# Clinical Trial Documentation


Module 6 Topic 5

# Trial Documentation

- Necessary for conduct of trial- From Scratch to Finish
- Examples:
  - Protocol
  - Investigator's Brochure
  - Informed Consent Document

# Definition of Protocol

"Written mechanism that describes how the study design will be implemented."

**Per ICH-GCP (1.44)**

"A document that describes the objectives, design, methodology, statistical considerations and organization of a trial. It also gives the background and the rationale for the trial."

# Why a protocol?

- Check if objectives can be achieved
- Check feasibility of the study
- Maintain standardization throughout the project
- Prevent failure to collect critical information
- Lay down rules
- Obtain approval from regulators and ethics committee
- Apply for funds
- Easier to write an article

# Drafting a Study Protocol

- TITLE
  - Short, Specific
  - Version and date
  - Phase of the study
  - Main area of interest
  - Broad objective included
- NAMES OF INVESTIGATORS
  - Principal investigator, Co-investigator
  - Sponsor
  - Addresses and contact details
- NAME OF THE INSTITUTION
  - Single center or multicentric study

# Drafting a study protocol

- TITLE :
  - A Phase IV study to compare the antihypertensive effects of ramipril compared to amlodipine as monotherapy in newly diagnosed patients with mild to moderate hypertension
  - Version Final 1, 1 January 2007
- NAMES OF INVESTIGATORS
  - Dr ABC (Principal investigator), Dr XYZ (Co-investigator)
  - Best Pharmaceuticals (Sponsor)
  - Addresses and contact details
- NAME OF THE INSTITUTION
  - Patient Well being Hospital, Mumbai

# Drafting a study protocol

- INTRODUCTION:
  - Synopsis of disease and pathogenesis
  - Review of literature related to study
  - Statement of the problem and study justification
    - Limitations in current knowledge or therapy
    - Why is study important?
    - What is it expected to change?
    - How study results will be useful for the medical community?

# Drafting a study protocol

- INTRODUCTION:
  - Importance of mild to moderate hypertension
  - How ACEI and CCBs work in brief?
  - Statement of the problem and study justification
    - No direct comparison study in development programmes
    - Any of the drugs used as first line therapy
    - Give us evidence on which drug to begin with as monotherapy

# Drafting a study protocol

- OBJECTIVES
  - Primary (Must evaluate)
    - What you actually desire to achieve
    - Dictates design and methods
    - Dictates sample size and power of the study
    - Main variable of analysis
  - Secondary (Good to evaluate)
    - What you would also like to achieve
    - May not dictate study design and methods

For achieving study objective, you MUST achieve primary objective, regardless of secondary objective

# Drafting a study protocol

- OBJECTIVES
  - Primary
    - BP lowering efficacy of amlodipine vs that of ramipril in newly diagnosed patients with mild to moderate hypertension
  - Secondary
    - Effect of amlodipine vs ramipril in reduction of systolic BP
    - Effect of amlodipine vs ramipril in reduction of ischemic cardiac events ( non fatal MI, unstable coronary artery disease, stable angina )
    - Effect of amlodipine vs ramipril on fasting blood sugar and glycosylated hemoglobin

# Drafting a study protocol

METHODOLOGY

Design of study

State:

- Survey: retrospective, current, prospective
- Experiment
- With control group or without control group
- Randomized or not randomized
- Parallel-group or crossover
- Open, single-blind or double-blind
- Interventional or non interventional

# Drafting a study protocol

- Disease definition
- Detailed schedule of examination preferably in assessment table
- Detailed schedule of intervention (if applicable)
- Follow up including period
  - Parameters to be checked in follow up
- Duration of study ( for individual and the total study)

# Drafting a study protocol

- Study population
  - Selection
  - Recruitment process
  - Inclusion and exclusion criteria ( Broad vs narrow)
  - Withdrawal
  - Number to be screened/recruited (Sample size)

# Drafting a study protocol

- Efficacy/ endpoints
  - Should be considered carefully to ensure they are both clinically meaningful and achievable within the limits of the trial design
  - Primary efficacy measure ( based on primary objective)
  - Secondary efficacy variables ( based on secondary objective)
- Efficacy analyses
- Safety analyses

# Drafting a study protocol

- Safety Reporting
  - Serious Adverse Events and other adverse events
  - Safety reporting responsibilities with details
  - Definitions of mild, moderate and severe AEs
  - Abnormal ophthalmological examination findings
  - Patient Discontinuations (All definitions)
    - Due to side effects
    - Due to worsening of disease

# Drafting a study protocol

- Data collection
  - How?
    - Questionnaire
    - Observation
    - Examination
  - By whom?
    - Interviewers – training
    - Ophthalmologist/ optometrists
    - Level of supervision

# Drafting a study protocol

- Statistical analysis plan
  - Prevents collection of unnecessary data
  - Avoids failure to collect crucial information
  - Better estimates of sample size for analysis of subgroups

# Protocol waiver vs violation

**Protocol waiver:**

Prospective,

requested by investigator and approved by medical monitor or clinician

Mainly based on I/E criteria

**Protocol deviation or violation:**

Retrospective

Found during monitoring etc

Based on I/E criteria, compliance, drug accountability etc

Violation is a severe deviation
(often safety concerns)

# Drafting a study protocol

- Appendices
  - Case report forms (not always mandatory)
  - Informed consent
  - Institutional review board approval (in the final trial master file)
  - Questionnaire (if applicable)
  - Declaration of Helsinki
  - Financial requirements
  - Legal contracts as deemed necessary
  - Common Terminology Criteria
  - Any other important document (study specific)

# Protocol Synopsis Template

| | |
|---|---|
| **Title:** | **Be as specific and descriptive as possible** |
| **Rationale:** | **State justification for the study** |
| **Objective:** | **State either as question(s) to be answered or as hypothesis to be tested** |
| **Setting:** | **State where the study will be done and by whom** |
| **Design:** | **survey or experiment; retrospective, cross-sectional or prospective; parallel-group or crossover; open, single-blind or double-blind; etc.** |
| **Patients:** | **State number and type of patients, with essential inclusion criteria** |
| **Interventions:** | **State what will be done, how, when, how often, how long, etc.** |
| **Outcome measures:** | **State what will be measured for efficacy and for safety** |
| **Data analysis plan:** | **State how the outcome measures will be analyzed and presented** |

# Investigator Brochure

- Basic document required in a clinical trial of a new drug
- Compiles the clinical and non-clinical data relevant to the study of the product in humans
- The pharmaceutical company sponsoring the study provides a copy to each principal investigator prior to the start of a clinical trial

# Contents

- a description of the drug substance and the formulation
- a summary of the pharmacological and toxicological effects,
- a summary of information relating to its safety and effectiveness in humans, and
- a description of possible risks and adverse reactions to be anticipated, and the precautions or special monitoring that the investigator should take

# IB for Phase-I

- Preclinical information about the pharmacological and toxicological effects
- Pharmacokinetics and biological disposition in animals

**IB for Phase II/III**

- In addition to the earlier data
- Information relating to safety and from prior clinical studies
- Possible risks and side effects to be anticipated on the basis of the sponsor's or others' prior experience with the drug under investigation or with related drugs

# IB for Phase -IV

- Need not be elaborate.
- Can be made available as  Summary of product characteristics (SPC) ,product information leaflet, package insert
- Should include current, comprehensive complete information on the product

# Contents as per IB

- Title page
- Table of contents
- Summary
- Introduction
- Confidentiality statement
- Physical, Chemical and Pharmaceutical properties and formulation

# Contents as per IB (contd)

- Non-clinical studies
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- Effect on humans
  - Pharmacokinetics
  - Efficacy
  - Safety
  - Marketing experience

# Introduction

- Investigational product's generic name/trade name
- Active ingredient
- Pharmacological class
- Expected indications and advantages
- Rationale for study and general approach to be followed while evaluating the product

# Physical, Chemical, Pharmaceutical properties

- Chemical /structural formulae
- Analytical data
- Physical ,chemical pharmaceutical properties
- Formulation, stability
- Storage and handling conditions to be followed
- Any structural similarities with an existing product

# Non clinical studies

- Summary of pharmacological, toxicological and pharmacokinetic data obtained
- Methods used, results and discussion of the findings relevant to understand the unexpected and unintended effects in humans; preferably in a tabular format
- Pharmacodynamics, dose response studies therapeutic index, MTD etc must be explained clearly
- Marketing experience on dose route of administration, adverse drug reactions should be provided
- Names of countries where approval is obtained and countries where not obtained also to be provided

# Effect on humans

- Dose determination in humans
- Bioavailability
- Effects on special groups
- Kinetics in special groups
- Safety –information on all the AE observed so far, in different population, in all the trials conducted on the product should be included
- Special monitoring to be done on the product

# Informed Consent Form

**Guidance for Information sheets for adults**

- The level of detail should be appropriate to the nature of the study and the population to be studied
- Concern about Information Sheets (IS) are becoming lengthy and complex for recruitment purposes
- So, its recommended that, the IS divided into Part 1 and Part 2

# Part 1:

- What the research is about?
- The condition or treatment under study
- Voluntary nature of involvement
- What will happen to the participant during and after the trial?
- What usual treatment may be withheld?
- Participant's responsibilities
- Potential risks

# Part 2:

- Confidentiality and data protection
- Communication with the GP
- Indemnity and compensation
- Publication, etc.
- Which should be read and understood before the participant can decide whether they want to take part and give informed consent

# Language Used:

- Simple, non-technical terms
- Easily understood
- Short words, sentences and paragraphs with clear subheadings
- Manageable text & font size
- Bullet pointed lists used where instead of unbroken text
- Invitational tone instead of overly persuasive

# IS For Competent Adults: Part 1:

- Study title.
- Invitation paragraph.
  - "You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve
  - Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part."

# IS For Competent Adults: Part 1: (contd)

- What is the purpose of the study?
- Why have I been chosen?
- Do I have to take part?
  - "It is up to you to decide whether or not to take part.
  - If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.
    If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive."

# IS For Competent Adults: Part 1: (contd)

- What will happen to me if I take part? Expenses and payments
  - how long the participant will be involved in the research,
  - how long the research will last
  - how often they will need to visit a clinic or their surgery how long these visits will be.
  - what exactly will happen e.g. blood tests, x-rays, interviews etc.

# IS For Competent Adults: Part 1: (contd)

- Randomised Trial.
- Blind trial.
- Cross-over trial.
- Placebo.
  - Study involving video-/ audio-taping or photography.
  - Specify if expenses (e.g. travel, meals, child-care, compensation for loss of earnings, etc.) are available.
  - Whether any vouchers, gifts, etc, which you are intending to give as a 'thank-you' for participation.
  - Arrangements for any other payment.

# IS For Competent Adults: Part 1: (contd)

- What do I have to do?
- What is the drug, device or procedure that is being tested?
- What are the alternatives for diagnosis or treatment?
- What are the side effects of any treatment received when taking part?

# IS For Competent Adults: Part 1: (contd)

- What are the other possible disadvantages and risks of taking part?
- What are the possible benefits of taking part?
- What happens when the research study stops?
- What if there is a problem?
- Will my taking part in the study be kept confidential?
- Contact Details.

# Part 2 :

- What if relevant new information becomes available?

'Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue.

# Part 2 : (contd)

- What will happen if I don't want to carry on with the study?

'You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish'.

  - If you decide to continue in the study you will be asked to sign an updated consent form
  - Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue
  - If the study is stopped for any other reason, you will be told why and your continuing care will be arranged

# Part 2 : (contd)

- What if there is a problem?

**Complaints:**

‘If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number of PI as well as EC member secretary and chairperson).

# Part 2 : (contd)

- Will my taking part in this study be kept confidential?
  - ‘All information which is collected about you during the course of the research will be kept strictly confidential. If applicable: Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.’

# Part 2 : (contd)

- What will happen to any samples I give?
- Will any genetic tests be done?
- What will happen to the results of the research study?
- Who is organising and funding the research?
- Who has reviewed the study?
- should state that the patient will be given a copy and a signed consent form to keep.
- thank your participant for or taking time to read this sheet.

# General comments on information for children (minors) and young people

- When designing information sheets for children, researchers need to consider their
  - likely attention span
  - potential fear of hospitals/procedures
  - mental capacity if affected by disease
  - disease severity
  - previous experience of illness (some children have greater knowledge as the result of long term illness e.g. cystic fibrosis).
  - It is important to give information about how the study will affect the child at home, school and his/her social activities

# IS for children aged

**13 to 15**

- Study title
- What is research?
- Why is this project being done?
- Invitation to take part. Why have I been asked to take part
- Did anyone else check the study is OK to do?

**6 to 12**

- Study title
- Invitation paragraph
- Why are we doing this research?
- What is the medicine, device or procedure that is being tested?
- Why have I been asked to take part?