

Clinical Trial protocol and Investigator's Brochure

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- Clinical Trial Protocol – describes the study
- Investigators Brochure
 - describes the Investigational Product (IP)

Clinical Trial protocol

About the study

Why

What

When

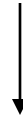
How

Trial Protocol - Contents

- General Information
- Synopsis / Summary
- Background Information
- Trial Objectives and Purpose
- Trial Design
- Selection and 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)
- References to literature that provide background for the trial
- 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 –
- 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 patients 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 trial

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

non-inferiority trial

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 trial

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

- the type/design of trial (e.g. randomized, blinding, placebo-controlled, parallel vs crossover, factorial design, phase I,II or III)
- measures taken to minimize bias
 - randomization
 - blinding

Trial Protocol - Contents

Trial Design

- trial treatments
- duration of subject participation, including screening & follow-up
- primary and secondary endpoints
- a schematic diagram of trial design, procedures and stages

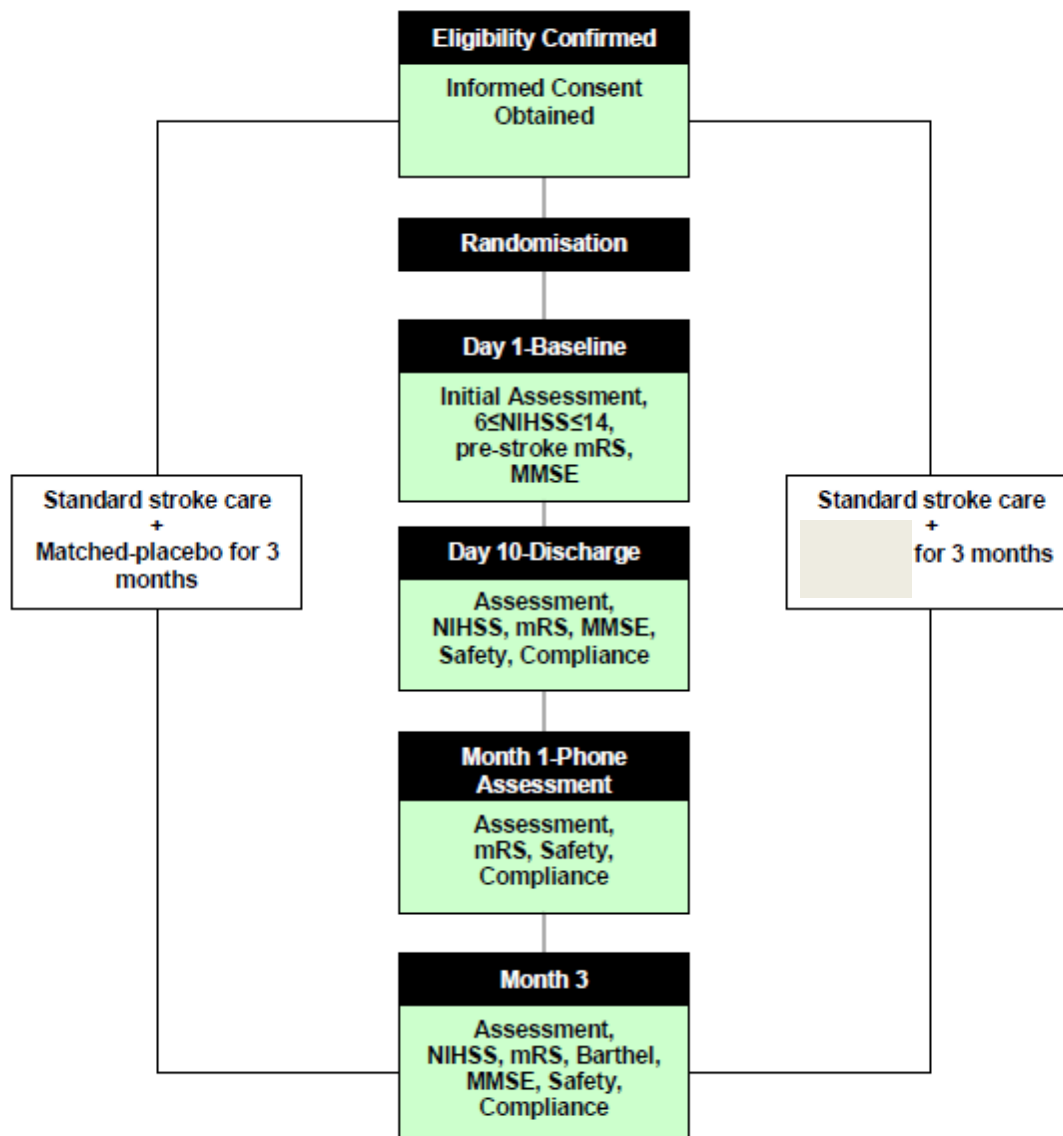
what will be done: at screening visit

at recruitment visit

at each follow up visit

clinical assessments, questionnaires, investigations

If blood / biological samples are collected storage, transport and destruction



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)

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 / comparatornames, 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 (\pm 1 week)

Secondary efficacy outcomes

NIHSS score at Day 90 (\pm 1 week)

NIHSS score at Day 10 (\pm 2 days)

Barthel Index at Day 90 (\pm 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



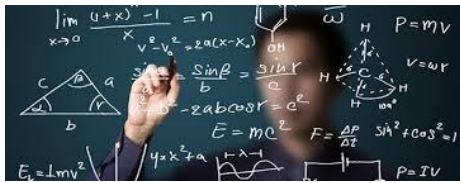
Statistics

- 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
- 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

- Ethics Approval – for each site separately
- Subject Informed Consent
- Confidentiality
- Protocol amendments

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

- Clinical and non-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
- Effects in Humans (clinical studies)
- 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: version 1.9

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 most important findings

- 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

Effects in Humans (clinical studies)

Introduction:

- a discussion of the known effects of the IP in humans
pharmacokinetics / pharmacodynamics / dose response / safety /
efficacy / other pharmacological activities
- a summary of each completed clinical trial



Investigator's Brochure

Effects in Humans (clinical studies)

Pharmacokinetics

A summary of :

- all pharmacokinetic aspects
- bioavailability using a reference dosage form
- population subgroups
(e.g., gender, age, and impaired organ function)
- interactions



Investigator's Brochure

Effects in Humans (clinical studies).....

Safety and Efficacy

- A summary and discussion of :
 - pharmacodynamics, efficacy, safety and dose response obtained from preceding trials (healthy volunteers and/or patients)
- adverse drug reactions (ADR)
 - ADR for all the clinical trials (including those for all the studied indications)
 - important differences in ADR patterns/incidences across indications / subgroups
 - possible risks and ADR to be anticipated on the basis of prior experiences
 - precautions or special monitoring to be done during the proposed trial



Investigator's Brochure

Effects in Humans (clinical studies).....

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 nonclinical 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)** Current *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)** Current *Step 2* version dated 11 June 2015

Thank you