Clinical Trial protocol and Investigator's Brochure

Dr. Nirmala Wijekoon

MBBS, MD, MRCP(UK), FRCP(Lond) FRCP(Edin) FCCP

- Clinical Trial Protocol – describes the study

- Investigators Brochure
  – describes the Investigational Product (IP)

Ethical considerations relating to clinical trials

- Is the trial capable of producing credible data?
- Are the rights, safety and wellbeing of participants ensured at each step ?

Clinical Trial protocol

About the study

Why
What
When
How

Trial Protocol - Contents

- General Information
- Synopsis / Summary
- Background Information
- Trial Objectives and Purpose
- Trial Design

  Selection & Withdrawal of subjects

  Treatment of Subjects

  Assessment of Efficacy

  Assessment of Safety

- Statistics
- Access to Source Data / Documents
- Quality Control and Quality Assurance
- Ethics
- Data handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements

Trial Protocol - Contents

- In multicenter trials - site specific information

on a separate protocol page

Trial Protocol - Contents

General Information

- Protocol title, protocol code, version and date

- Details (name, title, address, telephone numbers) of
  - sponsor / monitor (if other than the sponsor)
  - persons authorized to sign for the sponsor
  - sponsor's medical expert for the trial
  - investigators responsible for conducting the trial and taking trial-site related medical decisions
  - clinical laboratories and other technical departments / institutions involved in the trial
  - members of Data and Safety Monitoring Board (DSMB)

Trial Protocol - Contents

Synopsis / Summary

- Trial name
- Objective
- Trial design
- Study population – sample size
  inclusion / exclusion criteria
- Trial treatments
- Trial duration
- Outcome measures

maximum 2 pages

Trial Protocol - Contents

Background Information

- Name and description of the investigational product (IP)
- Summary of relevant findings from nonclinical and clinical studies
  - known and potential risks and benefits, to human subjects
  - justification for the route of administration, dosage, dosage regimen, and treatment period

  - extract from Investigator's Brochure –
- References to literature that provide background for the trial
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements

Trial Protocol - Contents

Trial Objectives and Purpose

A detailed description including : intervention

outcome

study population

non-inferiority *vs* equivalence *vs* superiority

eg. The primary objective of this study is to determine non-inferiority of the treatment with XY123 10mg BD versus AB321 10mg BD on cardiovascular deaths in adults with type 2 diabetes mellitus

To test the hypothesis that PQR 500mg daily is superior to placebo in improving functional outcome in patients with ischaemic stroke of intermediate severity

Trial Protocol - Contents

superiority

aims to show that the test product is better than the comparator (placebo/ active)

non-inferiority

aims to show that the test product is not worse than the active comparator by more than a small pre-specified amount. This amount is known as the non-inferiority margin, or delta

equivalence (most often bioequivalence)

aims to show that the test product is neither better nor worse than the comparator

Trial Protocol - Contents

Trial Design

credibility of the data from the trial depends on trial design

- Type / design of trial - IS IT APPROPRIATE ??
  - Phase I,II or III
  - Controlled / not controlled

    what is the control ? placebo / active comparator
  - Randomized / non-randomised
  - Double-blind / Single-blind / Not blinded
  - Parallel / crossover / factorial design

measures taken to minimize bias - randomization
- blinding

Trial Protocol - Contents

Selection and withdrawal of subjects

- Selection - inclusion criteria
  exclusion criteria

- Method of recruitment

- Subject withdrawal criteria
  - when and how to withdraw subjects from the trial treatment
  - type and timing of the data to be collected for withdrawn subjects
  - follow-up for withdrawn subjects

Trial Protocol - Contents

Treatment of subjects

- treatments to be administered - investigational product (IP)
  - placebo / active comparator

  names, doses, dosing schedule, the route/mode of administration, packaging and labelling, storage, treatment period

- concomitant therapy - medications permitted and not permitted
  - rescue medication

- procedures for monitoring subject compliance

  eg. self-maintained medication diary, counting tablets

  drug compliance chart maintained by the investigators

Trial Protocol - Contents

Assessment of efficacy

- efficacy parameters / outcomes / end points
- methods and timing for assessing

Eg. To test the hypothesis that PQR 500mg daily is superior to placebo in improving functional outcome in patients with ischaemic stroke of intermediate severity

Primary efficacy outcome is modified Rankin Scale grade at Day 90 (± 1 week)

Secondary efficacy outcomes

NIHSS score at Day 90 (± 1 week)

NIHSS score at Day 10 (± 2 days)

Barthel Index at Day 90 (± 1 week)

Trial Protocol - Contents

Assessment of safety

- safety parameters / outcomes / end points
- methods and timing for assessing

    Eg. neurological deterioration (assessed with NIHSS score) at Day 7

    death at Day 7

    death at Day 90

    total number of SAEs by Day 90

Trial Protocol - Contents

Assessment of safety…….

- Expected adverse effects and their management
- Procedures for recording and reporting AE / SAE / SUSARs
- type and duration of the follow-up of subjects after adverse events

Trial Protocol - Contents

Trial Design…..

- duration of subject participation, including screening & follow-up

- a schematic diagram of trial design, procedures and stages

  what will be done: at screening visit

  at recruitment visit

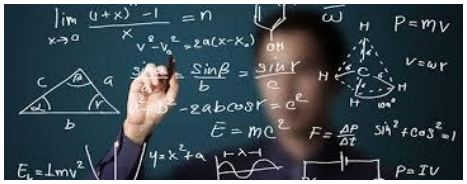
  at each follow up visit

  clinical assessments, questionnaires, investigations

Trial Protocol - Contents

Trial Design…..

- "stopping rules" for the trial
- accountability procedures for the IP and comparator
- maintenance of trial treatment randomization codes
  procedures for breaking codes
- identification of data to be recorded directly on the CRFs
  (i.e. no source data)
- If blood / biological samples are collected storage, transport and
  destruction



Trial Protocol - Contents

Statistics

- sample size calculation, including the power of the trial and clinical justification

  in multicentre trials, the numbers of subjects projected for each trial site should be specified

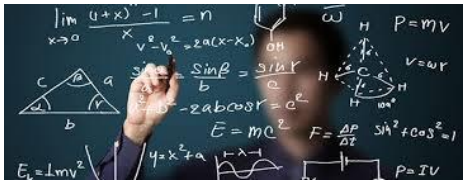
- method of analysis – 'intention to treat' vs 'per-protocol'

- statistical methods to be employed

  detailed description related to each efficacy and safety outcome

  categorical vs numerical; statistical tests; level of significance

- sub-group analyses planned



Trial Protocol - Contents

Statistics….

- timing of any planned interim analyses (done by DSMB)
  criteria for the termination of the trial

- procedure for accounting for missing, unused and spurious data

- procedures and justification for reporting any deviations from the original statistical plan

Trial Protocol - Contents

Direct Access to Source Data / Documents

- specify that the investigators/institutions will permit and provide direct access to source data/documents for

  - trial-related monitoring and audits
  - IRB/IEC review
  - regulatory inspections

Trial Protocol - Contents

Quality Control and Quality Assurance

- adherence to GCP standards
- adherence to GMP standards
- accreditation of laboratories
- trial monitoring / audits

Trial Protocol - Contents

Data Handling and Record Keeping

Case Report Forms (CRF), source documents, logs, communications with ERCs/regulatory bodies

Archiving

Trial Protocol - Contents

Ethics

ethical considerations relating to the trial

- Is the trial capable of producing credible data?
- Are the rights and safety of participants ensured at each step ?

Trial Protocol - Contents

Ethics

ethical considerations relating to the trial

- Is the trial capable of producing credible data?
- Are the rights and safety of participants ensured at each step ?
  - Subject Informed Consent
  - Confidentiality
- Ethics Approval - for each site separately
  - for each protocol amendment

Trial Protocol - Contents

Financing and Insurance

- payments to participants if any
- appropriate insurance (as per each country's regulatory requirements) for coverage of the patients' extra-care costs and to indemnify them for any harm caused by the trial

Publication Policy

- Writing committee
- Authorship
- Local publications

Trial Protocol - Contents

Supplements

- CRFs
- Assessment tools eg. mRS, MMSE, SF-36
- List of protocol deviations / violations
- Medication diary etc.
- Advertisements

Investigator’s Brochure

About the Investigational Product (IP)

Investigator's Brochure

- Non-clinical and clinical data
- Provides rationale for content in protocol
- The information should be - concise
  - simple
  - objective
  - balanced
  - non-promotional

  enables unbiased risk-benefit assessment

Investigator's Brochure

- type and extent of information available will vary with the stage of development

- extensive IB may not be necessary if the IP is marketed

  a basic product information brochure, package leaflet, or labelling may be an appropriate alternative

- if a marketed product is being studied for a new indication, an IB specific to that new use is needed

- IB should be up to date; reviewed at least annually

Investigator's Brochure

- Title page
- Confidentiality Statement (optional)
- Summary
- Introduction
- Physical, Chemical, and Pharmaceutical Properties and Formulation
- Nonclinical Studies
- Clinical studies (effects in humans)
- Summary of Data and Guidance for the Investigator

- References on publications and reports at the end of each chapter

Investigator's Brochure

Title page

Trial Name:
Sponsor's Name:

Product: XY 1234
Research Number /protocol code: SQR05
Name(s): Chemical
Generic (if approved) :
Trade Name(s) (if legally permissible)

Edition Number: version 2.0
Release Date: 9 October 2015

Replaces Previous Edition Number: version1.9
Date: 7 October 2014

Investigator's Brochure

- Chemical name: scientific name based on the chemical structure
- Generic (nonproprietary) name: nationally /internationally agreed name
- Trade Name: name given by the pharmaceutical company

eg. N-acetyl-p-aminophenol
paracetamol / acetaminophen (US, Japan)
panadol

Investigator's Brochure

Confidentiality Statement (optional)

- a statement instructing the investigator/recipients to treat the IB as a confidential document

Investigator's Brochure

Summary

- highlighting the significant physical, chemical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development

max. 2 pages

Investigator's Brochure

Introduction

- chemical name (generic and trade name when approved) of IP
- all active ingredients of IP
- pharmacological class of IP and compare with other drugs in the class (e.g. advantages)
- the rationale for performing research with IP
- anticipated indication (clinical use)
- general approach to be followed in evaluating IP

Investigator's Brochure

Physical, Chemical, and Pharmaceutical Properties and Formulation

- chemical formula
- relevant physical, chemical and pharmaceutical properties
- a description of the formulation to be used, including excipients (along with justification)
- instructions for the storage and handling
- any structural similarities to other known compounds

Investigator's Brochure

Nonclinical studies (animal studies)

Individual studies

Methodology

species tested / number and sex of animals in each group
unit dose (eg. mg/kg) / dose interval / route of administration
duration of dosing / information on systemic distribution
duration of post-exposure follow-up

Results

- nature, frequency, severity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- Dose response

Discussion

relevance of the findings to the therapeutic and the possible unfavourable effects in humans

Investigator's Brochure

Nonclinical studies (animal studies).....

Summary & discussion of the important findings of **all** animal studies

- pharmacodynamics

- potential therapeutic activity
- actions other than intended therapeutic activity (safety)

- pharmacokinetics

- pharmacokinetics in all species studied
- their relationship to the pharmacological and toxicological findings in animals

- toxicology

- Carcinogenicity
- Reproductive toxicity
- Genotoxicity (mutagenicity)

single dose and repeated dose studies

Investigator's Brochure

Clinical studies (effects in humans)

- Introduction:

  a discussion of the known effects of the IP in humans

- A summary of each completed clinical trial

- A summary and discussion based on all preceding clinical trials

  - pharmacokinetics of IP
  - safety and efficacy of IP
  - marketing experience (if available)

Investigator's Brochure

Clinical studies (effects in humans).....

Marketing Experience

- countries where the IP has been marketed or approved
- all the countries where the IP did not receive approval/registration for marketing or was withdrawn
- any significant information arising from the marketed use
  e.g. formulations, dosages, routes of administration, ADR

Investigator's Brochure

Summary of Data and Guidance for the Investigator

an overall discussion of the non-clinical and clinical data

AIM: to provide investigators with

- most informative interpretation of the available data
- understanding of anticipated ADR or other risks and precautions needed for a clinical trial
- guidance on recognition and treatment of possible overdose and ADR based on previous experience

References

- **ICH HARMONISED TRIPARTITE GUIDELINE - GUIDELINE FOR GOOD CLINICAL PRACTICE: E6(R1)** *Step 4* version dated 10 June 1996 *(including the Post Step 4 corrections)*

  The final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA

- INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE.**ICH HARMONISED GUIDELINE INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2)** *Step 2* version dated 11 June 2015

Thank you