

From Protocol to Clinical Study Report

An overview of clinical study process

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How do you see a clinical trial?

Lifecycle of a clinical trial



CONCEPTUAL PHASE



PLANNING PHASE



IMPLEMENTATION
PHASE



ANALYSIS/REPORTING
PUBLICATION PHASE

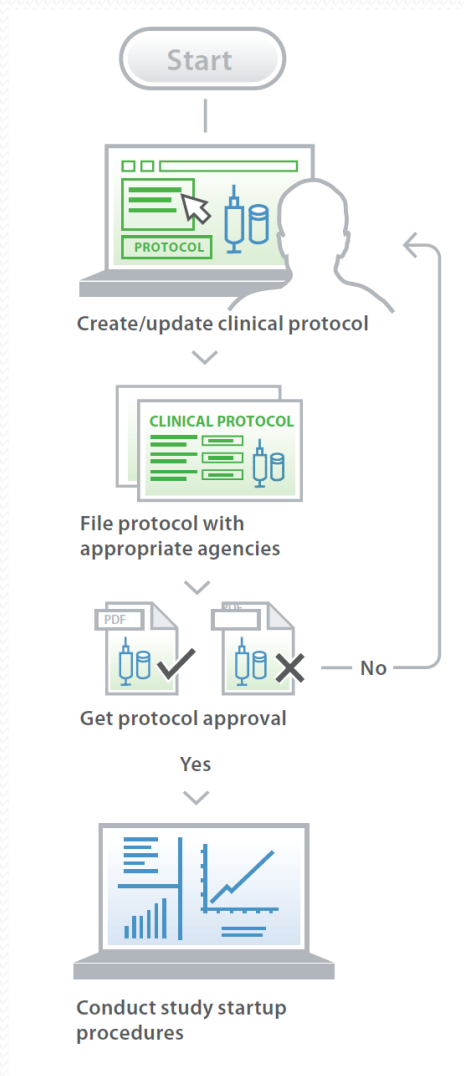


Lifecycle of a clinical trial – Conceptual

- Protocol Synopsis finalized
- Schedule of Activities finalized
- Submit for funding and go through the review process (***AS REQUIRED***)

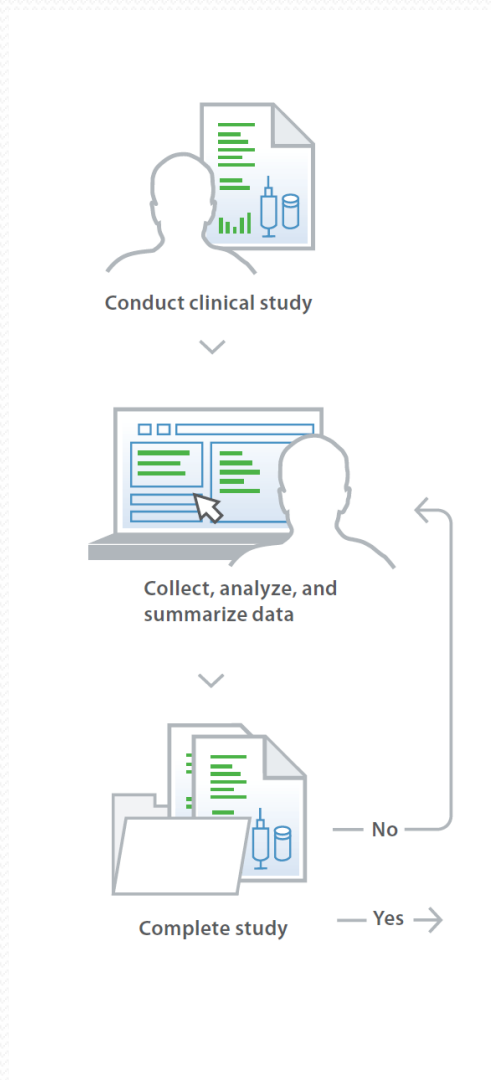


Lifecycle of a clinical trial – Planning



- Protocol finalized
- Site(s) selected and budget/contract negotiation completed
- ICF and recruitment material finalized
- CRFs finalized
- Build database
- Operations Manuals (SAE reporting, IMP management, CRFs instructions, Laboratory procedures, various procedures) completed
- IRB and CA submissions completed and approvals obtained
- Site subcontracts/payment schedule in place
- Contracts with third party vendors (CRO, labs, etc.) finalised
- DSMB established
- IMP supplies procured
- Finalize IMPs packaging/labeling
- Clinical supplies (e.g. lab kits) procured
- Post study on www.clinicaltrials.gov or www.who.int/ictrp
- Initiation (SIV) Meeting completed

Lifecycle of a clinical trial - Implementation



- Distribution of study IMP to site(s)
- Enrollment of subjects, treatments administered
- Convene DSMB (as required)
- Answer Protocol/CRF questions
- Take incident calls:
 - SAEs
 - Deviations
 - Premature Withdrawals
 - Unblinding
- Maintain continuous communication with IRB and CA
- Data query process
- Serology completed and results transferred
- Clean database
- Database Lock
- Transfer database to Biostatistics

Before database lock
Stat Analysis Plan
MUST be signed off

Lifecycle of a clinical trial – Analysis and Publication



Conduct study
closeout procedures



Create/update clinical
study report



File clinical study report
with agencies

End

- Study Close-out procedures
- Perform primary/ secondary analysis
- Statistical Analysis Report Finalized
- Write CSR
- Provide CSR to IRB and CA
- Post results on www.clinicaltrials.gov
- Write publication
- Submit manuscript
- Post-hoc analysis- if required

The Process of Conducting Clinical Trials from an Operational perspective:

- Fully understand the full lifecycle of any clinical trial, regardless of the phase (1-4) or indication



- Love the process, not the compound under study
- The process is always the same and is here to stay
- Avoid unnecessary complication but keep it simple!!!
- Develop a **REALISTIC** timeline and work scope in the planning phase of a study

Timelines and work scope

- According to a study (Cutting Edge Information www.cuttingedgeinfo.com), companies stand to lose between \$600,000 and \$8 million for each day that clinical trials delay a product's development and launch.
- Only 6% of clinical trials are completed on time, and 72% of trials run more than one month behind schedule (Cutting Edge Information 2004).
- One child dies every 20 seconds from a disease that could be prevented from with a vaccine.

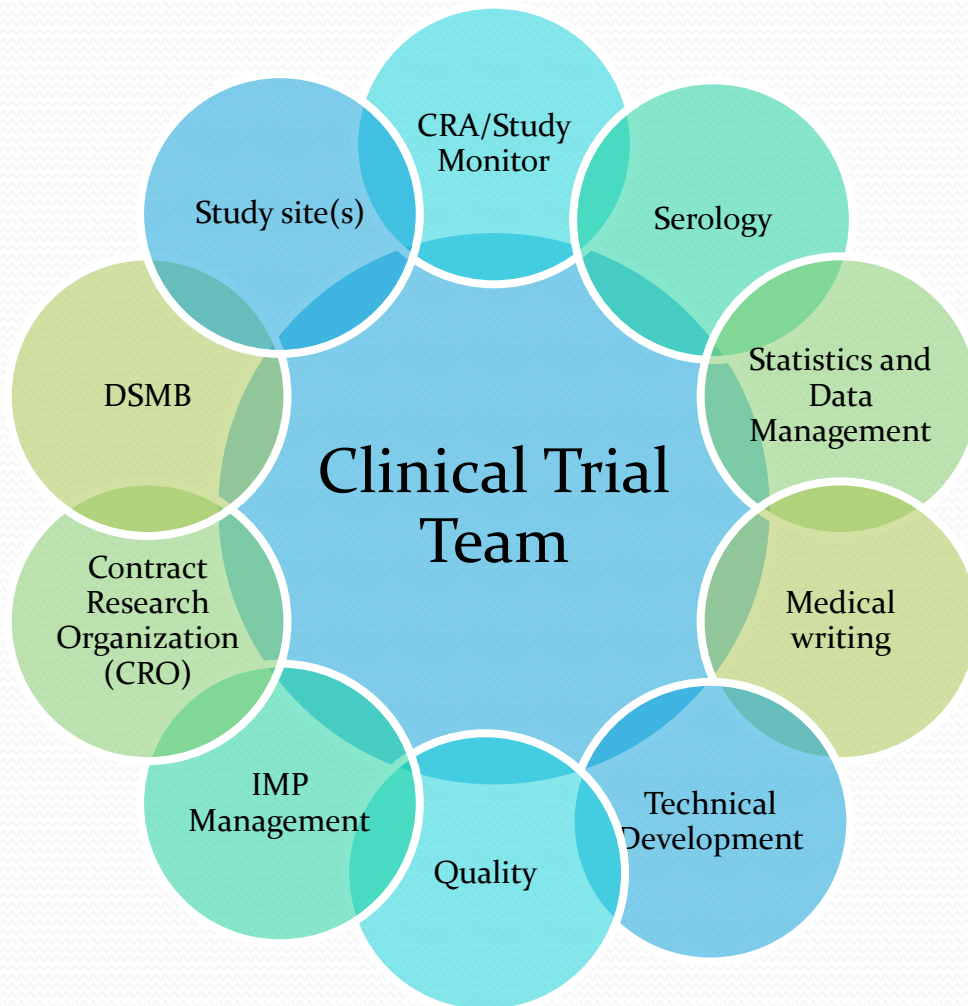


To save time:

- **During the planning phase:**
 - Create a scope of work document clearly delineating who is responsible for what: sponsor, CROs, External Vendors, Sites, Monitors
 - Create a detailed timeline of all activities that need to be completed at each step of the project (use Excel, Microsoft Project, SmartDraw, etc)
- **During the implementation phase:**
 - Ensure continuous adherence to the timelines and tasks
 - Maintain continuous communication
 - Build and maintain good and strong relationship with all people involved (both internal and external to the institution)
 - Don't be afraid to raise issues early on and work on finding solutions
 - And always remember that ... **It Takes a Small Army to Run a Clinical Study and you need to guide the Army to Success!!!**

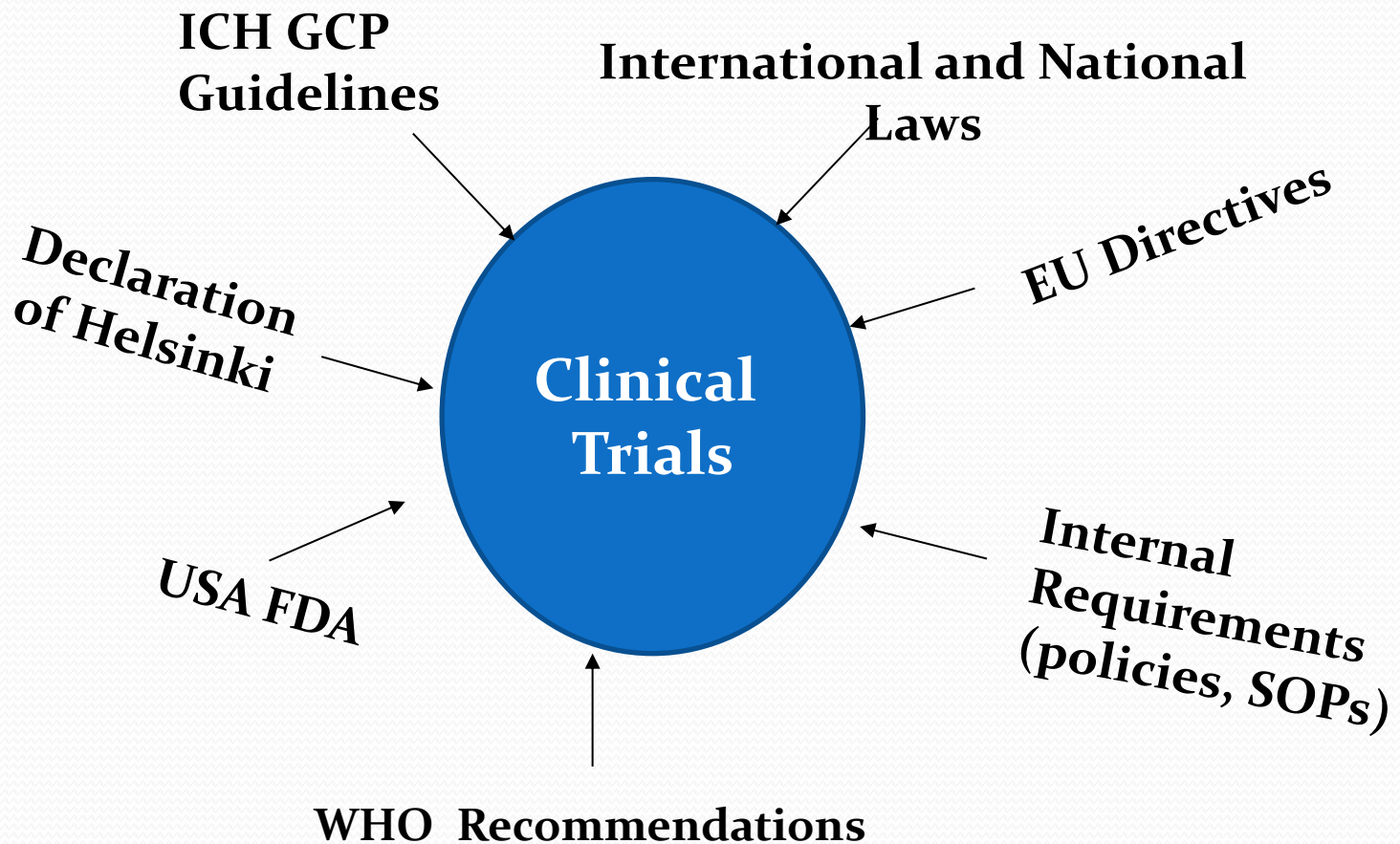


Clinical Trials Require Cross Functional Teams



- A team involved in the preparation, conduct and close-out of a clinical trial.
- Overall responsibility for the trial
- The team includes, but is not limited to, the Clinical Trial Leader, Clinical Trial Manager, Physician, Clinical Research Associate(s), other functional representatives, and their counterparts from the CROs contracted to perform the sponsor's trial-related duties

The Legal Framework [1]



The Legal Framework [2]

Most important document deriving from ICH:

“The Good Clinical Practice” (GCP) Guideline

- GCP guidelines set an international ethical and scientific standard for the
 - protection of human rights of subject participating in clinical trials
 - assurance of the safety and efficacy of the newly developed compounds.
- GCP Guidelines include definitions of
 - Conduct of clinical studies, Ethical Committees, monitoring conventions, source data verification (SDV), data protection, content of trial protocol, investigator brochure (IB), methodology of data analysis
 - Roles and responsibilities of
 - Clinical trial sponsors (e.g., Pharma Companies),
 - Clinical research Investigators, and
 - Monitors (Clinical Research Associates = CRAs)
- ICH-GCP Guidelines are translated into national laws in most countries and are the basis of today's standards for Clinical Development.

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The Protocol [1]

- **Describes:**
 - ✓ Objectives
 - ✓ End-points
 - ✓ Design
 - ✓ Methodology
 - ✓ Statistical Considerations
 - ✓ Organization
- **Should be:**
 - ✓ Scientifically sounding
 - ✓ Ethical
 - ✓ Clear and complete
 - ✓ Feasible
 - ✓ Agreed
- **Follows**
 - ✓ ICH Guidance for Industry (E6 Good Clinical Practice)
 - ✓ Internal standards (template) and SOPs

The Protocol [2]

- Lays out who, what, why, when, where, how
- Safeguards participants
- Safeguards study integrity
- Midcourse changes are often appropriate (even necessary)
 - However too many changes mean sub-optimal conceptual and planning phases

NOTE: allow enough time for study planning and preparation

- Time required: up to 6-9 months from Protocol to First Subject First Visit (FSFV)

Protocol Amendments – Key Definitions

- **Protocol Amendment**

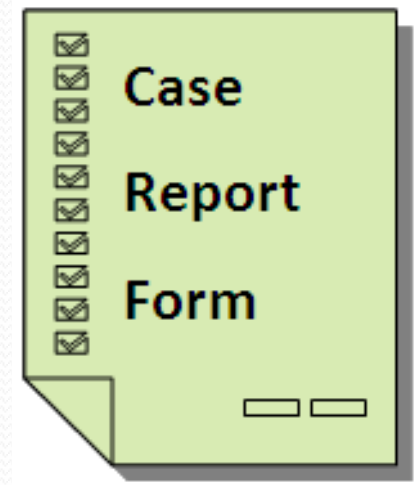
- a written description of change(s) or a formal clarification of a protocol.
- It's also known as “Summary of changes”

- **Amended Protocol**

- the original protocol with all protocol amendment changes incorporated, issued for each amendment produced.
- after the ethical and regulatory submissions, any change to the protocol is considered an amendment.

Collect data: The Case Report Form (CRF) [1]

- Subject's data are collected on the **Case Report Form (CRF)**
- The **CRF** is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject (ICH GCP).
- **Case Report Form Collation**: The set of data collection forms to be used within the specific trial. They are designed in close accordance with the generic standard **CRFs** of sponsor template and provide the basis for the study-specific database
- eCRF (often referred as eDC) are (most) often used



The Case Report Form (CRF) [2]

- A good protocol leads to a simple, clear CRF, built from a standard template:
 - ✓ Restrictive
 - ✓ Tested
 - ✓ No duplication and potential for misinterpretation
- To ensure data integrity it is important that:
 - ✓ Good documentation practices are followed for source data and records
 - ✓ Process are in place to ensure data quality and security
 - ✓ Processes are validated

Investigator selection

- Qualified by education, training & experience to assume responsibility for the conduct of the trial
 - Evidence of his qualification through CV
- Sufficient time and resources (staff and facilities) to properly execute the trial
- Responsible for medical care of trial subjects
- Comply with GCP and local regulatory requirements
- Comply with the study protocol
- Ensure that the study staff is adequately qualified and knowledgeable about study procedures and vaccines
- The Investigator should be evaluated for compliance, e.g. previous internal audits and regulatory authority documentation (i.e. FDA Debarment List and Disqualified / Restricted List)

Study Site selection

- **Facilities should be adequate for the execution of the trial, including :**
 - ✓ Computer equipment
 - ✓ Refrigerator (lockable or - if not - located in a room which is locked)
 - ✓ Devices are calibrated and maintained (thermometer, centrifuge,etc.)
 - ✓ Laboratory equipment / procedures
 - ✓ Storage of study documentation and ancillary supplies
 - ✓ Archiving facilities
 - ✓ Fax machine / scanning and e-mailing capability
 - ✓ Working space for CRAs
- **Site should be selected based on:**
 - ✓ Access to patient population/geographic distribution
 - ✓ Past performance of investigator/coordinator team
 - ✓ Projected number of subjects/anticipated enrollment rate
 - ✓ Lack of competing studies
 - ✓ Availability of required equipment or specialized staff

Select and Contract with External Vendors

- Laboratory for safety labs
 - Laboratory for immunogenicity assessment
 - Data Management and statistics
 - Electronic diaries
 - Manufacturer of IMP
 - Primary and secondary IMP packager and distributor
 - Monitoring
 - PV
 - Ethical and regulatory submission/approval
-
- Obtain bids from ~2-3 vendors to compare prices/services early in planning
 - All vendor contracts should be completed prior to outsource any service

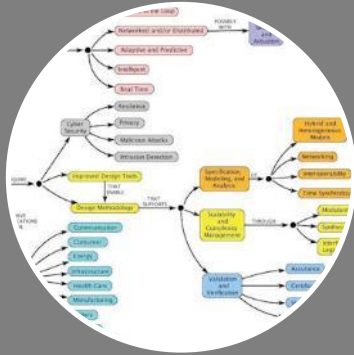
What is the number one limiting step in any clinical trial?

- Study IMP!!!
- Study IMP!!!
- Study IMP!!



Ensure that all aspects related to the study IMP are planned and managed in parallel to the study design and set-up (if possible from the conceptual phase)

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Study Start

- Requirements to start a clinical study include:
 - ✓ Authorization by the local Competent Authority (CA) as applicable for the respective country (NRAs)
 - ✓ Approval from Ethics Committee/ Institutional Review Board (EC/ IRB)
 - ✓ Authorization for the manufacture and/or importation of Investigational Medicinal Products
 - ✓ Proper training provided to the Study staff
 - ✓ Written contractual agreements with Investigators and Service Providers (CROs, Labs)

Purpose of monitoring clinical trials

- Clinical trial monitoring is an integral part of **Good Clinical Practices**
- The purposes of clinical trial monitoring are to verify that:
 - ✓ The rights and well-being of human subjects are protected.
 - ✓ The data collected and reported are accurate, complete, and correspond to source documents.
 - ✓ The conduct of the trial is in compliance with the protocol, GCP, and regulatory requirements.

Ensure Monitoring

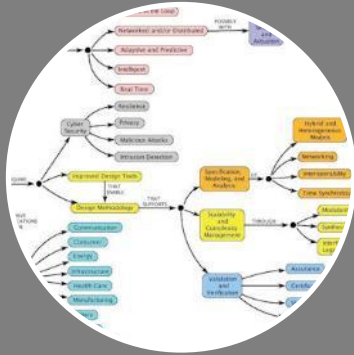
- Monitors must be familiar with:
 - ✓ Good Clinical Practice (GCP)
 - ✓ Local Regulatory requirements
 - ✓ Study protocol
 - ✓ Investigational product
 - ✓ Internal standards (Sponsor and Site SOPs and manuals)

Monitors can be either internal or external (CRO) personnel

Safety reporting in clinical trials

- Adverse Events that occur during clinical trials must be collected and reported
 - in a timely, comprehensive, and consistent manner
 - in accordance with Good Clinical Practice (GCP) and current local/regional regulations and internal procedures (PV)
- Serious Adverse Event (SAE): Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
- All SAEs that occur during interventional clinical trials must be reported to Sponsor within 24 hours of the Investigator becoming aware that an event occurred, regardless of causality
- The safety database is usually managed by Pharmacovigilance (PV)

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Clinical Study Report and Posting

- **The Clinical Study Report (CSR) includes:**
 - ✓ CSR synopsis
 - ✓ Objectives
 - ✓ Methods
 - ✓ Study administrative structure
 - ✓ Subjects disposition, demographics
 - ✓ Immunogenicity (efficacy) and safety results and interpretation
 - ✓ Overall conclusions

- **Posting study information a publicly accessible database**
 - ✓ Clinical Trials.gov is a web site that provides patients, family members, health care professionals , easy access to information on clinical studies on a wide range of diseases and conditions
 - ✓ Countries registry and WHO <http://www.who.int/entity/ictrp/search/en/>
 - ✓ Most pharma companies commit to a timely disclosure of designs and results of all interventional clinical studies on a publicly accessible database within one year after the end of the trial (according to Disclosure of Clinical Research Information Policy).

Additional activities to be performed

- Share Results with Subjects
- Notify subjects of their individual treatment assignment
- Submit CSR and/or reports to the IRBs and Regulatory Authorities as applicable
- Present Results to Conferences
- Write Manuscript
- Develop and submit press release with findings/if relevant

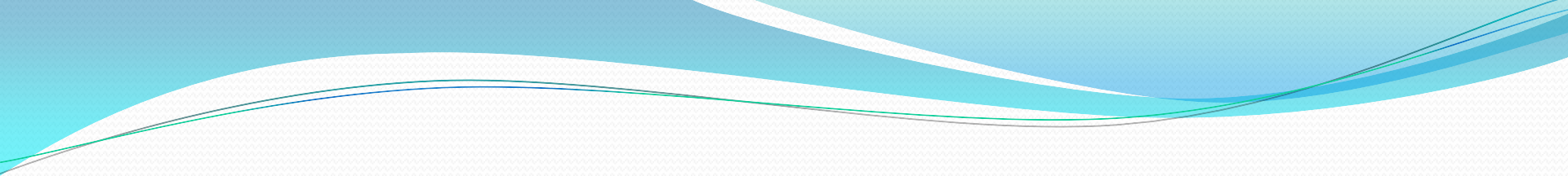
The Finish Line: Anywhere from 1-X (up to 5-7) years later!!!



Key Points to Remember

- Have a work plan with **realistic timelines** from day 1 (re-evaluate timelines along the way as required)
- Set-up a **motivated** and **skilled** clinical trial team
- There will be many obstacles along the way that will impact timelines, **don't get discouraged!** Just figure out how to go **around, over, under** or **through** the obstacle and you will reach the **finish line!!!**





THANK YOU