Project Management 101: for Clinical Trials

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Agenda

Outlook of Clinical Research

Conceptual/Planning Phase

Implementation Phase

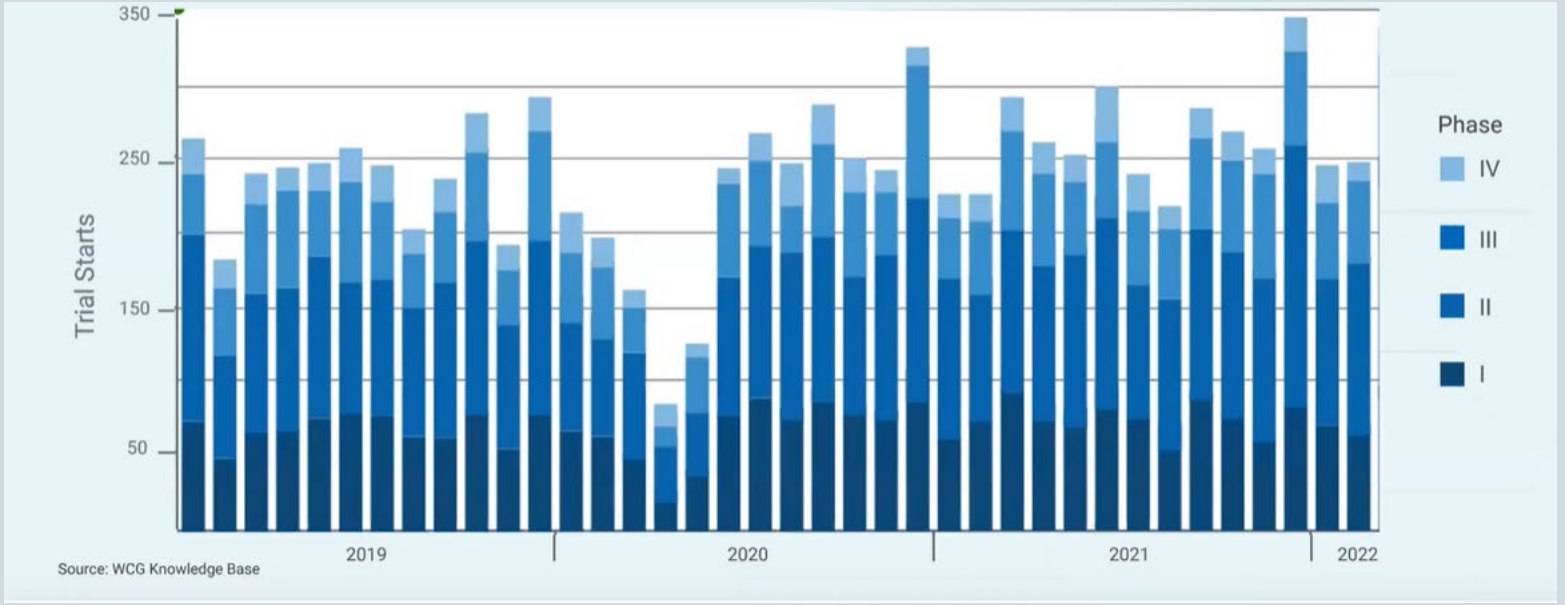
Closeout Phase/CAPAs

Center for Health + Technology?

- CHeT is a clinical research organization within the University of Rochester.
- **We are comprised of five units:**
  - *Clinical Trials Coordination Center*
  - *Clinical Materials Service Unit*
  - *Outcomes (Patient-reported outcome measures)*
  - *Innovation (research using novel technologies/ sensors, decentralized trials)*
  - *CHeT Analytics (Data modeling and predictive analytics)*
- Our team designs and conducts multi-center clinical trials with collaborators from across the globe to accelerate clinical research and advance the development of therapeutics.
- Since its inception over three decades ago, we have ran trials that have led to FDA approval of 7 drugs in Parkinson's and Huntington's disease.

Outlook of Clinical Research

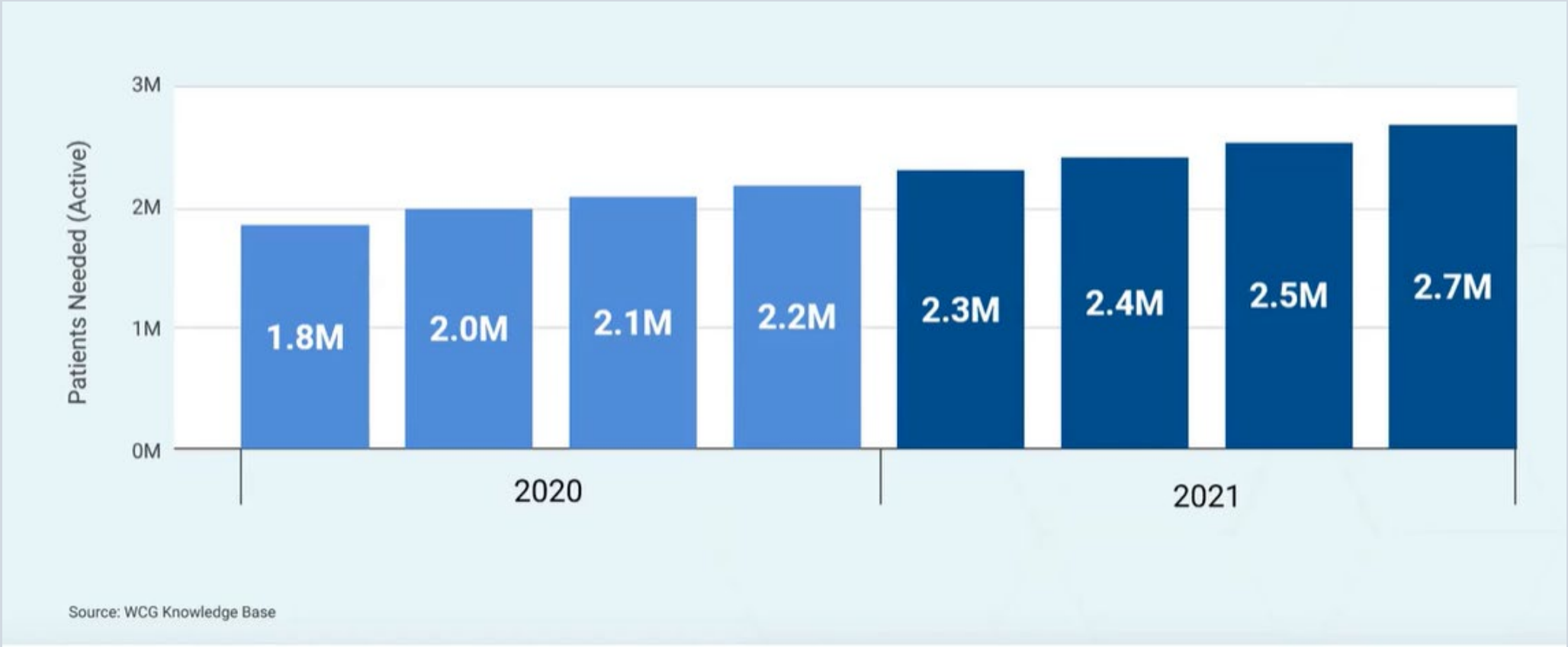
Industry Sponsored Study Starts



* This does not include COVID studies

Source: https://ClinicalTrials.gov

Need for Participation is Increasing



Current Challenges

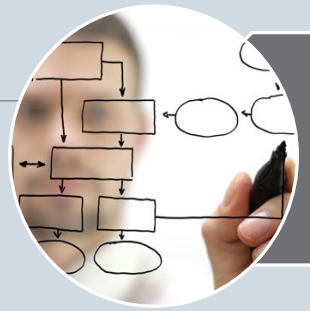
97% of Physicians do not participate in clinical trials and site staffing challenges

5% of patients participate in clinical trials

~70% of potential participants live more than 2 hours away from a trial site

Trial Enrollment is decreasing over time, some are reporting a 50% decrease

Solutions



Streamline processes for every phase of the trial. Prioritizing your time.

Recruitment and Retention

https://www.aacp.com/2019-national-workforce-study

Scenario

You are approached by your supervisor or department to be the project manager for an upcoming clinical trial. It may be a multi-center study or a single study site but they aren't sure.

You will need to do some of or all of the following:

- Develop the protocol and consent
- Identify and oversee other sites (if applicable)
- Oversee the vendors: drug, lab, imaging
- Develop recruitment measures
- Maintain clinicaltrials.gov
- Closeout the trial and finalize a final report

Problem: You have never been a project manager. Where do you even start?

General Tips

- **Break the trial into three main phases**:
  - Conceptual/Planning
  - Implementation
  - Closeout

- **Know who to approach for help and guidance:**
  - Regulatory Specialist (TrialMaster File)
  - Finance Representative – Budget
  - Contract – ORPA or legal liaison
  - Quality Assurance
  - RSRB

- **Remember:** If it is not documented, it didn't happen. Track your phone conversations if not already documented.

Conceptual/Planning Phase

Key Planning Activities

- Protocol/Consent
- Confidentiality Agreement
- Scope of Work
- Budget
- Vendor Identification
- Case Report Creation
- Database Build
- Steering Committee Selection
- Site Selection by Steering Committee
- Site Selection Survey
- Data Safety Monitoring Board Selection
- ClinicalTrials.gov registration
- Creation of Recruitment Materials
- Creation of Study Plans and Work Ins.
- TrialMaster File (General and for Sites)

Standard Operating Procedures (SOPs)

- It is important to develop site-specific **Research SOP's**, utilize the ones you have as a research site and use these as a jumping off point for clinical trials management.
- An SOP will describe and provide guidance on the development and management of clinical trials. Your sponsor may require an audit of your SOPs.
- **Include policies on (if applicable):**
  - Study Start-Up (TrialMaster Files, Protocol and Consent Development, etc.)
  - Database Build and Validation (RedCap is not Part 11 compliant so may need to research another database system for your trial if required by sponsor)
  - Database Lock
  - Safety Monitoring
  - Training
  - Quality Assurance
  - Audit Procedures

Confidentiality Agreements

- You may be provided a confidentiality agreement by your sponsor to use or you may need to create one for your site(s).
- This may be needed in order for you or your sites to receive additional information:
  - Protocol Synopsis
  - Schedule of Activities
  - Per Subject Fee
- In general, once there is an executed subcontract; there is no need to have new staff sign the Confidentiality Agreement, as staff employed at the site are bound by confidentiality terms in the subcontract.

Clauses of a Confidentiality Agreement?

- Key clauses to look for:
  - Purpose of the exchange
  - Definition of what constitutes confidential information
  - Time limit for confidentiality
  - Ability to retain one copy of materials
  - Confirm no conflict between CDA and trial contract

- Confidential Information ***does not*** and ***should not*** include study data

- Study data cannot be exchanged under a confidentiality agreement – that would require a data transfer agreement. Different obligations on the sending and receiving party if obtaining study data.

Budgets

- Using the Protocol Synopsis, Schedule of Activities, Scope of Work, and other related documents, develop a budget, which shall describe the costs of activities performed during the course of the planned agreement.
- Present this budget to your Sponsor and work with Sponsor to negotiate mutually acceptable compensation for the activities requested and an appropriate timeline for payments (milestone payments vs. at specific time points vs. a combination of the two)
- When applicable, the budget shall include a proposed Per-Subject Fee (PSF) to be paid to the participating clinical sites (if applicable)

APX-037 Per Subject Fee Schedule (SAMPLE)

ASSESSMENTS	Unit cost	Screening	Screening	Treatment	Telecom	Treatment	Telecom	Treatment	Telecom	Treatment	Follow Up	Total Per Subject	UNSCHED VISIT
Visit #		(2)	(1)	-		1		2		3	4		
Week			(1)	-		4		13		26	28		
Study Days		(30)	(7)	-		28		91		182	196		
Phone Contact					7,14,21		56,84		119,147,175				
Written Informed Consent	100	xxx											
Inclusion / Exclusion		xxx											
Demographics, Med Hst, Genetic Confirmation		xxx											
Physical Exam		xxx		xxx		xxx		xxx		xxx	xxx		
Vitals: BP, HR,		xxx		xxx		xxx		xxx		xxx			
Weight, Height, BMI		xxx								xxx			
Serum Pregnancy Test		xxx											
Urine Pregnancy test						xxx		xxx		xxx			
Prior / Baseline		xxx											
Baseline signs and		xxx											
Clinical Lab Evaluation (CBC, Chem Panel;		xxx		xxx		xxx		xxx		xxx			
FARS Exam			xxx	xxx				xxx		xxx	xxx		
T25FW			xxx	xxx				xxx		xxx	xxx		
Frazatin Protein: Platelet, PBMCs (blood), RBC,				xxx				xxx		xxx			
Frazatin mRNA, Blood				xxx				xxx		xxx			
Frataxin, Muscle biopsy				xxx						xxx			
FRDA Lymphocyte Biomarker Panel, Blood,				xxx				xxx		xxx			
IFN-g Levels, Blood sparse sampling				xxx				xxx		xxx			
IFN-g Levels, Blood frequent sampling sub								xxx		xxx			
Rev of ECG and ECHO performed at least 6 mos		xxx											
ECG		XXX Optional						xxx		xxx			
ECHO		XXX Optional						xxx		xxx			
Dispence Study Drug (Unblinded pharmacist				xxx		xxx		xxx					
Dose given at Study visit								xxx		xxx			
Educate on dosing Technique and schedule				xxx		xxx		xxx					
Drug Compliance						xxx		xxx		xxx			
AE/SAE Assessment						xxx		xxx		xxx	xxx		
Concommitant Meds						xxx		xxx		xxx	xxx	8	
Functional Staging of				xxx				xxx		xxx			
ADL				xxx				xxx		xxx			
9HPT			xxx	xxx				xxx		xxx			
Vision Testing (LCSLC)				xxx						xxx			
Auditory Testing (LiSN-S)				xxx						xxx			
Audiogram				xxx									
PedsQL, PROMIS QOL,				xxx				xxx		xxx			
Clinical Global				xxx		xxx		xxx		xxx	xxx		

Contracts

- **Overview of the Process**
  - Clinical Trial Agreement (CTA) negotiated and executed between University of Rochester and Sponsor

- **If a multi-center study:**
  - Site Contracts have flow down language from the sponsor's contract
  - Terms and Conditions of the subcontract are prepared
  - Study team identifies selected sites
    - Provides list of PIs, coordinators, administrators at each site to ORPA
  - Office of Research and Project Administration (ORPA) sends out subcontract to sites
    - Subcontracts negotiated by ORPA – timeline can be 1-6 months
  - Signed subcontract must be returned before the site can enroll subjects

General Trial Master File

- **PM Responsibility:** Collecting, handling, and safeguarding regulatory study documents throughout the lifecycle of a study, and conducting ongoing file review throughout each study phase, including review for accuracy and consistency between documents.

- A Master Tracker should be maintained to track key site documents. Tabs and columns can be added to or removed from the Master Tracker Template based on discussions with Sponsor and study-specific needs.

- **TMF should include but is not limited to the following folder structure:**
  - Trial Management
  - Central Trial Documents
  - Regulatory
  - IRB
  - Site management (if applicable)
  - IP and Trial Supplies
  - Safety Reporting
  - Central and Local Testing
  - DATA Management
  - Statistics

Scope of Work

- The narrative description of a project's work requirement. It defines project-specific activities, deliverables and timelines for providing services to the Sponsor or vendor. A SOW ensures expectations are clear and agreed-upon between the parties.
- Will be many pages long: many of ours top out at 50+ pages
- **Some Items to address:**
  - Protocol Development
  - Site Selection
  - Investigational Product
  - Site Monitoring
  - Operations manual
  - Database Design

ID	Task/Description	SPONSOR	PRINCIPAL INVESTIGATOR	CTCC	BIOSTATISTICS	VENDORS	Comment
A. Distribution of Case Report Forms (CRFs) or eSource Document Worksheets							
1	Ship sufficient CRF Source Documents or eSource Document Worksheets to sites						EDC will be utilized. Source Docs prepared and provided to sites by CTCC
B. Distribution of Operations Manual							
1	Perform power analysis to determine sample size estimates. Distribute the Operations Manual to site investigators and coordinators, Study Group and Sponsor staff prior to initiation of the study.						
C. Data Management							
1	Finalize a Data Management Plan which will include an SAE reconciliation plan.						SPONSOR must approve formally
2	Develop Clinical Data Management System						SPONSOR must approve formally
3	Develop additional software manuals incidence reporting, study notification, Monitor tracking, RAF Process, clinically significant lab, eMedWatch, Payment Tracking, Query Resolution Tracking, Other Metrics Report						SPONSOR must approve formally
4	Set up (Video, MRI, PET) repository SFTP site and transfer process						Sponsor to contract with vendor to receive and read FILES during trials. At conclusion of trials, SPONSOR will provide HSG
5	Helpdesk support and IT training for all sites						
6	Move Database to Production.						
7	Conduct validation including Production Qualification Run (PQR).						
8	Provide read-only access to the CTDMS.						
9	Provide access to standardized or study specific reports						
10	Initiate live data entry.						

Transfer of Obligations

- The responsibility for performing study-related activities and obtaining regulatory documents should be negotiated with the Sponsor through the SOW and documented per the Transfer of Obligation prior to study initiation.
- The Transfer of Obligation should be placed in the Trial Master File.
  - Example: If the Sponsor is responsible for regulatory document collection, they must forward a list to the PM noting the documents they will collect.

Study Timeline

- **Study timeline**
  - Populate with study milestones
  - Serves as a reference for the study team, sponsor, vendor
  - One document – easy to update
  - Aids the department in determining how to adequately staff the project
- **Can be created in:**
  - Microsoft Project (pictured)
  - Word
  - Excel
  - Tableau

Task Mode	Task Name	Duration	Start	Finish	Predecessors	Comments
	MS PROJ TEMPLATE_ABBREVIATED	**773 days**	**Tue 1/1/19**	**Thu 1/13/22**		**Adjust dur & pred as req**
	CONCEPTUAL PRE-STUDY	**20 days**	**Mon 4/1/19**	**Fri 4/26/19**		
	RFP to Final Proposal Submitted	0 days	Mon 4/1/19	Mon 4/1/19		
	Final Agreement Signed	0 days	Fri 4/26/19	Fri 4/26/19	3FS+1 mon	
	EARLY PLANNING	**162 days**	**Wed 1/2/19**	**Tue 8/20/19**		
	Kick-off meeting	1 day	Wed 1/2/19	Wed 1/2/19		If available
	RSRB Approval	1 mon	Wed 7/24/19	Tue 8/20/19	4FS+3 mons	
	IMPLEMENTATION	**192 days**	**Tue 1/1/19**	**Wed 10/2/19**		
	Sites Selected, under contract, IRB approved	6 wks	Wed 8/21/19	Wed 10/2/19	4,7	
	Database Development	0 days	Tue 1/1/19	Tue 1/1/19		When contracted
	Investigational Material Shipped to 1st Activated Site(s)	0 days	Tue 1/1/19	Tue 1/1/19		
	ENROLLMENT & TREATMENT PERIOD	**531 days**	**Thu 9/19/19**	**Tue 10/19/21**		
	ENROLLMENT PHASE	**251 days**	**Thu 9/19/19**	**Sun 9/13/20**		
	First Subject Screening	0 days	Thu 9/19/19	Thu 9/19/19	9FS-2 wks	
	First Subject Enrollment/Randomized	0 days	Sat 10/19/19	Sat 10/19/19	14FS+30 edays	
	25% Enrolled/Randomized	0 days	Wed 12/18/19	Wed 12/18/19	15FS+2 emons	
	50% Enrolled/Randomized	0 days	Tue 3/17/20	Tue 3/17/20	15FS+5 emons	
	75% Enrolled/Randomized	0 days	Mon 6/15/20	Mon 6/15/20	15FS+8 emons	
	100% Enrolled/ Randomized (LSFTx)	0 days	Sun 9/13/20	Sun 9/13/20	15FS+11 emons	
	TREATMENT PHASE (LSFT to LSLT)	**0 days**	**Mon 8/23/21**	**Mon 8/23/21**		**When appropriate**
	100% Subjects complete treatment (LSLTx)	0 days	Mon 8/23/21	Mon 8/23/21	19FS+12 mons	
	F/U VISITS POST TX TO STUDY COMPLETION (LSLV)	**0 days**	**Tue 10/19/21**	**Tue 10/19/21**		**When appropriate**
	100% Subjects complete final study visit (LSLV)	0 days	Tue 10/19/21	Tue 10/19/21	21FS+2 mons	
	CLOSEOUT	**50 days**	**Wed 11/3/21**	**Thu 1/13/22**		
	Monitoring completed	2 wks	Wed 11/3/21	Tue 11/16/21	23FS+2 wks	
	All subjects secured	2 wks	Wed 11/24/21	Thu 12/9/21	25FS+1 wk	
	Post DB lock c/o visits (preparedness)	2 wks	Fri 12/31/21	Thu 1/13/22	30FS+1 wk	
	DATABASE LOCK FOR FINAL ANALYSIS	**20 days**	**Thu 12/2/21**	**Thu 12/30/21**		
	All vendor data transferred to DB	0 days	Thu 12/2/21	Thu 12/2/21	25FS+2 wks	
	Database lock	0 days	Thu 12/23/21	Thu 12/23/21	26FS+2 wks,29FS+2 wks	
	Data Transfer to Biostats	0 days	Thu 12/30/21	Thu 12/30/21	30FS+1 wk	

Site Selection – High Level

- **The PM or designee will send the following to the potential investigative sites:**
  - Site Interest letter - a letter introducing the potential study
  - Protocol synopsis and Schedule of Study Activities
  - Site Feasibility Survey information
  - Request for Investigator's and Coordinator's signed and dated current (as of date of the confidentiality statement is sent) Curricula Vitae (CV's) or Biographical sketch (if federally funded).
  - Request for Human Subject Protection Program (HSPP) Certification for those study personnel having direct patient contact. (This may also be obtained at a later date once the site is chosen.)
  - Request for Investigator’s and Coordinator’s Good Clinical Practice (GCP) training certification
  - Conflict-of-Interest, if required by Sponsor and/or study group.

Selected Sites

- **Once a site has been selected and has agreed to perform the study the following may be sent to the site:**
  - Follow-Up Site Letter
  - Critical Activities Checklist
  - Final protocol
  - Model Informed Consent Form
  - Investigator's Brochure or Package Insert (for approved investigational product)
  - Conflict of Interest Guideline
  - Conflict of Interest Disclosure
  - Any other required items will be sent to the site for completion
  - IRB submission, review, and approval.

Implementation Phase

SIGNIFIES THE START OF PARTICIPANT ENROLLMENT

Meeting Agendas/Minutes

- Develop an agenda and meeting template that is approved by Sponsor
- Determine the types of meetings (Ops, Team, Sponsor), frequency, and attendees

[Project/Study/Team Name and Acronym]

MEETING NAME/PHASE (Choose)

[Meeting Date]

Document Type (Choose)

Meeting Access Information:	[Enter remote access link and/or telephone numbers]	
Attendees *unable to attend		
Meetings (Scheduled)	[Meeting Name]	Date [DD-MMM-YYYY]
	[Meeting Name]	Date [DD-MMM-YYYY]
	[Meeting Name]	Date [DD-MMM-YYYY]
	[Meeting Name]	Date [DD-MMM-YYYY]
Holidays, Closings and Time Off		

Topic	Agenda Item	Date Identified	Discussion/Action Item	Responsible Person or Team	Target Completion Date	Actual Completion Date	Status/ Final Resolution
SELECT							SELECT
SELECT							SELECT
SELECT							SELECT
SELECT							SELECT
SELECT							SELECT
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Data Transfer Agreements

- All data transfers, consideration is given so that any variables subject to The Health Insurance Portability and Accountability Act of 1996 (HIPAA) or other privacy regulations and other potentially identifying information are transferred only when necessary and are provided via a secure mechanism.
- The method of data transfer as well as the appropriate documentation should be agreed upon by both the sending and receiving parties to assure an accurate and complete transfer.
- DTS should contain, but not be limited to, the following components:
  - Version Control/Summary of Changes
  - Contact Information
  - General description of the type of data that is being transferred
  - Data File Structure (ASCII, SAS, etc.)
  - Data File Transfer (specifications regarding, frequency, dates as applicable, cumulative/incremental, blinded/unblinded, file naming conventions, delivery method, documentation, confirmation of receipt)
  - Test transfer information, if applicable
  - Information on communication regarding issues with the transfer, or data quality issues
  - Identification of the recipient of the data
  - Data File Contents (data dictionary, or other documentation that describe the data files, variable mappings, etc.)
  - Signature of those approving the DTS

Data Safety Monitoring Board

- The blinded and un-blinded statisticians are involved in the creation and review of SMC charter.
- The data may be requested in an aggregate form, grouped by treatment but with treatment unknown (e.g., blue or green arm), or fully un-blinded to the treatment.
- **Types of data may include, but are not limited to:**
  - Adverse Events
  - Serious Adverse Events
  - Study drug discontinuations, suspensions
  - Concomitant medications
  - Safety Laboratories
  - Vital signs
  - Occurrences of un-blinding by study sites
  - Overall enrollment and enrollment by site
  - Number of subjects that have withdrawn or completed
  - Protocol violations

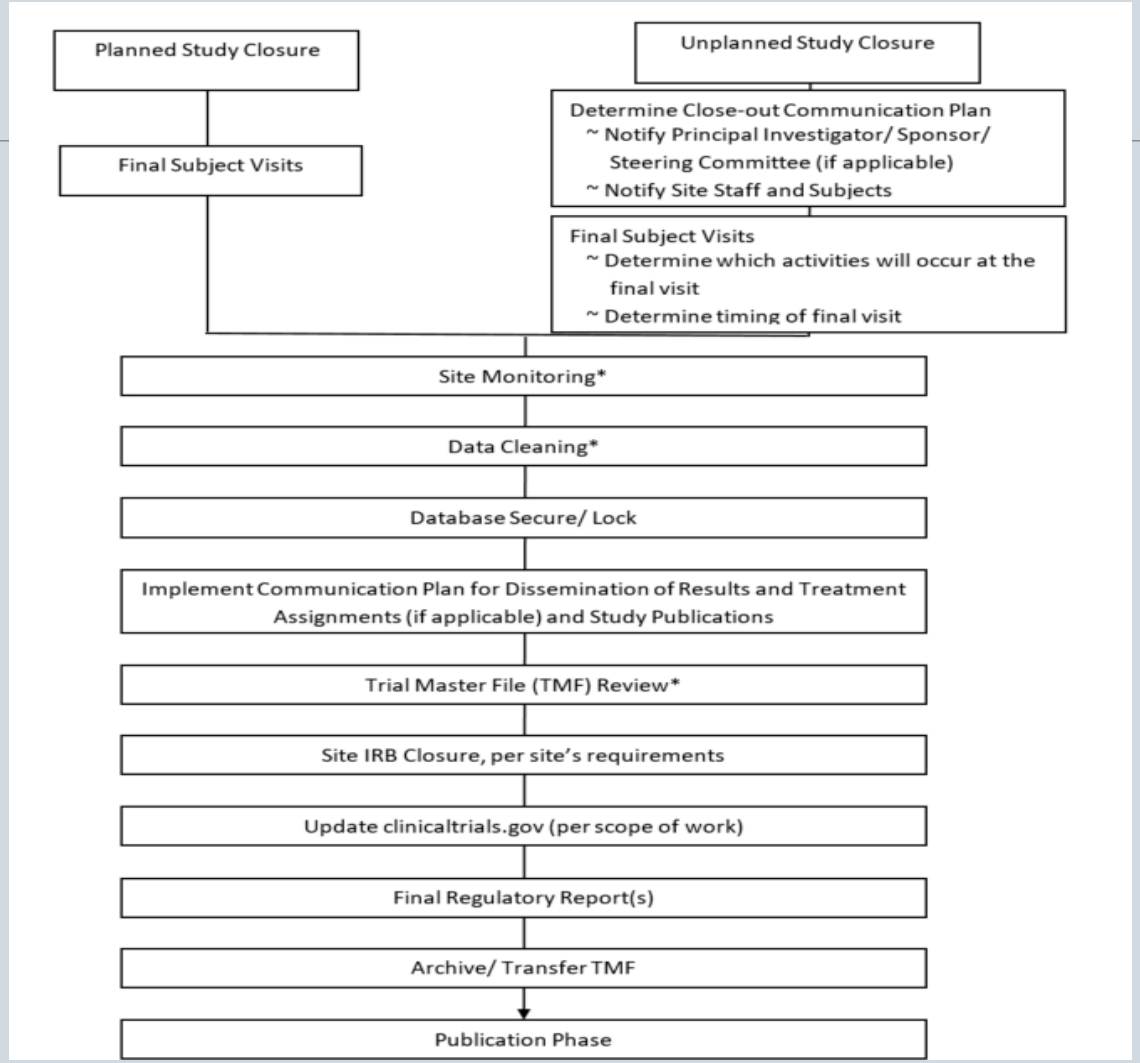
Closeout Phase

CLOSEOUT ACTIVITIES

Key Closeout Activities

- Closeout communication plan
- Treatment assignment disclosures
- Monitoring
- Survey of IRB/IEC Closure Requirements
- SAE reconciliation
- TMF reconciliation
- Final DSMB/SMC meeting
- IP reconciliation & disposition
- Return of study supplies/equipment
- Final site payments
- Final regulatory reports
- Database closeout
- Data analysis
- Publication
- Final study summary

Flow of Closeout Tasks



Closeout Checklist/Timeline

- Track tasks, projected completion dates, actual completion dates and responsible parties

Projected Completion Day/Date	Actual Completion Day/Date	Task Category	Task	Description/Comments	Responsible Party
Day 0		Data Management	Last Subject Last Visit (LSLV) Completed		
Day 1		Equipment	Notify Vendors of Closeout		
Day 1		Regulatory	Update to ClinicalTrials.gov	Update Study Status	
Day 1		Regulatory	Notify Rochester IRB (RSRB) of Study Status	Update Study Status	
Day 30		Site Monitoring	Last On-site Monitoring Visit		
Day 45		Site Monitoring	Review of final site monitor visit trip reports	Review and approve final site visits reports submitted by site monitor.	
Day 45		Data Management	Final Data Queries Issued	Per CTCC Data Management Plan data is reviewed and queries issued to resolve any data discrepancies.	
Day 45		Safety	Ensure all SAE follow-up is complete		
Day 46		Study Drug	Complete site investigational product (IP) accountability		

Survey of IRB/IEC Closure Requirements

- Does your IRB/IEC have different levels/tiers of closure (i.e., closed to enrollment but open for administrative purposes)?
- Does the Template Treatment Assignment Letter to subjects require your IRB's approval before sending the letter with the treatment assignment to the subject?
- Are you required to keep the study open with your IRB/IEC until you provide the treatment assignments to subjects?
- Are you required to keep your IRB/IEC open for submission of the primary abstract?
- Are you required to keep your IRB/IEC open for submission of the primary manuscript?

Monitoring closeout visits

- Occurs when all study subjects have completed their last study visits per the protocol
- Early site closeout may occur in some instances
- Sites that close prior to database lock may need to re-open to address queries that arise during preparation for database lock and study closure.
- Schedule and plan closeout monitoring visits across sites
  - Final source verification
  - Close any open action items
  - Final IP accountability/authorization for destruction or return
  - Review of Trial Master File and archiving procedures
  - Final review of lab sample shipment to central lab/biorepository
  - Management/return of equipment & study supplies

Closeout Communication Plan

- Communication of results to sites
- Communication of results to participants, families & advocacy groups
- Teleconferences/webinars & letters
- Public release

Treatment assignment disclosures

- Facilitate providing all sites with subject treatment disclosure information to be provided to study subjects.
- Treatment assignment letter- template letter to be provided to each subject.
- IRB/IEC review and approval may be required.
- Following database lock and unblinding, each site is sent a list of treatment assignments.
- Each participant should be provided with the approved letter with their treatment assignment included.
- If a subject does not want to know their treatment assignment, document when the information was offered to the subject and when they declined.

TMF Reconciliation and Archiving

- Coordination Center TMF site files reconciled with site essential documents
  - Instructions for site file review
  - Site Archiving Form
- General and site files are archived according to the Project Management Plan

Data Management

- Last subject last visit (LSLV) completed
- Final data queries issued/resolved
- Final vendor data transfers (eg, central lab, EKG, etc)
- Final data review
- Database lock
- Data transfer to Biostatistics
- Statistical analysis

Final DSMB/SMC meeting

- A final meeting of the SMC/DSMB may take place to conduct assessment of study safety data per the Safety Monitoring Plan
- Letter may be distributed to sites
- Meeting materials and minutes for final meeting (as well as from meetings from duration of study) should be collected and archived with TMF

Final Reconciliations

- Final investigational product reconciliation and disposition
  - Documentation of IP accountability and destruction for all distributed IP
- SAE reconciliation
- Biospecimens/digital reconciliation
  - Reconciliation specimens (may include clinical labs, biospecimens, video recordings and repositories)

Other Closeout Activities

- Study Supplies/Equipment
  - All study-related equipment and supplies are returned
- Final regulatory reporting
  - Final reports submitted to applicable regulatory authorities per FDA and ICH guidelines, or funding agencies.
- Administrative
  - Update status of sites and personnel in study systems/remove accesses to EDC system and others
- Final site payments
  - May be held if there are outstanding activities that haven't been completed (eg, site hasn't returned equipment or submitted biospecimens)

Final Study Summary

- Study Group (if applicable)
- Sponsor
- IND number (if applicable)
- Study name/Acronym
- Protocol number
- Version date of original protocol and protocol amendment(s)
- Primary outcome measure(s)
- Duration of treatment
- Patient population
- Final number of sites
- Number of enrolling investigators
- Enrollment period
- Enrollment goal met (Yes/No)
- Number of subjects enrolled
- Investigational Product(s) (IP)
- IP manufacturer
- IP packager
- IP distribution center
- Personnel

ClinicalTrials.gov

- Federal regulations and NIH policy require the responsible party to report results information for the clinical trial no later than 1 year after the Primary Completion Date
  - **The *Primary Completion Date*** is the "date that the last subject was examined or received an intervention to collect final data for the primary outcome measure" of the study
- **Scientific information is submitted as four separate modules:** Participant Flow, Baseline Characteristics, Outcome Measures and Statistical Analyses, and Adverse Events
  - Results are reported by study arm or comparison group
- **Participant Flow:** numbers of participants who started, completed, and dropped out of each period of the study based on the sequence in which interventions were assigned

ClinicalTrials.gov (cont.)

- **Baseline Characteristics:** demographics, such as age and gender, and study-specific measures
- **Outcome Measures and Statistical Analyses:** prespecified Primary Outcome and Secondary Outcome measures
  - May also include other prespecified outcomes, post hoc outcomes, and any appropriate statistical analyses
- **Adverse Events:**
  - Tabular summary of all anticipated and unanticipated Serious adverse events
  - Tabular summary of anticipated and unanticipated other adverse events exceeding a specific frequency threshold
- **Administrative Information:** point of contact for study results, etc.