exams, EKGs and clinical labs, if needed. Assists the team during subject visits. Schedules Night Attendants and Independent Rater visits. Maintains site tracking logs in real time.
- Reviews self-report measures for completeness
- Completes record abstraction of source documents, conducts required study measurements, and completes study Case Report Forms in accordance with best practice methods. Maintains regulatory binders, case report forms, source documents, and other study documents. Resolves data entry errors.
- Works closely with the sponsor to ensure site compliance

OUTSIDE ROLES (may or may not be affiliated with Clinical Site, paid per use):

- Clinical Labs
- EKG
- Night Attendants

Appendix

Table 2: Detailed distribution of research tasks for each Phase 3 study are presented in the table below.

Activity	Responsibility of (✓):			
	MPBC	Principal Investigator*/ Delegated to Project Manager	Therapy Team	Study Coordinator
Study Design		*PI MUST do, all other items may be delegated		
Design and write protocol and protocol amendments	✓			
Review protocol/Amendments		✓	✓	✓
Obtain study measures	✓			
Design eCRFs	✓			
Design informed consent form template	✓			
Review and comment on informed consent form template		✓		
Print & distribute informed consent				✓
Write/update investigator brochure	✓			
Distribute investigator brochure, obtain Read and Acknowledge	✓			
Create source documents	✓	✓ Will review		✓ Will review
Study Set-Up				
Secure import approvals, as needed	✓			
Collect regulatory documents	✓			✓
Ethics/IRB submissions	✓	✓ (As needed)		✓(As needed)
Collect Ethics/IRB approvals and Roster	✓	✓ (As needed)		✓ (As needed)
Determine investigator budget	✓	✓		
Negotiate investigator budgets	✓	✓		
Develop investigator agreement template	✓			
Obtain signatures from required personnel for all investigator agreements (contracts, 1572*, Financial Disclosures)	✓ send for signature, collect when final	✓* sign as appropriate	✓ sign as appropriate	✓ assist in obtaining, file in ISF
Design & distribute Study Reference Manual	✓			
Submit study to clinicaltrials.gov	✓			

Request Certificate of Confidentiality from FDA	✓			
Conduct Site Initiation Visit	✓	Attend	Attend	Attend
Train study site co-ordinators	✓	✓		
Complete GCP, HIPAA, CITI, CSSRS Training, as appropriate	✓	✓	✓	✓
Delegate responsibilities through the site team on Site Responsibility Log	✓ Receive copy	✓*		
Identify & negotiate contract for central laboratory	✓			
EKG outside of clinical team		✓		
Physician, as needed, at least one on staff per site (therapists may not perform physical exams on their own subjects)		✓		
Confirm therapy treatment room set up	✓ will review at SIV	✓		
Approve investigator documentation prior to drug release	✓			
Set up Investigator Site File	✓			✓ maintain file
Design study progress tracking system	✓			✓ update files
Drugs & Study Materials				
Contact Local DEA Agent- or equivalent		✓		
Submit for Schedule I license- or equivalent		✓		
Background Check	Will assist	✓	✓ as selected	
Confirm drug storage set-up	✓ will review remotely	✓		
DEA Inspection- or equivalent		✓		
Sign DEA agreement form for drug distribution- or equivalent		✓	✓ as selected	
Ship Study supplies (drug tests, pregnancy tests, measures etc.)	✓			
Drug Management				
Maintain Drug Securely (Accountability/Administration/Cabinet entry logs)		✓	✓ as selected	
Maintain DEA 222 or equivalent forms		✓		
Distribute drug (couriers/shipping)	✓			
Dispense Study Drug		✓	✓	

			as selected	
Account unused/returned drug		✓	✓ as selected	
Destroy unused/returned drug		Discuss with Sponsor		
Provide payment for drug destruction	✓			
Study Management/On Study Activities				
Conduct monitoring visits, create reports (internal) confirmation, follow up letters (to site)	✓	Be available for visits		Be available for visits, File correspondence, follow up from visit
Provide site management	✓	✓		
Manage Sponsor Team Meetings in "pods"	✓			
Manage Internal Site Team Meetings		✓		✓
Provide Therapy Feedback	✓			
Provide ongoing training	✓			
Report Protocol Deviations	✓ track	✓	✓	✓
Prepare & submit annual reports to MOH (if needed)		✓		✓
Provide Annual Status Report to regulatory agencies	✓			
Ongoing IRB Submissions, as agreed upon	✓	✓		✓
Provide study tracking reports (participants, supplies etc.)				✓
Administer and process investigator payments	✓			
Tracks list of expenses for invoicing				✓
Provide source and eCRF	✓			
Perform eCRF Data Entry				✓
Review subject measures and subject source		✓	✓	✓ for correctness and data entry
Final Database Review and Sign off		✓		
Filing of study records and correspondence	✓			✓
Over-see the Independent Rater Pool	✓			

Schedule Subjects with the Independent Rater				✓
Participant Recruitment		✓		✓
Perform Phone Screening		✓	✓	✓
Perform Screening Visits		✓	✓	
Perform Enrollment Confirmation	✓ Provide feedback	✓		✓
Secure Night Attendants for overnight visits				✓
Perform Experimental, integrative and follow up visits and calls		✓	✓	
Manage laundry, groceries, office supplies				✓
Conduct close-out visits	✓			
Archive essential study documents	✓	✓		✓ Assist
Provide Final Dataset	✓			
Complete final Clinical Study Report	✓	✓ Provide Review		
Submit final Clinical Study Report to regulatory agencies	✓			
Coordinate Publication	✓			
Project Management				
Provide project management oversight	✓	✓		
Set up Monitoring Plan	✓			
Provide guidance on Media interactions	✓			
Provide ongoing study information for presentations	✓			
Provide status reports				✓
Write & distribute newsletters to investigators	✓			
Maintain Therapy Training Portal	✓			
Safety				
Set up SAE reporting plan	✓	✓		
Provide SAE telephone coverage	✓ Medical Monitor/CRA	✓		✓ Subjects can call
Liaise to obtain SAE clarifications and follow-up support documents	✓ Medical Monitor/CRA	✓ Provide updates as needed		✓ Obtain medical records as needed
Provide full database entry into Sponsor's SAE database	✓			
Code AE's	✓			

Code concomitant medications	✓			
Code medical histories	✓			
Write SAE narratives		✓		
Provide medical review of SAEs	✓	✓		
Forward SAE document/forms (including MedWatch/CIOMS as specified) to Principal Investigator	✓			✓ Study Coordinator
Submit SAE reports to regulatory authorities	✓ in U.S./Canada	✓ (as needed per country requirements)		
Compose & distribute safety alert letter to Ethics Committee/IRBs as agreed	✓	✓		
Compose & distribute safety alert letter to investigators	✓			
Provide review of safety data in eCRFs	✓	✓		
Reconcile SAE's between safety & clinical databases	✓			
Provide medical monitoring services	✓			
Biometrics – Clinical Data Management				
Develop and maintain project data management and validation plans	✓			
Design/build database	✓			
Conduct secondary in-house review of eCRF for completeness	✓			
Generate/resolve queries	✓ generate			✓ resolve
Conduct validation/plausibility checks	✓			
Develop data transfer sets	✓			
Review and Lock database	✓			
Archive database post-database lock	✓			
Ship/receive project-related documents to Principal Investigator at the conclusion of the project	✓ ship			✓ receive
Biometrics – (Biostatistics & Scientific Programming)				
Protocol development & review (includes study design and sample size calculation)	✓			
Randomization codes generation	✓			
Create and populate AE coding	✓			

tables				
Create database specifications and annotated eCRFs	✓			
Create statistical analysis plan (includes text and mock-ups)	✓			
Create analysis data set & programming specifications	✓			
Program analysis data sets, tables and listings	✓			
QC analysis data sets, tables and listings (includes checking inferential analysis model assumptions)	✓			
Unblind study	✓			
Provide unblinded tables, figures, listings, and patient profiles to sponsor, biostatistician, and PI	✓			
Write statistical report	✓			
Perform exploratory analyses (not to be included on a summary table)	✓			
Write statistical section of the clinical report	✓			