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# Study Initiation, Implementation and Termination

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**Georgetown University Medical Center**

**The human tendency to regard little things as important has produced very many great things.**

**Georg Christoph Lichtenberg**
***(1742 - 1799)***

# Study Initiation

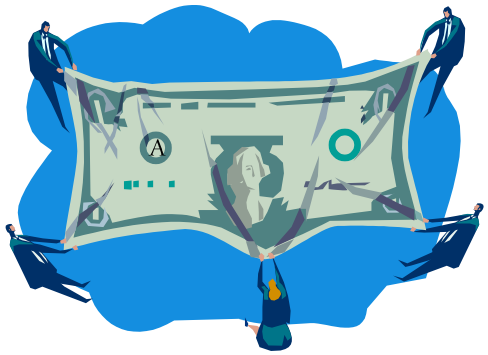
- Feasibility
- Contract
- Budgeting
  - Including Medicare Coverage Analysis (MCA)
- IRB submission and approval
- Regulatory “binder” and FDA required documents as indicated
- Recruitment planning
- Training begins

# Feasibility

- Feasibility includes:
  - Budget Evaluation
  - Resources
    - Facilities
    - Equipment
    - Staff
    - Subject Population
    - Enrollment expectation: number and timeline

# Feasibility: Budget

- Is the budget reasonable for the time that will be spent on the project?
- There are tools that are available to assess fiscal feasibility.



# Feasibility: Resources

- Facilities
  - What type of space is needed?
  - Does the site have the space that is required?
  - Is the space available when we will need it?
- Staff
  - Do we have the appropriately trained staff
  - Do the staff have capacity to take on more

# Feasibility: Resources

- Equipment
  - What type of equipment is needed to complete the study
    - What equipment is provided by the sponsor and what must be provided by the site?
  - Are other departments involved in the use of the equipment? Examples: Radiology, CRU, dietary, laboratories

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# Feasibility: Subject Population

- Does the department have the specific target population?
- Do we have other studies that are already studying this group?
- If the department has the target population are the numbers consistent with recruitment expectations?

# Feasibility: Enrollment Expectation

- Is the timeline to begin enrollment realistic?
- Is the timeline to complete enrollment realistic?
- Can the institutional regulatory and budget piece be completed within these timelines.

# Site Selection

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# Contract / Budget

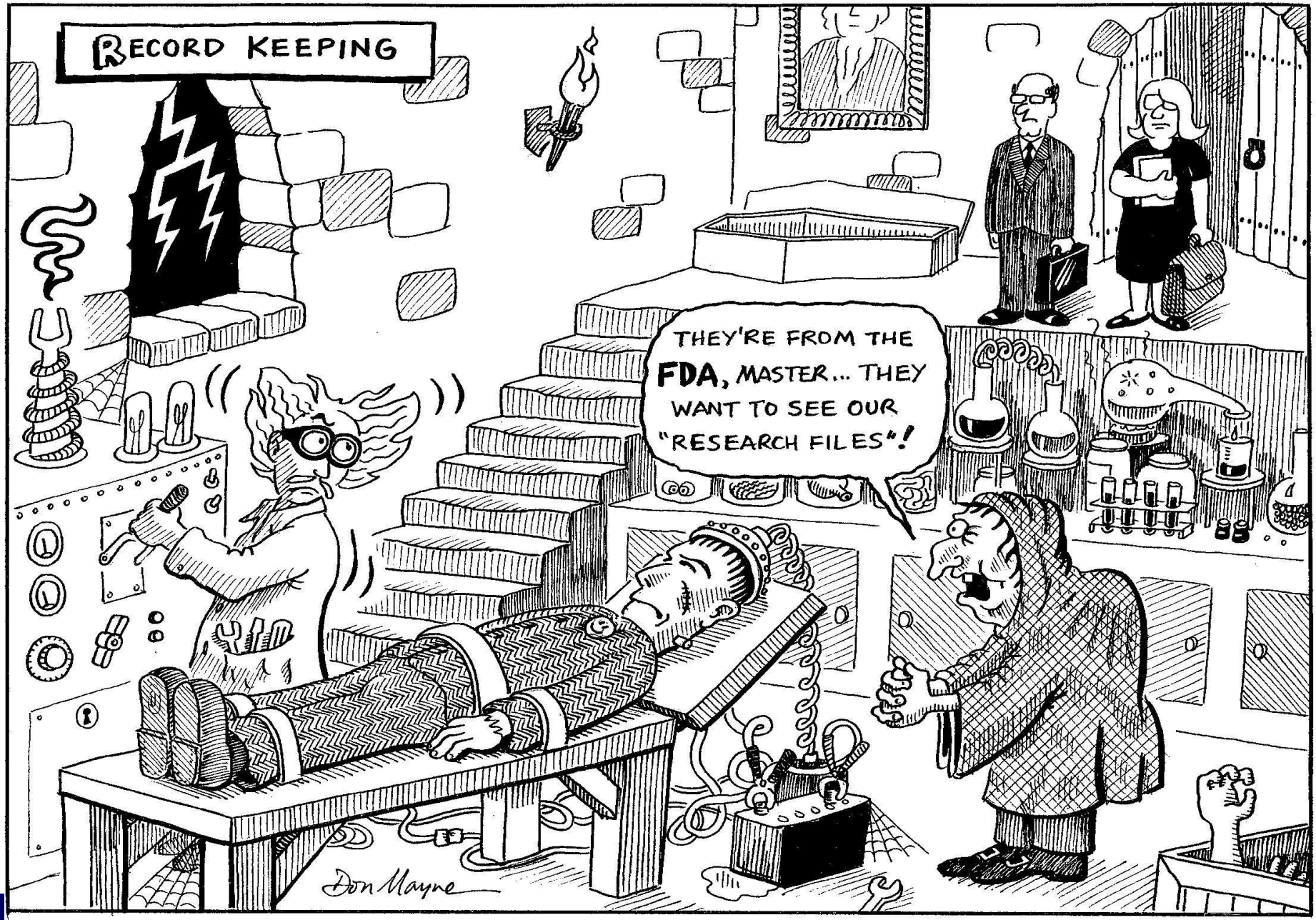
- Be sure to submit to your contracting office in a timely manner
- Provide information on all sites completing study
  - GHUCCTS has a multisite contracts
- Provide specific needs to the budget analyst

# IRB

- IRB should be submitted along with contract
- Submission should include:
  - Recruitment plan
    - Advertisements
    - EHR review
    - Outside clinics
    - Outreach
  - ICF and Informed consent plan
  - Identification of staff that will conduct research procedures
- Ensure required training and disclosures complete

# Regulatory Binder or eReg Binder

- Helps study sites achieve and maintain regulatory compliance
- Requirements vary based on study
  - Sponsors often provide
  - If not provided - still required
- Institution may have specific requirements or checklists
- eReg binders more commonly used



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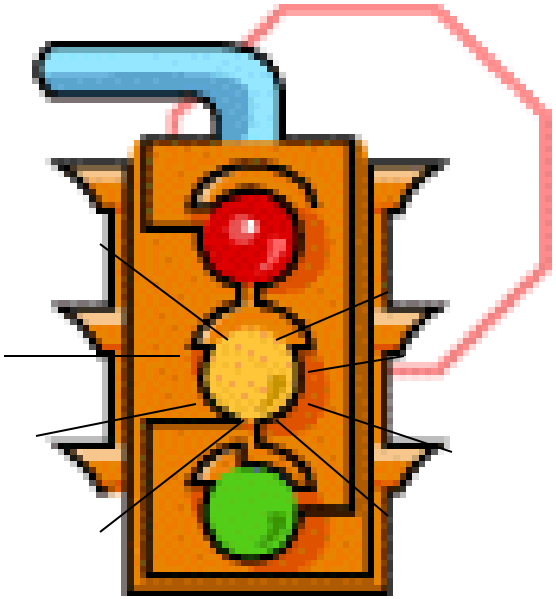
# Study Initiation Visit



# Study Initiation Visit

Sponsor's Purpose of the Initiation Visit:

- Ensure that Investigators receive information and training on:
  - Investigator Responsibilities
  - Test article
    - Background/Pre-Clinical Information
    - Storage
    - Accountability
  - Case Report Forms
    - Completion Instructions
  - Study Timelines
    - Enrollment period/Recruitment procedures
    - Interim analyses

# Study Initiation Visit

## Sponsor's Purpose of the Initiation Visit:

- Ensure that Investigators receive information and training on:
  - Protocol and Laboratory
  - Monitoring / Study Contact
  - Staff:  training, availability
  - Facilities:  equipment, storage, monitoring area
  - Inventory Supplies
  - Review Regulatory Documents

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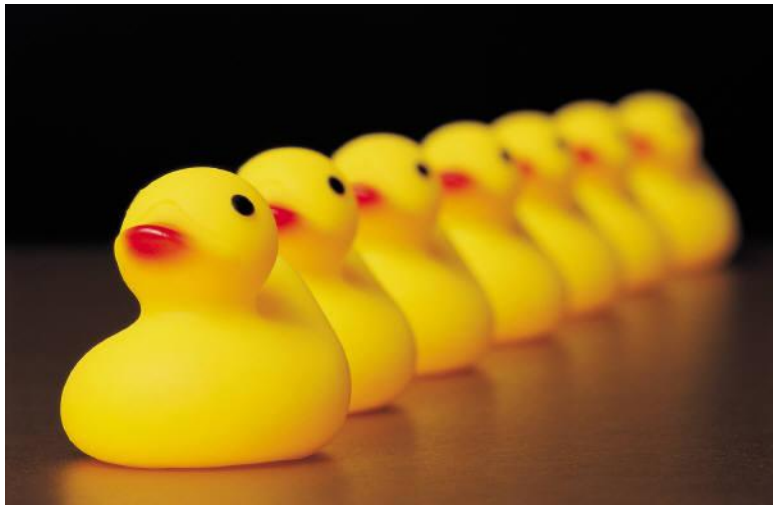
# Study Initiation Visit

## Preparation for the SIV:

- Invite attendees
  - Includes ancillary departments as needed
- Read the protocol
- Read the investigator brochure
- Organize study records/start Regulatory Binder
- Establish roles and responsibilities of site personnel
- Come prepared with succinct list of questions

*Study Initiation Visits are not just for FDA regulated studies!*

# Ready to GO!



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# Implementation

- Recruitment
- Enrollment
- Conduct
- Documentation
- Closeout

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# DATA

Adequate enrollment provides a base for

Participant retention resulting in

Evaluative data

Genevieve Frank, ICON,CRA, SoCRA SOURCE-Feb 2004

# How many studies recruit on time?

A. 20-30%

B. 30-40%

C. 50-60%

D. 70-80%

Only 20-30% recruit on time

*Reference: Association of Clinical Research Professionals*

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# Providers are Key to Enrollment in Clinical Trials

94% of *Americans* say their provider has never talked to them about clinical research

Only 20% of eligible patients are offered a clinical trial

Yet 75% of people who are offered a clinical trial enroll

- SOCRA Source Feb 2010 Padberg

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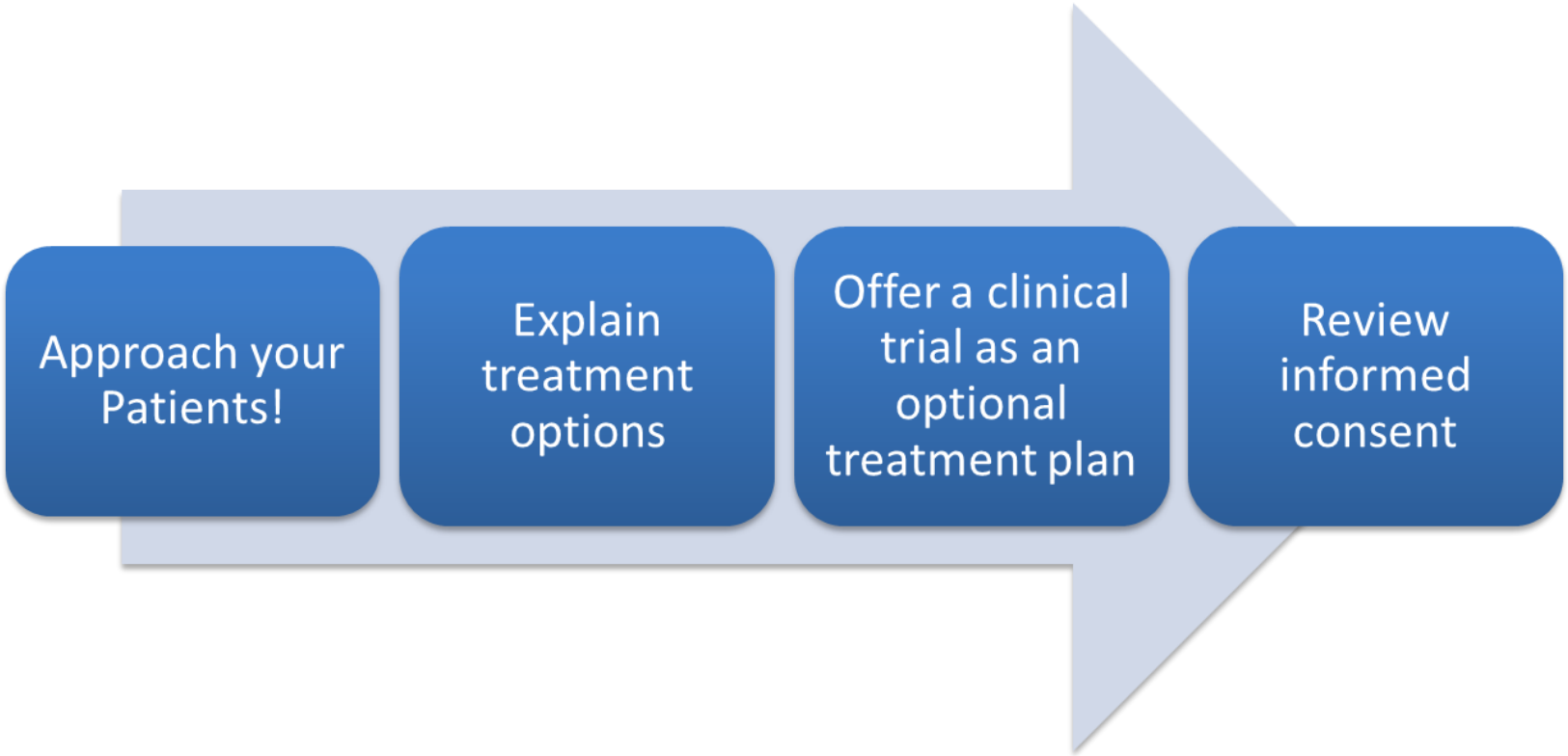
# Recruitment



# Why do people participate in research?

Motivations

- Altruistic
- Seeking more effective treatment
- Seeking hope for severe or life threatening illness
- Earn money
- Trust their providers

# Recruitment

- It is important to plan carefully for recruitment so that recruitment goals can be met in the allotted timeline.
- Recruitment is often more difficult than anticipated
- Time consuming (often costly)
- Requires flexibility

# Recruitment

- Consider where you will advertise, who will screen the calls, e-mails that come in and how they will be scheduled once recruited.
  - The longer the subject waits the more likely you will loose them in the process

# Recruitment Strategies

- Develop project identity
- Other Providers / Dear Colleague letters
- Advertisement
- ClinicalTrials.gov
- Patient Specific Networks
- Community Engagement
- Recruitment Compensation

# Track Recruitment Measures

- How subject became aware of study
- Date inclusion criteria met
- Reasons for excluding
- Ratio of volunteers screened to those enrolled
- Screen number
- Enrollment number

# Enrollment

- Defined as the process of entering a person into a study.
  - A subject is enrolled in the study once a ICF is signed.
  - Some studies consider enrollment when a subject completes the screening phase.

# How many participants continue in a study once enrolled?

A. 90%

B. 75%

C. 60%

D. 45%

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# 75% of participants continue after enrollment

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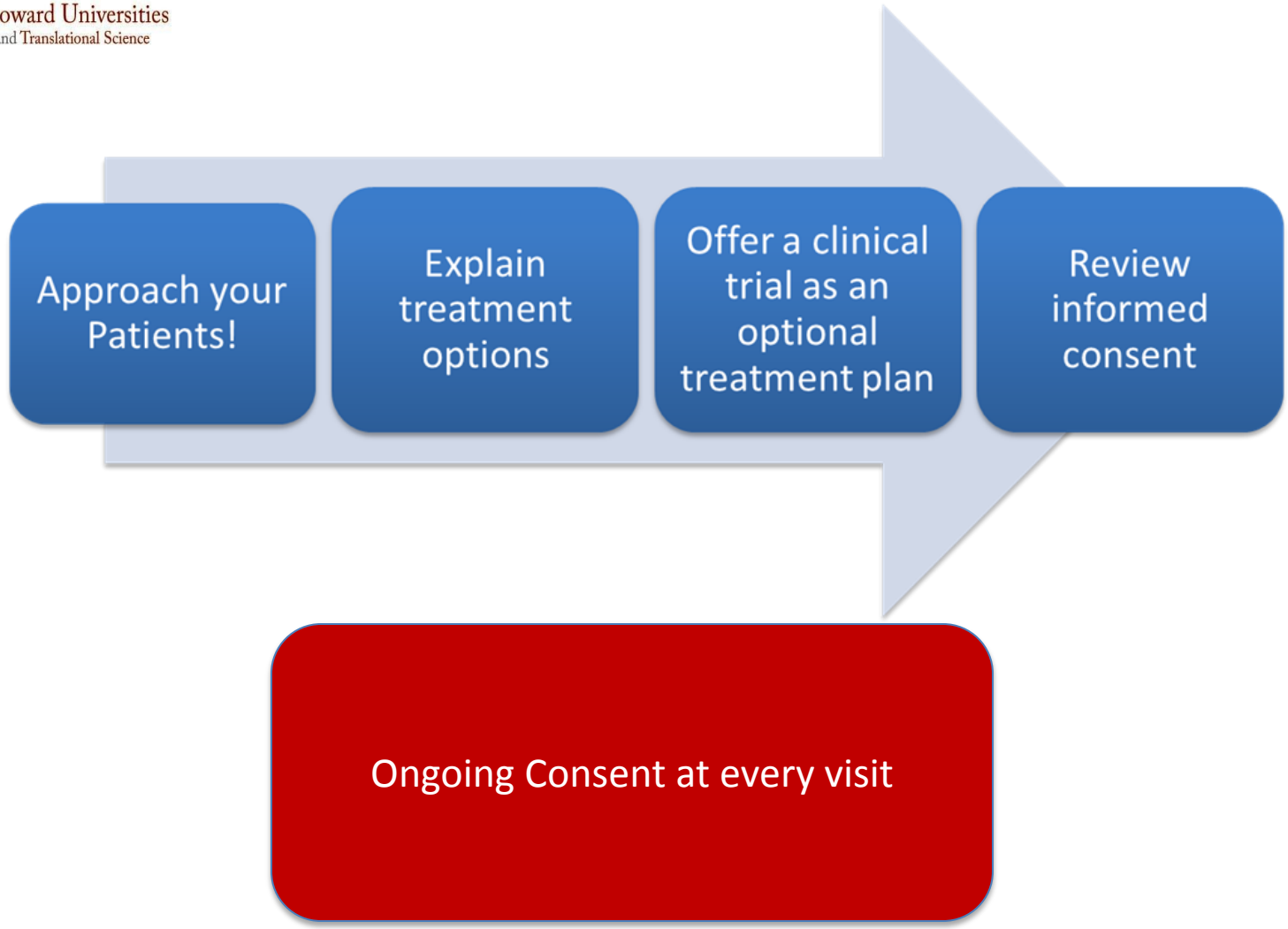
# Retention



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# Conduct

## Essentials of the Study Visit

# Essentials of the study visit

- Concomitant medication evaluation
- Adverse Event (AE) assessment and tracking
- Drug dispensation
- Study specific procedures
- Required PI visits
- Subject tracking

# Organizing the Study Visits

- It is essential to organize the study visit into a process flow, maximizing protocol compliance
  - When screen subjects complete the less expensive screen procedures first
- Many sponsors will provide source documents, in the form of a flow sheet or checklist, to help ensure thorough data collection
- All necessary materials, including drug, source documents and questionnaires, should be organized prior to the study visit

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# Study activities timeline

## Stress testing procedures on the GCRC.

| Time interval | Steroids | Neuropeptide RPP/PPP | Plasma Catecholamine | HR / BP* | Questionnaires ** | Physical stress : Immersion of hand in ice water 1 minute | Social Stress: N-Back (portion of the Trier Social Stress) | Total Blood Volume |
|---|---|---|---|---|---|---|---|---|
| Tube type | Red top tube | 2-EDTA Purple Tops | Na Heparin Green Top | | | | | |
| Blood draw amount | 2ml | 6ml | 2ml | | | | | |
| **Baseline** | | | | X | | | | |
| **Time 0** Admit to the GCRC and insert IV | | | | | | | | |
| **15 minutes** | X | X | X | X | | | | |
| **20 minutes** done immediately after bloods drawn | | | | | X | | | |
| **40 minutes** Ensure there is 5 minutes rest after completion of the questionnaires | | | | | | X | | |
| **41 minutes** done immediately after hand is removed from water | X | X | X | X | | | | |
| **56 minutes** done after a 15 min rest | X | X | X | X | | | | |
| **60 minutes** | | | | | | | X | |
| **63 minutes** done immediately after N-Bach complete | X | X | X | X | | | | |
| **78 minutes** done after a 15 min rest | X | X | X | X | | | | |
| **Provide light meal** | | | | | | | | |
| **Total blood volume** | **10 ml** | **30 ml** | **10 ml** | | | | | **50 ml** |

* Heart Rate and Blood pressure to be complete prior to blood samples taken

** Questionnaires include: 1.Perceived Stress Scale 2. State-Trait Anxiety Inventory (STAI) 2 pages

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# Organizing the Study Visits

| VISIT | If not done, WHY? | TESTS/PROCEDURES/INSTRU |
|---|---|---|
| Visit 1<br>Screen | | ☐ Informed Consent (signed, dated, Protocol Versio<br>☐ Symptom & Medical Review plus Physical Exam<br>☐ Documentation of HIV infection<br>☐ Record PPD (or chest x-ray if history of positive I<br>☐ Record Vaccination Review (Pneumovax, Hep A<br>☐ Record CXR if done as SOC<br>☐ Record CBC-diff if done as SOC<br>☐ Record Renal/Electrolytes/glucose/albumin if don<br>☐ Record LFTs if done as SOC<br>☐ Record Fasting Lipid Panel (Chol, LDL, HDL, T(<br>☐ Record CD4+ T-cell count if done as SOC<br>☐ Record HIV-1 RNA (bDNA or PCR) if done as S<br>☐ Record RPR/VDRL if done as SOC<br>☐ Toxoplasmosis Quantitative if done as SOC<br>☐ Record CMV Ab if done as SOC<br>☐ Record HepBSAg if done as SOC<br>☐ Record HepBSAb if done as SOC<br>☐ Record HepB core Ab if done as SOC<br>☐ Record HepB DNA if done as SOC<br>☐ Record HCV Ab if done as SOC<br>☐ Record HCV RNA if done as SOC<br>☐ Record EBV Ab if done as SOC<br>☐ Confirm subject is not on lympho depleting agent<br>**Samples collected, processed and shipped to central repository**<br>☐ Recipient Blood<br>☐ Recipient Urine |
| **Date:** | | **Name of Reviewer:** |

#03-142 (flow sheet rev 2-17-05)
PI: Aruna Nataraian, MD pager 202-668-1335

Name: _____ DOB: _____ Date: _____

**Day 6**

| Sched. Time | Actual Time | Assessment | Date/time/ Initials | Comments |
|---|---|---|---|---|
| 0000 | | Flush all 3 heparin locks with 3cc of 10unit /cc heparin flush | | |
| 0000-1600 | | NPO, except study water. | | |
| 0000-1600 | | Subject to remain supine. | | Subject can have head of bed up 45 degrees so they can use bedpan / urinal. If they are unable to urinate in a bedpan can use a bedside commode. |
| 0645 | | Subject to empty bladder.<br>(Do not need to save after measured.)<br>VOLUME_____ | | Pt can get up to use BR |
| 0650 | | Wt._____(kg)<br>Used to calculate water load | | Pt can stand for wt. Pt to return to supine position after wt. and remain supine for the remainder of the study. **Bring scale to bedside.**<br><br>Provide subject a bedpan or urinal for urine collections. |
| 0730-0830 | | Oral load of (20ml/kg) bottled water at room temp ingested slowly over 60 minutes<br>***If nausea occurs during the study. Page PI immediately.**** | | Amount given_____<br><br>Amount Consumed_____<br>Time completed_____ |
| 0730 (every 30 mins) | | Right<br>1. BP _____/_____<br>HR _____<br>Left<br>2. BP _____/_____<br>HR_____ | | **Can use automated BP monitoring.**<br>**Supine with head on small pillow.** |
| 0730 (Must be given at 0730) | | **All Subjects:**<br>1. Enalapril / placebo 2.5mg po<br>2. Lithium Carbonate 600 mg po | | All medication will be sent from pharmacy. Must use **bottled study water** for water load to take medications. |

# AE Assessment and Concomitant Medication

- AE tracking and concomitant medication assessment often go hand in hand and should be evaluated simultaneously at each visit.
- At each visit changes in health history, including acute changes and increased severity of already documented problems, should be evaluated.
- Assessment of Adverse Events must include:
  - Timing of onset
  - Severity
  - Treatment: including concomitant medications and non pharmacologic interventions.
  - Timing of resolution or plans for follow-up
  - Relationship to drug to be evaluated by the PI

# AE Assessment and Concomitant Medication

- Concomitant Medication Assessment to include:
  - Changes in previous medication
    - Starting or stopping a medication
  - New medications
    - Ensure that the new drug is not exclusionary
- Concomitant medication information should include:
  - Full name of medication
  - Specific dose and route
  - Date medication started or dose changed
  - Date medication stopped if applicable
  - Should be tied to an event or change in health history

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# Tools for Tracking AEs and Concomitant Medications

- Medication logs
  - Allows you to keep a running look at the subjects current medication and evaluate changes at each visit
- AE flow sheets
  - Allow for thorough assessment of ongoing as well as past, yet not resolved AEs.

# Drug Dispensation

- Understand the sponsor's expectation and the institution's policies regarding drug dispensation and associated documentation before dispensing any drug
- Some sponsors require the use of IVRS, a telephone interactive dispensation tracking method.
- You must plan ahead as several steps may be required prior to drug dispensation
- Always ensure proper dispensation procedures
  - Right subject, right drug, right route

# Drug Dispensation

- During the study visit
  - Collect all unused drug for reconciliation and compliance documentation
  - Discuss and document any compliance issues with the subject
  - Dispense / re-dispense the medication for the next required interval

# Study Specific Procedures

- Have scheduled all study procedures that require interdepartmental collaboration to coincide with the study visits when possible.
- Utilize study checklists and flow sheets to make sure all procedures are completed in the order required
  - Example: blood drawn after the cognitive testing is done, or bloods drawn prior to dosing that day

# Required PI Visits

- The protocol may require the PI to assess the subject at given intervals
- This should be scheduled with the PI in advance
- Assist the PI by providing the requirements for that visit in a flow sheet or checklist format
- Understand what to do if PI can not see the subject at the required time point
  - Can a co-investigator fill in?
  - Can the visit be postponed?
  - Can the PI component be moved?

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# Subject Tracking

- It is essential to track subjects progress through the protocol
  - Both anticipated and actual visits should be documented
- Protocols usually provide “a window” for the study visit.
  - Example: visit 2 should occur on study day 10 with a window of one day before or after allowable
- Tracking anticipated visits ensures that visits are not missed or occur outside the window
- The sponsor may provide you a tracking tool and may require it faxed to the CRA at specified intervals.

# Drop-outs

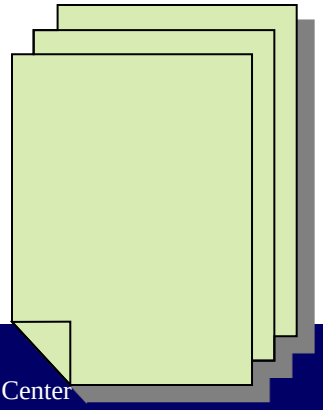
- Subjects may choose to withdraw from the study at any point or the investigator may decided it is in the best interest of the subject to withdraw
- Whenever possible it is important to complete any required safety assessments
- Detailed documentation of drop-out essential
- Notification of the sponsor and IRB required if the withdraw is due to an AE

# Lost to follow-up

- Subjects will on occasion fail to return for study visits and fail to follow-up with attempts to reach them. The coordinators should proceed as follows:
  - Document all attempts to reach the subject
  - After several attempts / days the coordinator must send a certified letter to the subject to document attempts at communication
  - If no response to certified letter subject is considered lost-to-follow-up

# Documentation

- Must be clear concise and “trackable”.
- All communication with sponsor as well as subject should be documented
- Use of logs and flow sheets ensures complete documentation
- Source Documents vs Case Report Forms



# Closeout

- Planned Closeout at full completion of the study
- Early closeout as a result of unanticipated problems.
  - Shepherd et al. – Early closeout is not rare
    - "as interim monitoring and stopping rules become more sophisticated and widely used, it is likely that more trials will terminate early"

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# Closeout

- Common requirements
  - Outstanding Data Forms and Query Forms
  - Subject data forms
    - AE logs, CRFs, other
  - Final Reports
  - Test Article Accountability
  - Final Financial Disclosure

# Closeout


- Record Retention
  - 2 Years following the approval of a NDA or 2 Year after sponsor notifies FDA that study discontinued
    - Site study files
    - Subject data
  - Sponsor could require longer – 15 years
  - Records remain at institution where study conducted if possible or notify sponsor of location change

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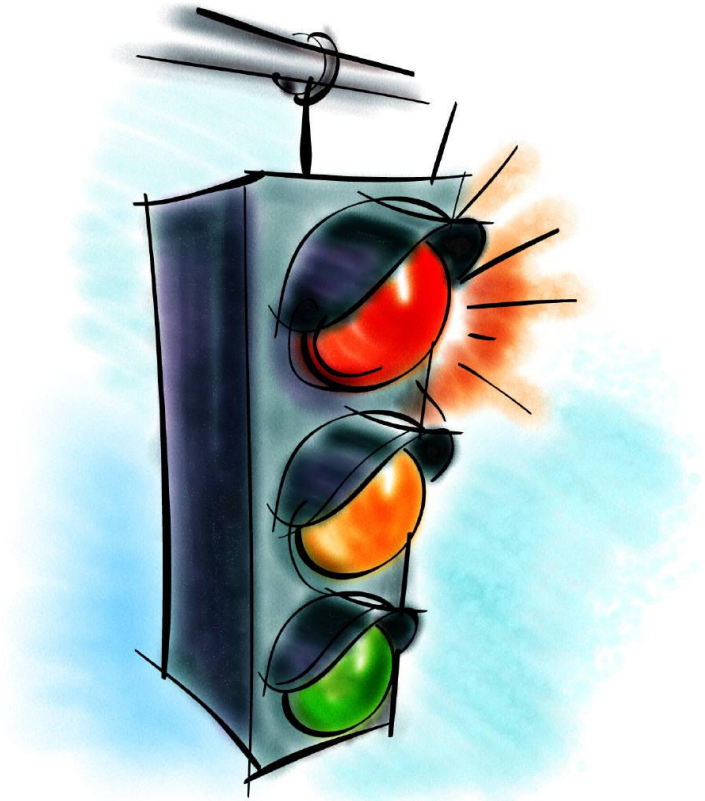
# Be Prepared and Think Ahead!

**You cannot escape the responsibility of tomorrow**
**by evading it today.**

Abraham Lincoln
16th president of US (1809 - 1865)

# Study Successfully Completed and Published!



# Questions