Roles of Investigators in the Managements of Clinical Trials

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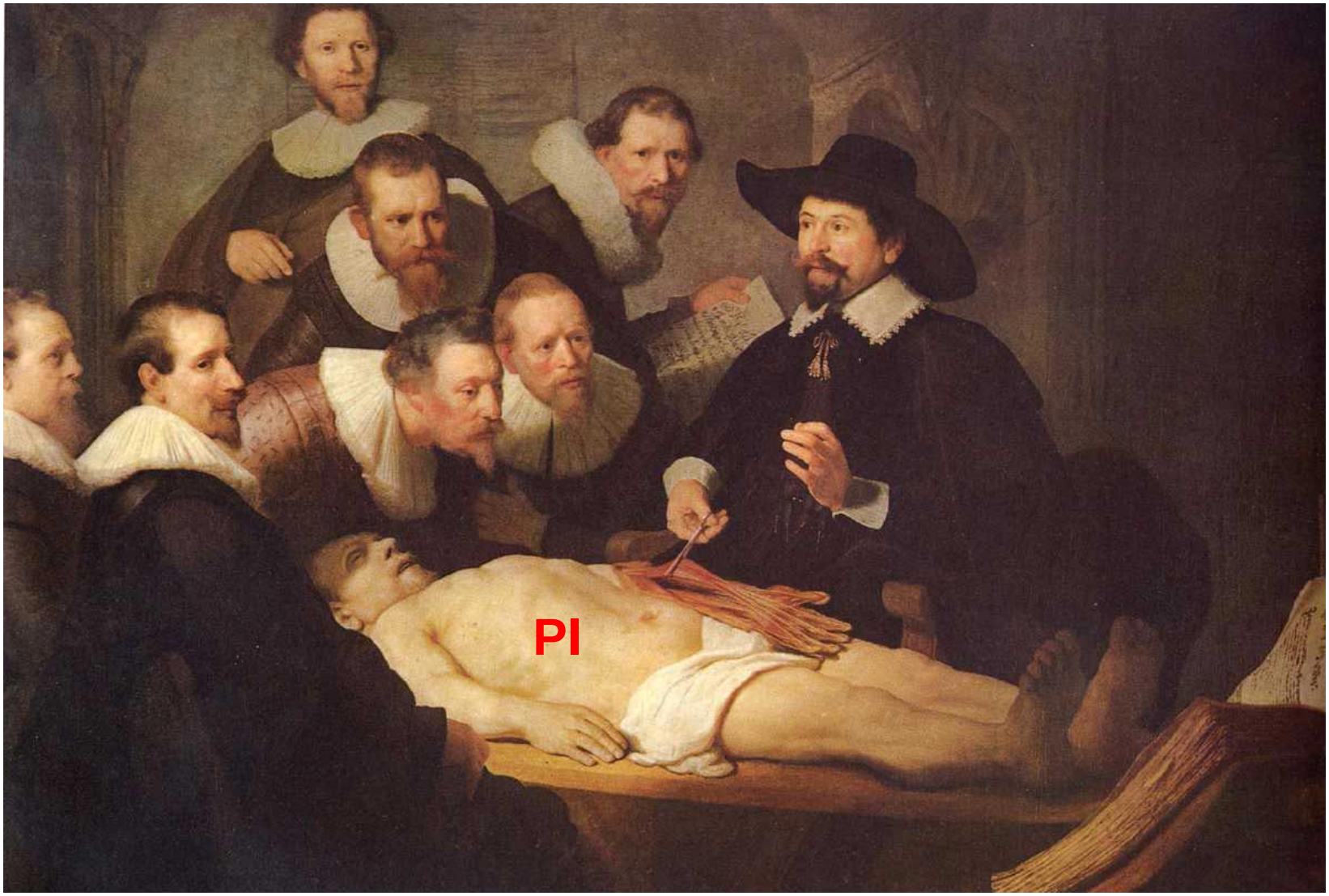
Learning Objectives

-----Original Message-----
From: benjamin_kuo@jirb.org.tw [mailto:benjamin_kuo@jirb.org.tw]
Sent: Wednesday, March 19, 2008 4:59 PM
To: HCM
Cc: JIRB-翠芬; 橈通 何
Subject: Re: Re: Workshop speaker]

Dear Chiimin,
Thanks for accepting this invitation.
Please be advised that the attendees of this workshop are 1.FERCAP steering committee members(about 10) 2.FERCAP-recognized IRB members (2 from each IRB total about 22) 3.FERCAP countries medical authority (India, Thailand, Indonesia,Mongolia and... Total about 10) 4. Taiwan government GCP inspector.(maybe 5) So, this talk is not to tell how to be a good PI, but is how to know is he/she a good PI or not. Some experience sharing will be very helpful.
Please do not hesitate to e-mail me if you need anymore information.
Best regards,
Benjamin

Sent from my BlackBerry® wireless handheld from Taiwan Mobile


PI

Outlines

- How to Manage a Clinical Trial: PI's Prospects
  - Tips for Evaluation of a clinic study
- What have I learnt from audits?
- Documentation

Why a PI Wants to Involve With Clinical Research/Trials

- For Scientific Purposes
- For Improvement in Clinical Practice
- For Other Purposes

How to Manage a Clinical Trial From Ideas to Publication

- Establishing study objectives
- Planning and coordinating the study
- The study protocol
- Study design
- Data management/ Statistical analysis
- Ethical considerations
- Study conduct

Idea?

- Not all ideas are good.
- Not all good ideas can be conducted.
- Ideas need to be re-constructed into a specific hypothesis that can be tested.

Idea?

- Has someone else had the same idea?
- Has the question really been answered before?
- What do you want your research to accomplish?
- Which journal might publish your results?

Study Plan

- Protocol writing
- Contract
- Drug supply
- Clinical conduct of study
- Data management
- Data analysis
- Report

Protocol writing

1. Prepare proposal synopsis
2. Sponsor evaluation of proposal synopsis
3. Writing of final protocol
4. Safety/quality control
5. Pre-study team meeting
6. Evaluation by sponsor
7. Submission to ethics committee
8. Ethics committee evaluation

Essential elements of a protocol

1. A scientific rationale
2. The objectives of the proposed study
3. A precise description of the procedures that will be preformed.

Study Protocol

- **Title page**
- **Summary**
- **Content**

1. Introduction
2. Objectives
3. Study design
4. Subjects
5. Drugs & dosages
6. Measurements
7. Data management and analysis
8. Study management
9. References
10. Tables
11. Figures
12. Appendices

Study Protocol

- **Subjects**

1. n
2. Inclusion/exclusion
3. Screening
4. Informed consent
5. Withdrawal/Rescue
6. Compensation

- **Measurements**

1. Schedule
2. Clinical procedures
3. Lab procedures
4. Adverse experiences

Who reads the protocol?

1. The Ethics Committee

   Ethics and safety considerations

2. Clinical Research Team

   Procedures

3. Monitor

   To ensure the investigator(s) complying

4. Authorities

   For regulation

Who writes the protocol?

1. Investigator = author
2. The investigator is not the author.

-Good companies will confer with their potential investigators.

-No investigator should agree to a protocol which is significantly flawed in science or is simply impracticable.

Tips for Evaluation of a Clinical study

- **Questioning the PI about why he/she agrees with the protocol**

Factors in the development and writing of a clinical protocol (1)

1. Formulating an approach
2. Establishing criteria for patient inclusion
3. Identifying and choosing safety parameters
4. Modifying dosing schedules and developing compliance checks
5. Identifying, choosing and evaluating efficacy parameters

Factors in the development and writing of a clinical protocol (2)

6. Developing time and event schedules
7. Preparing, packaging and dispensing study drugs
8. Preparing the introduction
9. Polishing the "boilerplate"

Factors in the development and writing of a clinical protocol (3)

10. Regulatory, patent and legal considerations
11. Ethical considerations
12. Completing and reviewing the initial draft
13. Improving the protocol

Factors in the development and writing of a clinical protocol (4)

14. Preparing data collection forms
15. Instructions for patients, investigators and study personnel
16. Continuation protocols
17. Comments on multicenter studies

Logical sequence in clinical study design

- Define and write drown a clear set of objectives
- Define the patient population
- Choose control treatments with which the experimental therapy is to be compared
- Choose an appropriate trial structure
- Select an appropriate sample size
- Organize the blinding and randomization procedures

Control

- ✓ Drug Trial
  1. No control
  2. Placebo control
  3. Active control
- ✓ Case-Control Study
  1. Population control
  2. Traditional control
  3. Family control
     - -Spouse
     - -Sib
  4. Neighbor/friend control

Control

- No control: avoid if possible
- Placebo: acceptable if no current standard therapy
- Active: desirable if a standard therapy exists (placebo may also be included)

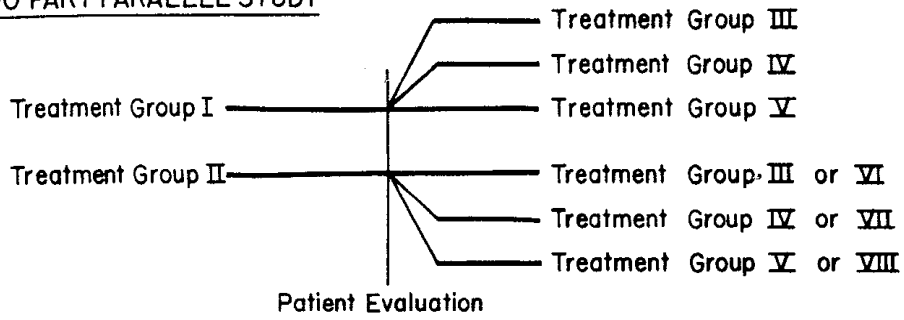
Classification of study designs
Parallel Designs (1)

1. COMMON PARALLEL DESIGNS

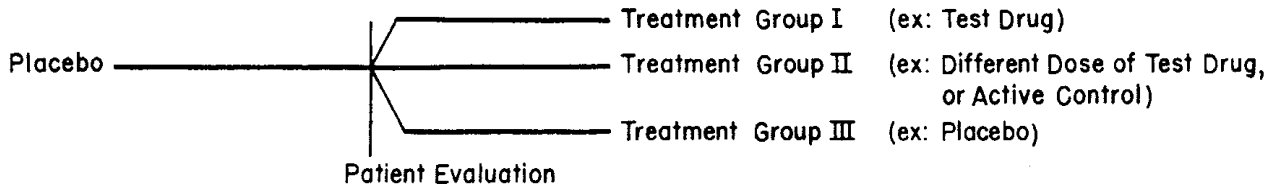
A.
- Treatment Group I
- Treatment Group II

B.
- Treatment Group I
- Treatment Group II
- Treatment Group III

2. TWO PART PARALLEL STUDY



3. PARALLEL DESIGN WITH PLACEBO INITIATION



Classification of study designs
Parallel Designs (2)

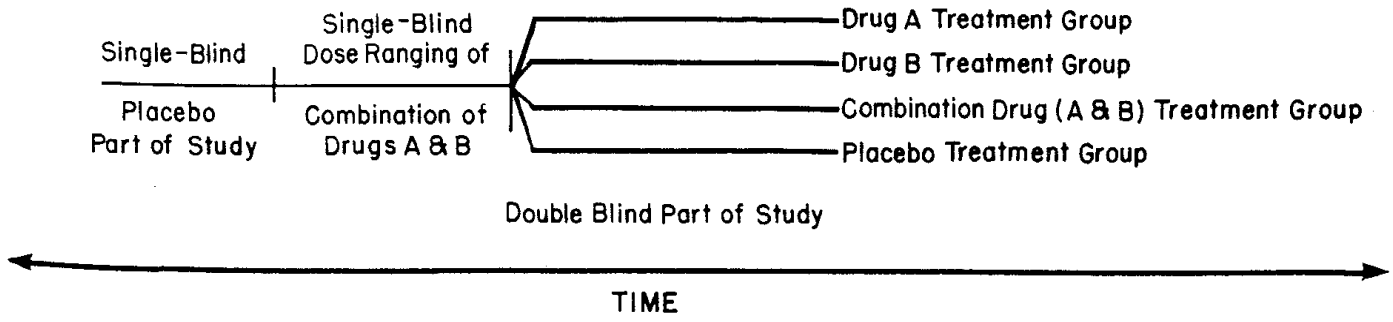
4. INTRODUCTION OF PLACEBO DURING TREATMENT

Treatment Group I	Placebo	Treatment Group I
Treatment Group II	Placebo	Treatment Group II
Treatment Group III	Placebo	Treatment Group III

5. MULTIPLE DOSES WITHIN EACH TREATMENT GROUP

Treatment Group I	Dose A	Dose B	Dose C	Dose D
Treatment Group II	Dose E	Dose F	Dose G	Dose H

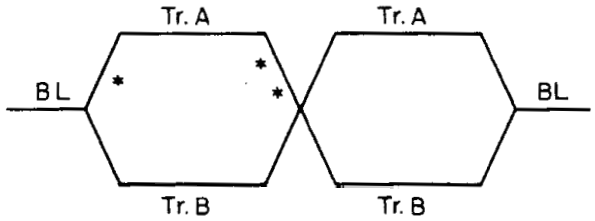
6. PARALLEL EVALUATION OF A COMBINATION DRUG



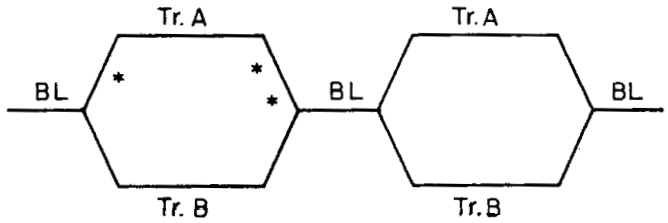
Classification of study designs
Crossover Designs (1)

1. SINGLE CROSSOVER WITH NO INTERVENING BASELINE

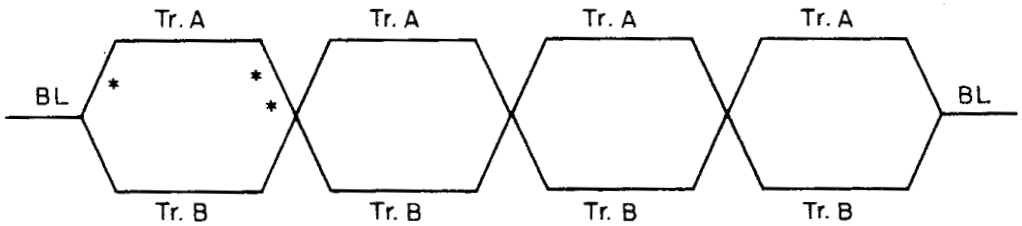
(i.e., No drug-free interval)



2. SINGLE CROSSOVER WITH INTERVENING BASELINE



3. DOUBLE CROSSOVER WITHOUT INTERVENING BASELINES



Classification of study designs
Crossover Designs (2)

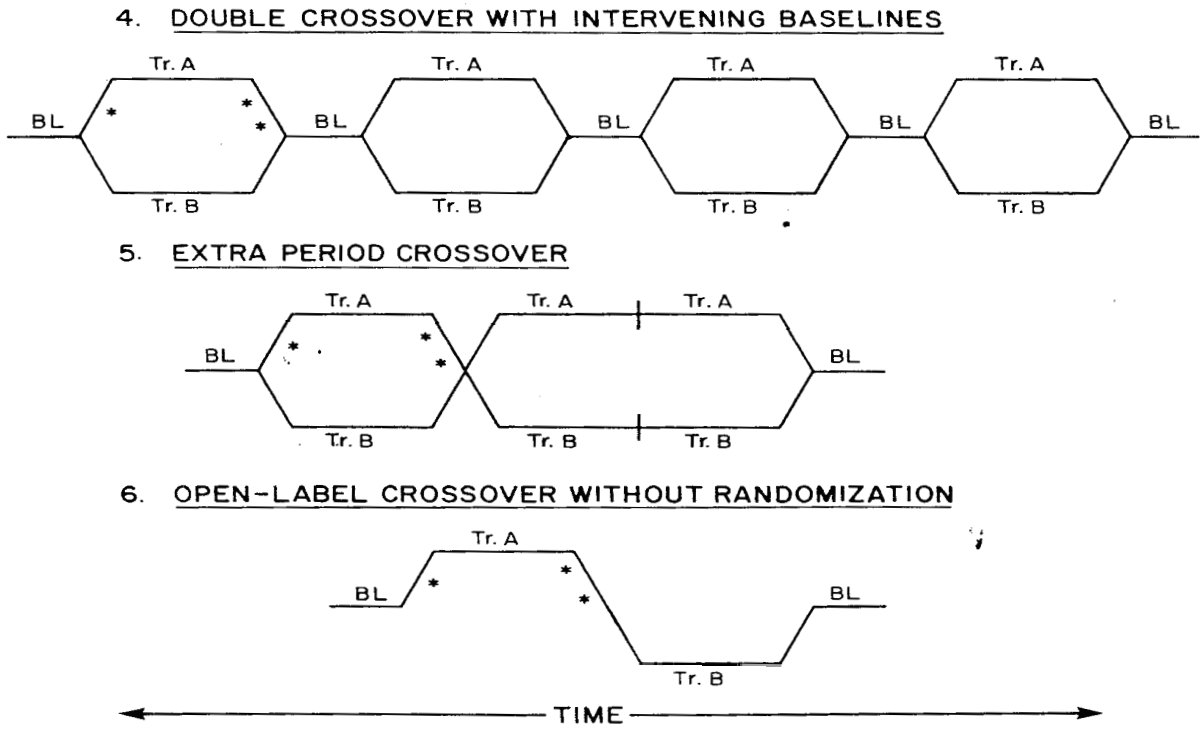


FIG. 5.2. Selected schemata for crossover studies. **Schemata 1 to 5** may be open label, single blind, or double blind. BL, baseline; Tr.A, treatment A; Tr.B, treatment B. *, Dose ascension part of each period. **, Dose taper part of each period. All baselines that occur after treatment has been initiated include washout of drug. In **schema 1**, there is usually a brief washout period between treatments A and B. Although the change from one treatment to another in all schemata is shown as being time dependent, it is possible that this change may be dependent on the condition of the patient's disease state.

Developing time and event schedules

TABLE 19.30. *Study time and events schedule*

		Period 1 baseline A		Period 2 treatment A							Period 3 baseline B			Period 4 treatment B							Period 5 follow-up	
Event	Weeks: Screen	2	4[a]	5	6	7	9	12	15	16[b]	17	18	20[a]	21	22	23	25	28	31	32[b]	33	36
Admission criteria	X																					
Informed consent	X																					
Medical/seizure history	X																					
Physical exam	X								X										X			
Neurological exam	X								X										X			
Investigator's assessment	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X
Vital signs	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X
Electrocardiogram (ECG)	X								X										X			X
Electroencephalogram (EEG)	X								X										X			
Laboratory																						
Hematology	X		X			X		X	X				X			X		X	X			X
Blood chemistry	X		X			X		X	X				X			X		X	X			X
Urinalysis	X		X			X			X				X			X			X			X
Pregnancy test (when applicable)	X		X						X				X						X			X
AED plasma levels[c]	X	X	X		X	X	X	X	X		X	X	X		X	X	X	X	X		X	X
Adverse reactions	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X
Dosage record	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X
Seizure record	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X
Physician's global evaluation									X										X			
Study discontinuation record																						X

[a]Dosage ascension of test medication initiated. Week numbers refer to end of week.
[b]Dosage taper/discontinuation of test medication.
[c]AED, antiepileptic drug.

Choosing between a parallel and cross-over study (1)

Parallel trial is essential:

* If the disease is short-term, or potentially curable by the treatment, or potentially lethal

Parallel trial is desirable:

* Even if the disease state is chronic
* In cases where long treatment periods are required (eg.longer than 3 months)
* Where there are more than 3 treatments to be compared.

Choosing between a parallel and cross-over study (2)

Cross-over trial is possible:

* When the disease state is chronic and will return to its pre-treatment state when a treatment is finished.
* For up to 3 treatments (more are possible but not desirable) provided that it can be demonstrated that treatment effects will not carry-over from one treatment period to a subsequent one.

Choosing between a parallel and cross-over study (3)

Parallel trial are:

* Generally to be preferred
* Likely to require more patients than a cross-over
* Less likely to suffer complications in trial execution
* Less likely to suffer large numbers of patient-withdrawals
* Likely to be shorter
* Likely to be easier to analysis statistically

Choosing between a parallel and cross-over study (4)

Cross-over trial are:

* Second choice !
* Likely to require fewer patients
* More likely to be difficult to execute
* More likely to suffer patient withdrawals
* Likely to be longer overall
* More likely to be complicated in analysis and interpret

Blinding

- Open: avoid if possible
- Blind-at-Randomization: better than open !
- Single-blind: often acceptable with objective responses
- Double-blind: should be preferred whenever possible

Contract

1. Preparation of draft contract
2. Prepare of budget
3. Sponsor budget/contract approval
4. Signing of contract

Drug supply

1. Import license application
2. Packaging and blinding

Clinical conduct of study

1. Ethics committee approval
2. Start-up meeting
3. Screening of subjects
4. Consent
5. Clinical phase
6. End of clinical phase

What is Informed Consent?

A process by which a subject voluntarily confirms his or her willingness to participate in a trial, after having been informed of all aspects of the trial.

The process may include subject recruitment materials, verbal instructions, questions/answer sessions and measures of subject understanding.

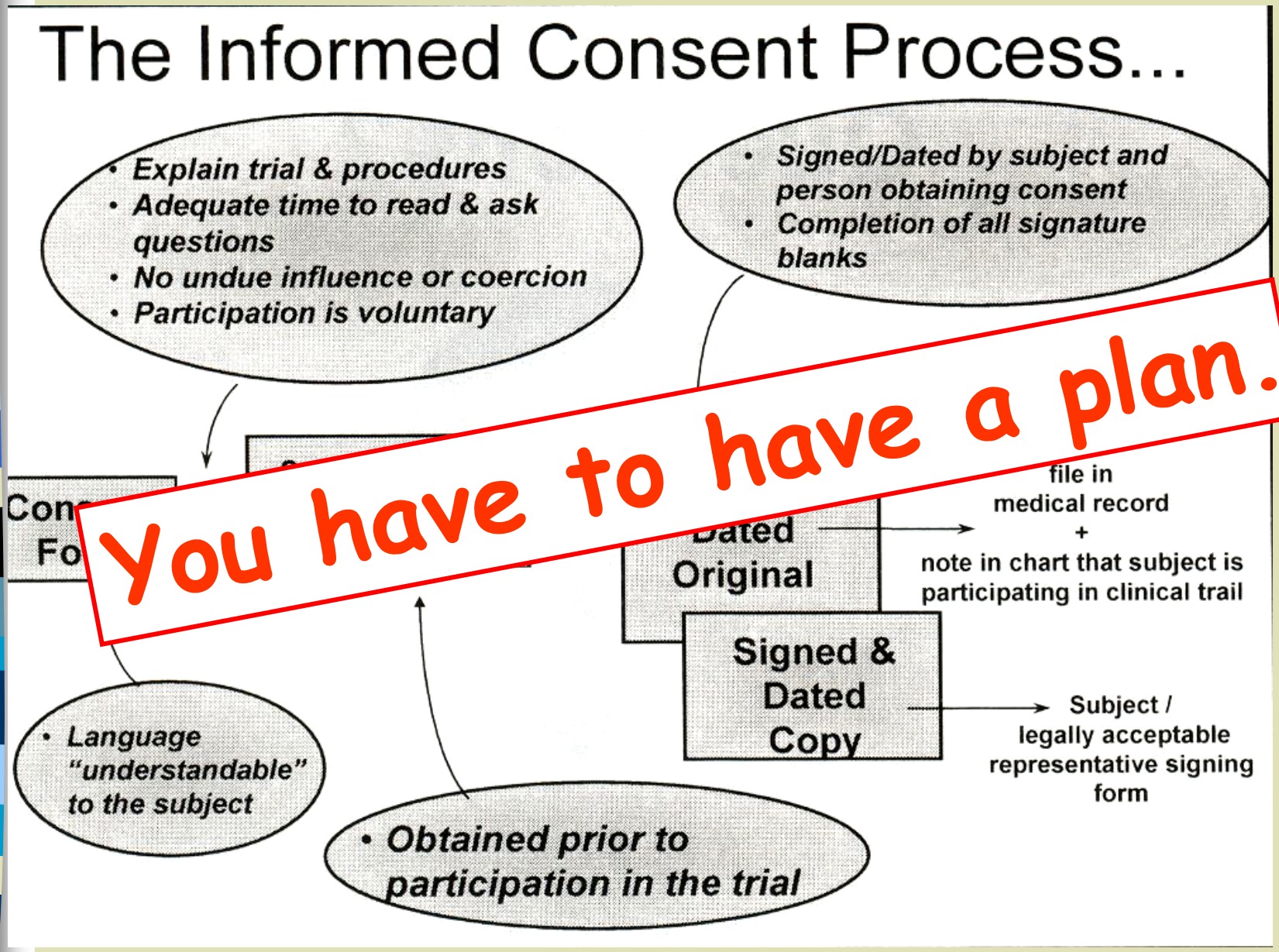
The Informed Consent Process

Informed consent is more than just a signature on the informed consent document.

It is a **Process** to give subjects opportunity to agree to participate

Importance of Informed Consent

- To assure that participation is voluntary and that the rights, welfare and safety of subjects are protected.
- The consent form document serves as confirmation of the consent process.
- A study site responsibility


The Informed Consent Process...
• Explain trial & procedures
• Adequate time to read & ask questions
• No undue influence or coercion
• Participation is voluntary
• Signed/Dated by subject and person obtaining consent
• Completion of all signature blanks
You have to have a plan.
Dated Original
file in medical record + note in chart that subject is participating in clinical trail
Signed & Dated Copy
Subject / legally acceptable representative signing form
• Language "understandable" to the subject
• Obtained prior to participation in the trial

The Consent Process Plan

- Identify the obstacles to subject participation and ways to overcome the obstacles

  -Transportation
  -Family
  -Work
  -Number of visits
  -Number of blood draws

The Consent Process Plan

- Identify words subject may not understand in consent form
- Compile list of questions the subjects may ask about the study and appropriate responses

The Consent Process Plan

- Decide who will conduct consent discussion
  - -Investigator may obtain consent
  - -Investigator may delegate responsibility to a *knowledgeable* person.
  - -Investigator is ultimately responsible for assuring informed consent has been appropriately obtained

The Consent Process Plan

- Decide where consent discussion will be held

  -Conduct in a quiet area

  -Subject should have adequate uninterrupted time

  -Easy access to a study doctor

  -Provide space for family members or friends to be present during the consent discussion

The Consent Process Plan

- Provide adequate time to explain the study and study procedures to the subject
- Provide adequate time for subject to read and consider
- Provide time for questions to be answered

WHO CAN SIGN THE CONSENT?

十、 同意與簽章

研究人員已詳細解釋有關本研究計畫之目的、性質與研究方法，及可能產生之危險與利益。

研究計畫主持人_____(簽章) 日期:_____

取得同意人員 （研究醫師或指定代理人）_____(簽章) 日期:_____

本人已詳細瞭解上述研究方法及參與本計畫之優點與潛在危險性。有關本試驗計畫之疑問，業經計畫主持人或指定代理人詳細予以解釋。本人同意接受為本研究計劃之自願受試者。

受試者簽章_____ 日期:_____

法定代理人(受試者於法律上屬無行為能力人及獲禁治產權宣告者)

簽章:_____ 日期:_____

口頭同意之見證

茲證明研究人員已完整地向受試者解釋本研究內容與相關細節。

見證人簽名_____ 日期:_____

When Should Informed Consent Be Obtained?

- Obtain consent after approval by Sponsor and IRB/IEC/Agency
- Obtain consent prior to altering care of the subject for purpose of participating in research study
- Obtain consent prior to initiation of any clinical procedures that are performed solely for purpose of determining eligibility for research

Documentation of Informed Consent Process

- Check that contact information is complete on original and copy given to subject
- Provide subject with a copy of the signed and dated informed consent document or second signed and dated original
- File the original signed and dated informed consent document in the subject file
- Document study participation in medical records of subject

Updates to the Informed Consent Document

- The consent document may be revised when:

  -Protocol amendment(s) are necessary
  -New relevant safety information becomes available
  -New information becomes available that might influence the subject's decision to participate/continue in the clinical study

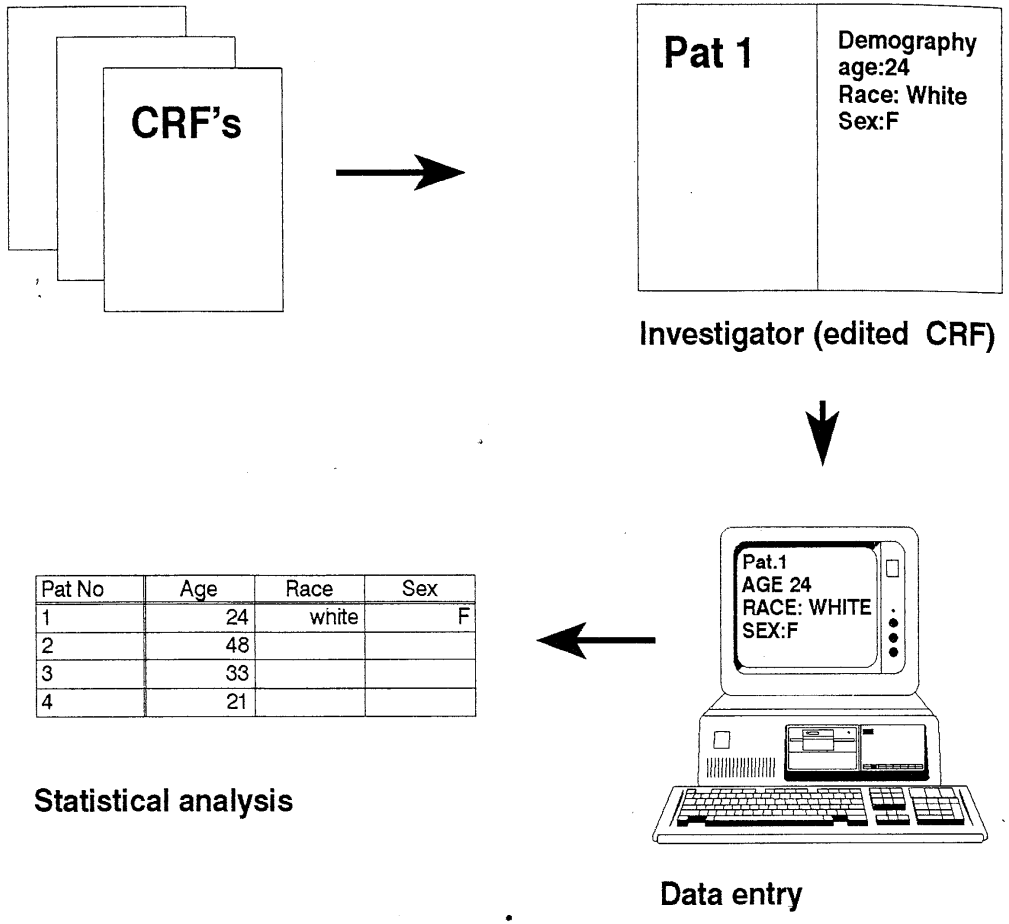
Tips for Evaluation of a Clinical study

- Questioning the PI about why he/she agrees with the protocol
- **Check on the documentation of informed consent process**

Categories of data collected in clinical studies

- Demographic data
- Pre-treatment medical history and pre-treatment disease state
- Data on prognostic factors
- Dosing and exposure data
- Efficacy measurements
- Adverse event data
- Vital signs data
- Hematology and clinical chemistry results
- Other safety data, e.g. ECG,EEG
- Health economic data
- Other routine data on clinical care and monitoring

Data management and statistical analysis



Data management/analysis

1. Assay
2. Data cleaning
3. Data entry
4. Statistical analysis

Study management

1. Records management
2. Randomization
3. Discontinuation of the study
4. Study personnel and responsibilities
5. Audit

Study Staff

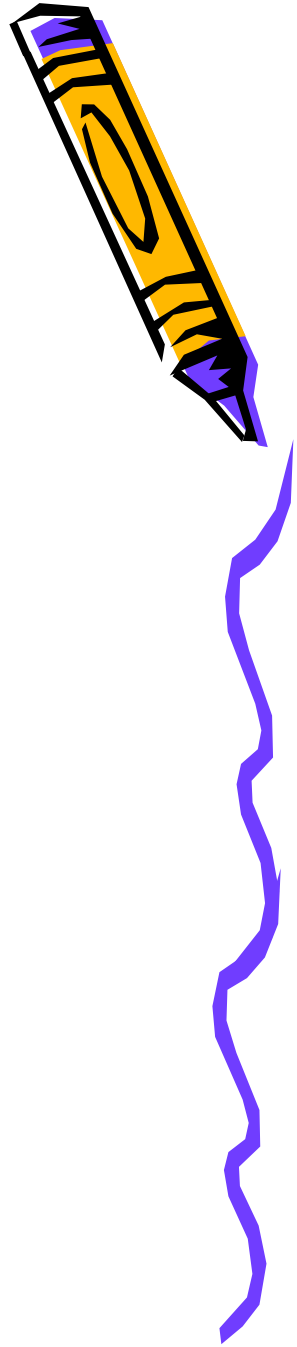
- It is unreasonable to expect colleagues,commonly junior staff, who have other full time work commitments to help you conduct a clinical study without adequate prior warning and training.

Tips for Evaluation of a Clinical study

- Questioning the PI about why he/she agrees with the protocol
- Check on the documentation of informed consent process
- **Evaluation of the infra-structure of the study site, focusing on the site personnel responsibilities**

Study Report

1. Compiling of final report
2. Safety/quality control
3. Finalization
4. Prepare publication
5. End of study



Milestones for study plan

1. Deadline for the final protocol
2. Date of ethics committee approval
3. Start and end dates for the study
4. Start and end dates for statistical analysis
5. Deadline for final report

Responsibilities of the investigators (1)

- To supply credentials (e.g. provision of curriculum vitae)
- To familiarize himself with the properties of the investigational drug
- To ensure confidentiality of information
- To provide adequate resources and time to conduct the clinical trial
- To inform staff involved
- To ensure that recruitment rate of patients is sufficient
- To reach agreement with the sponsor regarding the protocol, Good Clinical Practice , monitoring procedures and publication of data
- To submit the protocol to an ethics committee
- To obtain informed consent from the study subjects

Responsibilities of the investigator (2)

- To establish a system for drug handing and accountability, randomization and blinding
- To ensure proper collection and handing data
- To report adverse events and assure patient safety
- To agree to data validation, source document verification and audit
- To provide a report of the trial
- To assure retention of trial documentation/patient records
- To take medical responsibility for the study subjects and provision of emergency resuscitation equipment
- To provide subjects with a card indicating they are in trial with a contact telephone number

Commitment

- [C] thing one has promised to do
- [U] state of being dedicated or devoted

Tips for Evaluation of a PI?

- Questioning the PI about why he/she agrees with the protocol
- Check on the documentation of informed consent process
- Evaluation of the infra-structure of the study site, focusing on the site personnel responsibilities
- **Judging the PI for his/her commitment**

Ethical Considerations

- Respect for autonomy
- Doing good
- Not doing harm
- Justice

Tips for Evaluation of a PI?

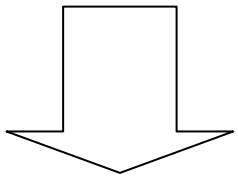
- Questioning the PI about why he/she agrees with the protocol
- Check on the documentation of informed consent process
- Evaluation of the infra-structure of the study site, focusing on the site personnel responsibilities
- Judging the PI for his/her commitment
- **Judging the PI for the concept of ethical considerations**

What have I learnt from audits?

Clinical Research/Trial

It is Not a

"Industry"



It is

Good Clinical Practice

- **What is GCP?**
  - A Set of Rules

- **Why we need the GCP?**
  - The clinician now is an investigators.
  - The patient now I an investigation subject.
  - A way to improve clinical practice

Common Problems in Clinical Research/Trial

- inform consent
- protocol adherence/deviation
- data inconsistency
- drug accountability
- Adverse events (experience)

AE

- **adverse event (or experience):**
  - **Any untoward medical occurrence** in a patient or a clinical investigation subject administered a treatment and which dose **not necessarily have a causal relationship with this treatment.**
- **adverse drug reaction (ADR):**
  - **reaction related to any dose**
- **serious adverse event (experience):**
  - **death**
  - **prolonged inpatient hospitalization**
  - **severe on permanent**
  - **life-threatening**
  - **cancer**
  - **overdose**
  - **congenital anomaly**

AE

- sources of AE:
  - progress note of doctors and nurses
  - diaries completed by study subjects
  - other assessment forms
  - indication for concomitant drugs
  - abnormal lab data
  - reasons for withdrawals and dropouts
  - miss visits

Tips for Evaluation of a Clinical study?

- **Records of AE: numbers, etc.**

Advises for protocol adherence/deviation

- communicate before the protocol signed
- strictly adhered to the protocol
- If deviation occurs → document it
  →inform the sponsor and the IRB

Documentation

- If you do it, document it.
- If you document it, do it.
- If it is not documented, it did not happen.

Auditing/Inspection: PI's Prospects

- direct access to
  - study medication storage
  - case record forms
  - central source documentation

Documentation

- 3 forms of document: Master file, Source document, Case record forms
- Source document should be original and were signed by research associates/doctors and PI..
- No wipe-out
- Records must be kept properly.
- Case record forms must be completed immediately/ASAP.

Tips for Evaluation of a Clinical study?

- **Records of AE: numbers, etc.**
- **Check on the source document**

Tips for Evaluation of a Clinical study

- **Records of AE: numbers, etc.**
- **Check on the source document**
- **Check on the master file**