Clinical Trial Implementation Strategies: From a Coordinating Center Perspective

Cornelia Kamp, MBA

MSG Annual Meeting
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Effective Implementation Strategies:

- Are developed in the conceptual and planning phase.
- Apply the **KISS** strategy: **K**eep **I**t **S**imple **S**tupid! whenever possible
- If you sense something is not “quite right”, don’t wait until it becomes a real problem to identify the **ROOT** cause of an issue. Research the issue early and fix the root cause. Murphy’s Law guarantees that it will blow-up…it’s just a matter of time!

Implementation Strategy #1:

- Fully understand the full lifecycle of any clinical trial, regardless of the phase (I-IV) or indication
- Know what tasks can be done in parallel and what must be done sequentially
  - Whenever possible, process things in parallel
- The process stays the same
- Love the process, not the compound under study
  - Compounds are a “dime a dozen” and come and go.
- The process is here to stay

Life Cycle of a Clinical Trial

Grant Award and/or Parent contract established

- Protocol Synopsis finalized
- Schedule of Activities finalized

CONCEPTUAL PHASE

- Protocol finalized
- Model ICF finalized
- Sites selected
- Operations Manual/MOP completed
- CRFs finalized
- IRB approvals obtained
- Site subcontracts/ payment schedule in place
- Finalize Contracts with third party vendors (labs, ECGs etc.)
- Build database
- Finalize Study drug packaging/labeling*

PLANNING PHASE

Orientation or Initiation Meeting

- Enroll subjects*
- Distribution of study drug to sites
- Answer Protocol/CRF questions
- Take incident calls
  - SAEs
  - Dosage Adjustments
  - Premature Withdrawals
  - Drug Disclosure
- Data query process
- Clean/Close database
- Transfer database to Biostatistics

IMPLEMENTATION PHASE

Database Locked

Analysis

- Perform primary/ secondary analysis
- Submit abstract
- Submit manuscript
- Submit CTR
- Post-hoc analysis

ANALYSIS/ PUBLICATION PHASE

Implementation Strategy #2:

- Effective Project Management is essential to the success of any trial

So, What is Project Management?

- It is the discipline of organizing and managing resources in such a way that the project is completed within defined scope, quality, time and cost constraints.
- A project uses carefully defined sets of activities that utilizes resources (money, people, materials, energy, space, provisions, communication, quality , risk, etc.) to meet the pre-defined objectives.

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ANALYSIS/ PUBLICATION PHASE

A Good Project Manager (PM) is one who:

- Is highly organized
- Is remarkably flexible
- Has planned and executed a large birthday party (Ira Shoulson, MD), Bar-mitzvah / Bat-mitzvah or a large wedding
- Has Anal Retentive tendencies (OCD)..a good thing in this industry
- Can still see the forest through the trees
- Has excellent oral and written communication skills
- Can build strong relationships with all kinds of staff both internal and external to the institution
- Is not afraid to raise issues early on and work on finding solutions
- Willing to put in long hours
- Can influence others without direct reporting lines

Project Manager: multi-center vs. single center study

- The site coordinator may function as the PM for a small study (~1-3 sites), however, for larger multi-center studies typically >5 sites the PM is someone other than a site coordinator
- Be cognizant of potential rater bias when a site coordinator who sees/evaluates subjects also functions as the PM
  - Based on interaction with other site coordinators/investigators (e.g. may change how they rate subjects mid study, may identify AEs based on what other sites are seeing etc.)

Implementation Strategy #3

- To Manage a clinical trial well, it is essential that a project work plan, often called a scope of work document AND a **realistic** timeline be developed EARLY in the planning phase

Work Scope and Timeline

Note: See handouts for examples

- Create a scope of work document clearly delineating who is responsible for what: sponsor, SC, Project Team, External Vendors (Central Lab, ECG vendor, PK analysis, DNA analysis), Sites, Monitors
- Create a detailed timeline of all activities that need to complete in each phase of the Project Lifecycle
  - Collectively both documents will provide the roadmap for the overall project

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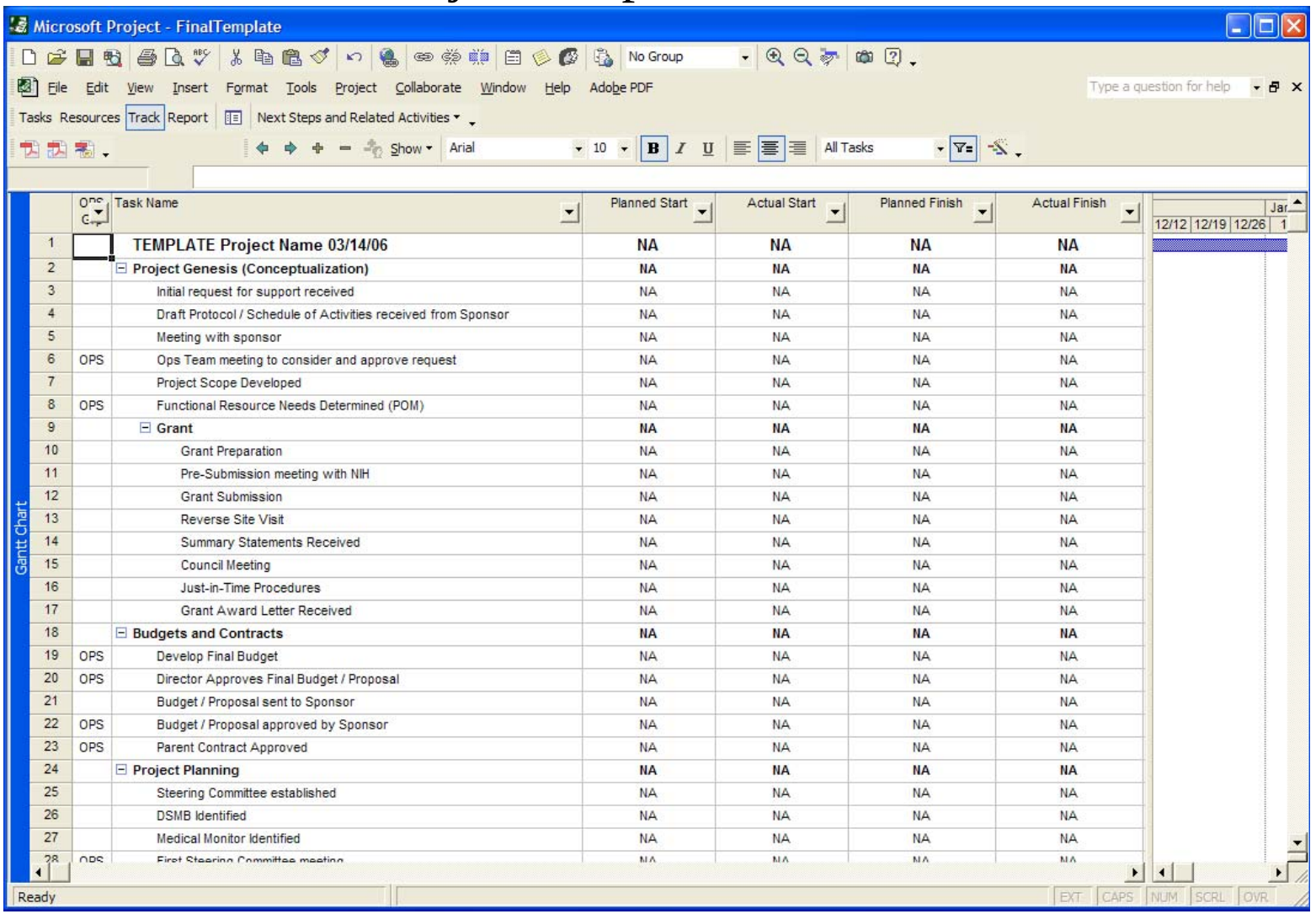
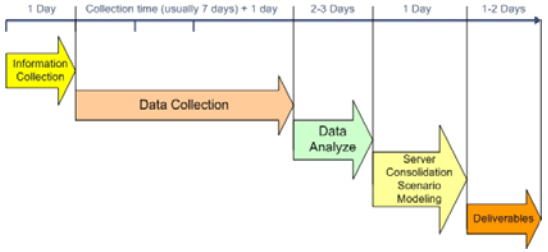
Project Management

Microsoft Project template or use Microsoft Excel



	OPS C...	Task Name	Planned Start	Actual Start	Planned Finish	Actual Finish
1		**TEMPLATE Project Name 03/14/06**	**NA**	**NA**	**NA**	**NA**
2		**Project Genesis (Conceptualization)**	**NA**	**NA**	**NA**	**NA**
3		Initial request for support received	NA	NA	NA	NA
4		Draft Protocol / Schedule of Activities received from Sponsor	NA	NA	NA	NA
5		Meeting with sponsor	NA	NA	NA	NA
6	OPS	Ops Team meeting to consider and approve request	NA	NA	NA	NA
7		Project Scope Developed	NA	NA	NA	NA
8	OPS	Functional Resource Needs Determined (POM)	NA	NA	NA	NA
9		**Grant**	**NA**	**NA**	**NA**	**NA**
10		Grant Preparation	NA	NA	NA	NA
11		Pre-Submission meeting with NIH	NA	NA	NA	NA
12		Grant Submission	NA	NA	NA	NA
13		Reverse Site Visit	NA	NA	NA	NA
14		Summary Statements Received	NA	NA	NA	NA
15		Council Meeting	NA	NA	NA	NA
16		Just-in-Time Procedures	NA	NA	NA	NA
17		Grant Award Letter Received	NA	NA	NA	NA
18		**Budgets and Contracts**	**NA**	**NA**	**NA**	**NA**
19	OPS	Develop Final Budget	NA	NA	NA	NA
20	OPS	Director Approves Final Budget / Proposal	NA	NA	NA	NA
21		Budget / Proposal sent to Sponsor	NA	NA	NA	NA
22	OPS	Budget / Proposal approved by Sponsor	NA	NA	NA	NA
23	OPS	Parent Contract Approved	NA	NA	NA	NA
24		**Project Planning**	**NA**	**NA**	**NA**	**NA**
25		Steering Committee established	NA	NA	NA	NA
26		DSMB Identified	NA	NA	NA	NA
27		Medical Monitor Identified	NA	NA	NA	NA
28	OPS	First Steering Committee meeting	NA	NA	NA	NA

Key Planning Milestones (Timeline)



- Funding
- Drug Supply
- Final Protocol/model ICF
- IND submission/approval – (must wait 30 days before starting the study)
- IRB approvals/subcontracts – (4-6 months to get approvals)
- Orientation mtg – (more than ½ the sites should have IRB approvals/subcontracts)

Key Implementation Milestones (Timeline)

- Drug Supply available at the site – (within days of the orientation mtg)
- FPI = First Patient In - (within days of the orientation mtg)
- FPO = First Patient Out - (determined by duration of treatment)
- LPI = Last Patient In – (based on planned enrollment period)
- LPO = Last Patient Out
- Database Lock – (eDC: 2 weeks following LPO; paper: 6- 8 weeks following LPO)
- Analysis Completed – (4 weeks post DBL)
- Abstract/Full Manuscript (abstract 2 weeks following completed analysis; manuscript 3 months post analysis)
- Submission of Regulatory Report (CTR etc.)

Implementation Strategy #4

- Manage the Clinical Trial Team which includes **OVER COMMUNICATION** with ALL of the players
  - Pretend the team members are like your kids….they never hear you the first time and even if they did hear you they don't listen
  - Remember everyone is busy with many competing priorities

The Clinical Trial Team

Includes some or all of the following depending on study:

- Sponsor (NIH, pharmaceutical, foundation, combination)
- Operational Project Team
- Steering Committee
- Site Team
- Vendors (e.g., central lab, primary & secondary drug packaging/labeling, central ECG, electronic diaries, etc.)
- *Data Safety Monitoring Board (DSMB)*
- *Independent Medical Monitor*
- *Endpoint Adjudication Committee*
- *Others?*

Operational Project Team

- Project Manager (PM)
- Database Manager (DM)
- Information Analyst (IA)
- Clinical Monitor (CM)
- Monitors [Clinical Research Associates (CRAs)]
- Statistical Programmer (SP)
- Administrative Assistant/Secretary (grants, mtg planning) (AA)
  - The industry has many different titles for the same type of general job responsibilities

Operational Project Team Role/Function

- Overall operational conduct of the study from planning through database lock, Clinical Technical Report (CTR) submission or comparable depending on country, publication
- Responsible for overall quality, ensure time lines are met and study conducted within budget
  - Project Teams typically meet weekly during the conduct of a study

Project Team

Sites

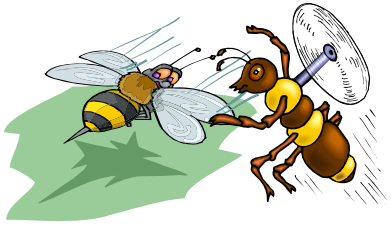
Steering Committee

Project Manager

Central Laboratory

Drug Supply Vendor

Providing complete operational oversight



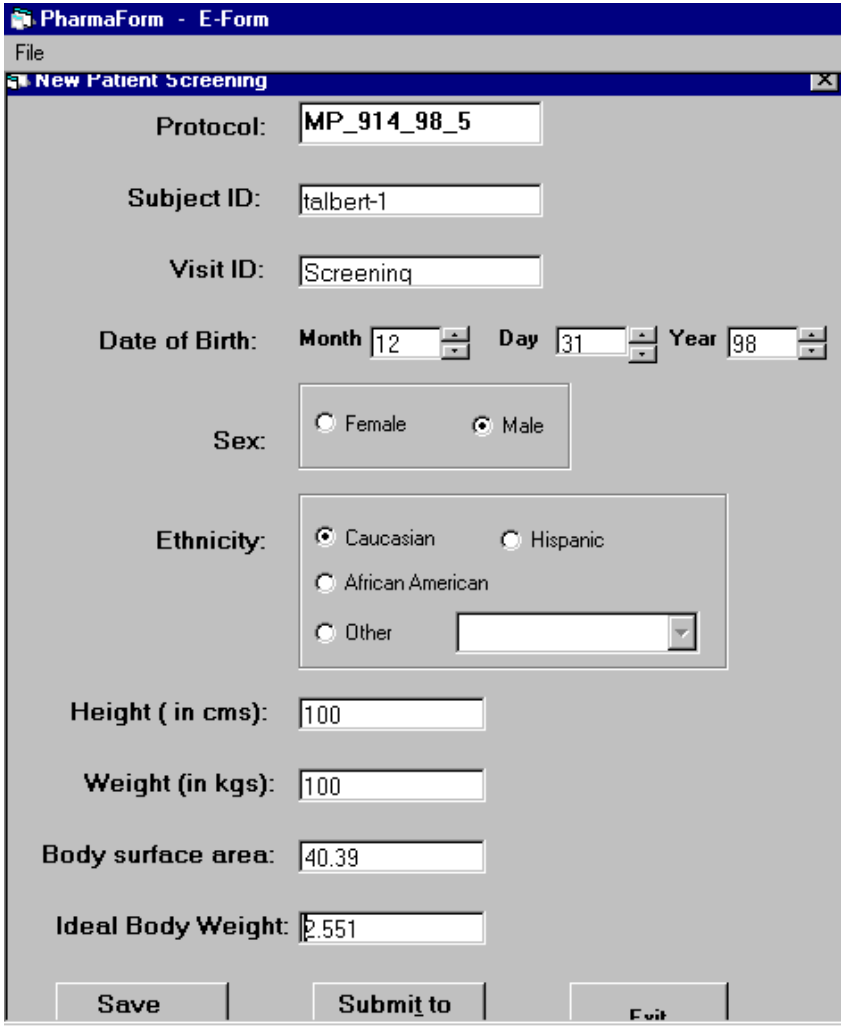
Monitors

Sponsor

Biostatistician

Implementation Strategy #5

- The outcome of the study is only as good as the data you collect on the CRFs. Make sure your CRFs capture all intended variables.
- Make sure the Biostatistician responsible for the analysis and the PI sign off/approve the CRFs BEFORE they are given to the DM group for creation of the database



Considerations for creating effective CRF:

- The primary and secondary endpoints will drive the data collected on the CRFs
- Only collect what you really need
- Only ask each question once (e.g., do not ask for height or gender on more than one CRF)
- Make sure the way the question is worded is clear and will provide the answer you are looking for
- Use validated instruments for critical outcome measures (especially important if submitting to the regulatory authorities for approval)
- If using validated instruments get appropriate approvals for use (many now require purchase: e.g. Beck's Depression Scale) or be sure references are included on the form
- Data will only be as good as the tools (CRFs) used to collect it on
- CRFs/eCRFs set the framework for the database
  - Most DM groups will not work on the DB set-up until the CRFs/eCRFs have been finalized

Implementation Strategy #6

The number one rate limiting step in any clinical trial is:

- Study Drug!!!
- Study Drug!!!
- Study Drug!!

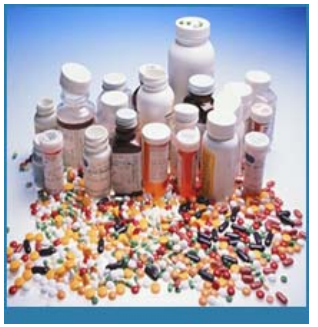
ACTIVELY MANAGE ALL ASPECTS OF THE STUDY DRUG AS EARLY AS THE CONCEPTUAL PHASE (INITIAL GRANT SUBMISSION)

Drug Supply

- Items for consideration:
  - Purchase active and matching placebo or have donated?
  - How will drug be delivered (e.g. Bulk shipment in drums, unit packaged, all at once, quarterly shipments)
  - Secondary packaging/labeling and distribution requirements?
  - Blindedness testing: Are active and placebo identical in: color, taste, smell, appearance, shape, size?
  - Stability testing: ambient and accelerated: how many lots of each or is it even required?
  - Expiry/retest issues?
  - Storage requirements: ambient, refrigerated, light sensitive, moisture sensitive?
  - Drug Accountability centrally and at site level
  - Site SOPs to address all aspects of study drug receipt, dispensing, return etc. (overall accountability)

Sources for Drug Supply Delays

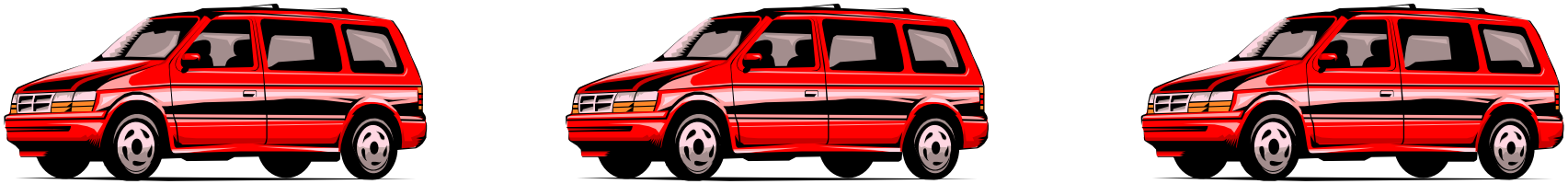
- Lack of sufficient animal toxicology data
- Held up in manufacturing: impurities found, long queue, API not available, stability issues
- Problems matching active with placebo supplies
- Failure to place order with enough lead time
- Custom delays (e.g. shipment exported/imported from other countries)



Unique Problem in NET-FSI

ABUNDANCE OF CREATINE

- 6,127 lbs worth = 3 tons, or the combined weight of 3 mini-vans:



18 Wheeler Arrives…….

3 Tons of Creatine: Where to Store in a cGMP compliant fashion????

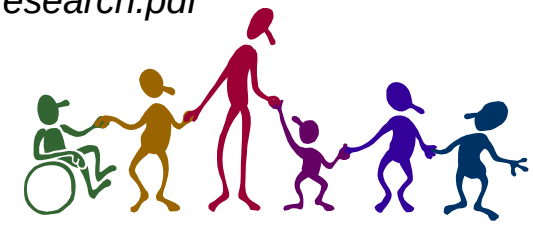
Implementation Strategy # 7

- Once you have solved the study drug supply problem (remember this problem is NEVER truly solved until LPO), make sure you have addressed **recruitment and retention!**

Site Selection and Enrollment

- Only 14% of studies have enrollment completed on time
- 81% of studies have enrollment that is delayed 1 to 8 months
- Significant effort should be spent on identifying appropriate sites and setting up realistic enrollment expectations (see sample site selection hand-out)
  - Always have a back-up plan
  - Be sure to train any back-up sites brought on board after study start and any new site staff at existing sites

Ref:101 Facts about Clinical Research: http://www.ciscrp.org/information/documents/101FactsaboutClinicalResearch.pdf



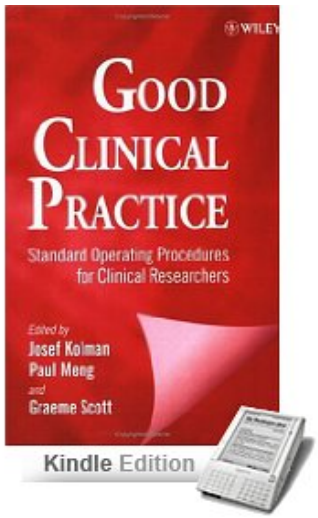
Implementation Strategy #8

- Make sure you have a set of Standard Operating Procedures (SOPs) for all procedural aspects of conducting a trial
- Sponsors, CROs, Coordinating Centers, Statistical Centers, Sites and any other vendor (e.g. central lab) engaged in the conduct of clinical trials should have SOPs in place. They ensure cGXPs are being met.

Standard Operating Procedures (SOPs)

- SOPs required for all aspects of running clinical trials
- Needed centrally by the organization managing the overall conduct of the study and at the site level

Ref: Good Clinical Practice: Standard Operating Procedures for Clinical Researchers; by Josef Kolman, Paul Meng, and Graeme Scott (Kindle Edition - Jun 15, 1998)



TOC for Typical Site SOPs

- Development and Administration of Standard Operating Procedures
- Managing Regulatory Inspections (FDA, Health Canada etc....)
- Managing Sponsor Audits (e.g. pharmaceutical, NIH, etc)
- Training and Personnel Training Records
- Archiving, Retention, Retrieval and Security of Study Documents
- Process for IRB Submission
- Participation in a Monitoring Visit
- Set up and Maintenance of the Investigator Site File (ISF)
- Adverse Events/Serious Events Reporting Process
- Informed Consent/Consenting Process
- Site Signature Log - Delegation of Authority
- Physical Exams (document who can do them, sign off etc.)
- Investigational Product Accountability

TOC for Typical Site SOPs

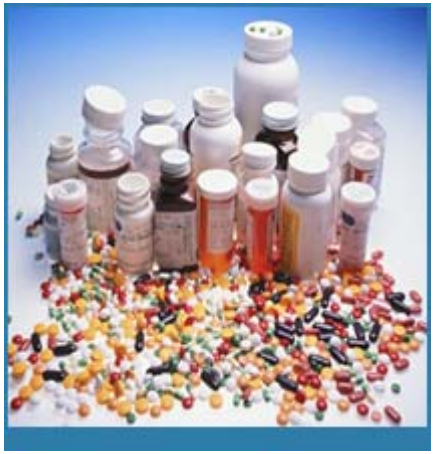
- Documentation for Receipt, Transfer and Return of Investigational Product
- Temperature Monitoring of Investigational Product
- Documenting Study Specific Contacts
- Subject Stipends
- Lost to Follow-up (SOP documents all the action taken by site to attempt to get subject to come in for the final visit etc...how many calls, and certified letters must be sent before the site considers the subject LTFU)
- Leave Against Medical Advice (if an inpatient study and the patient leaves prior to completion study and they leave against medical advice, what is the process and what form does the patient sign releasing the PI, institution from responsibility)
- Maintenance of Equipment (inspections, calibration, cleaning etc....details for each piece of equipment used in a trial including scales, BP equipment, ECG machines, DEXA machines etc.)
- Protection of Subject Personal Data
- Information Systems (general infrastructure, security, passwords protection etc.)

Key Points to Remember

- A successful study requires **constant and effective project management** from Day #1.

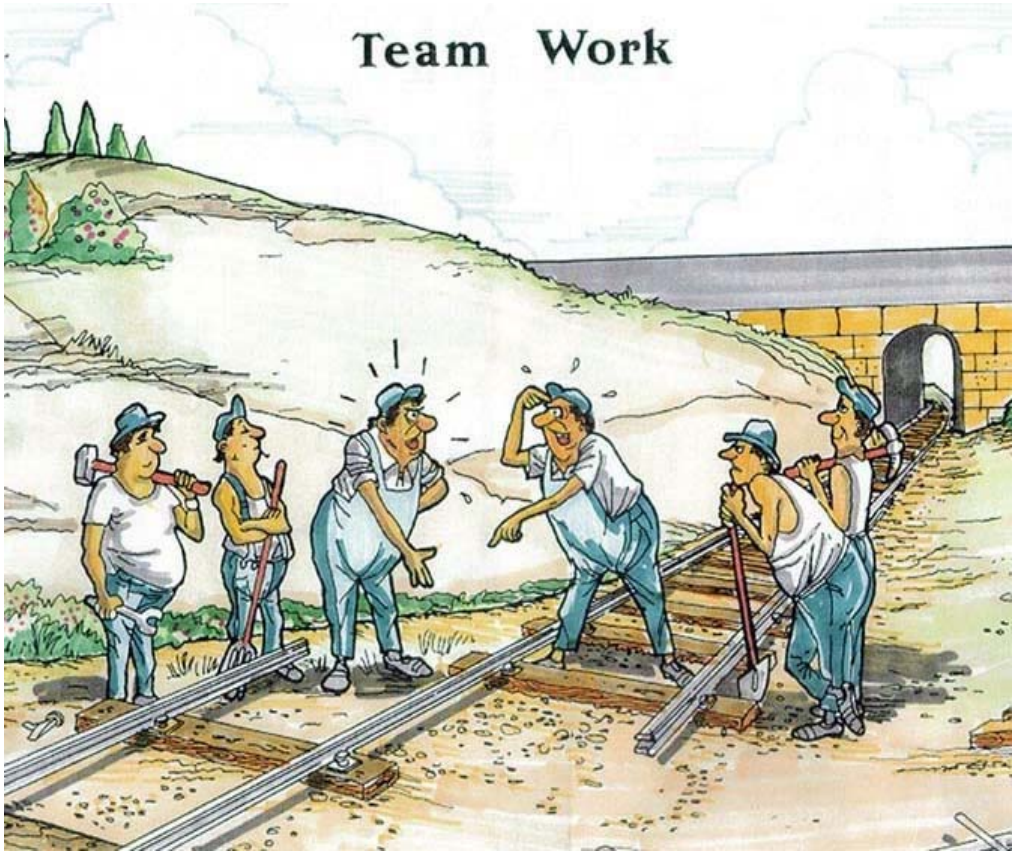
Key Points to Remember

- Manage all aspects of the **study drug supply chain** starting in the conceptual phase and put it on every agenda until LPO!!



Key Points to Remember

- It is a Team effort. The team's can be quite large depending on the phase of the study.
- Keep the entire team informed of all decisions.



Key Points to Remember

- Running successful clinical trials is not for the light hearted!!!!!!
- There are always road blocks along the way, don’t be discouraged, just figure out how to go around, over, under or through the road block and you will eventually get there!!!

QUESTIONS??