Research Protocol in Clinical Trials

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Introduction

- Standardization — everyone doing the same things in the same way — critical in a clinical research study, particularly for multisite trials
- Research that is not conducted in a standardized manner is unethical
  - research participants at risk
  - invalid data

Introduction

Several key documents

- Investigator's Brochure
- Operations manual
- Standard operating procedures (SOPs)
- Research protocol

Research Protocol

- a plan for the essential aspects of the proposed research
- must be approved by the designated IRB/ ERC
- any changes to the protocol
- ICH GCP guidelines — a research protocol for any study that involves human participants

Contents

- Why the study is being done
- What will be done in the study
- Where the study will be done
- Who is involved in the research study
- When study interventions will take place

Enough information to provide a clear and complete, but not overly detailed, description of the study

General information

- Protocol title, identifying number, version number, date
- Name and address of the sponsor and monitor
- Names and titles of the investigators responsible for conducting the study (address and telephone number of the trial sites)
- Name, title, address, and telephone number of the qualified physician who is responsible for all study-related medical decisions
- Names and addresses of all institutions involved in the study

Background information

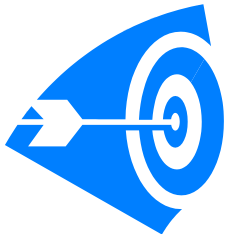
- A description of the issue the study is addressing (public health significance)
- Findings from preclinical or clinical studies that may be significant to the proposed study
- Summary of the known potential risks and benefits to human participants
- Description of the study population
- A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

Background information

- References to relevant literature and data
- Name and description of the investigational product or therapy
- Route of administration, dosage, dosage regimen and treatment period(s)

Study objectives

- Primary objective
  - either efficacy or safety
  - will dictate primary end-point
- Secondary objectives
  - secondary end-points



Study design

- Primary and secondary endpoints
- Study type
  - double-blind
  - placebo-controlled
  - parallel group
- Measures to avoid or minimize bias
  - randomization
  - blinding
- Dosage, dosage regimen, dosage form, packaging, and labeling of investigational products

Study design

- Expected duration of participant participation
- Sequence and duration of all study visits including follow-up
- Stopping rules or discontinuation criteria
- Maintenance of study treatment randomization codes and procedures for breaking codes
- Identification of any data to be recorded directly on the CRFs

Participant selection and withdrawal

- Inclusion criteria
- Exclusion criteria
- Withdrawal criteria:
  - When and how to withdraw participants
  - Type and timing of data to be collected for withdrawn participants
  - Whether and how participants are to be replaced

Treatment of subjects

- Names of all products to be administered (each arm)
- Doses
- Dosing schedules
- Route of administration
- Treatment period including follow-up
- Other medications or treatments permitted (including rescue medication) and not permitted

Assessment of Efficacy

- Specification of the efficacy parameters
- Methods and timing for assessing, recording, and analyzing efficacy parameters

Assessment of safety

- Specification of safety parameters
- Methods and timing for assessing, recording, and analyzing the safety parameters
- Procedures for obtaining, recording and reporting AEs
- Type and duration of follow-up of participants after AEs

Statistics

- Statistical methods
- Timing of any planned interim analyses
- Total number of participants to be enrolled (also for each study site)
- Reason for the choice of sample size
  - primary end-point measurement
  - superiority/ non-inferiority
  - clinical justification

Statistics

- Level of significance
- Criteria for termination of the study
- Procedures for reporting deviations from the statistical plan
- Selection of participants included in analyses
  - all randomized subjects
  - all treated subjects
  - protocol-compliant subjects

Direct Access to Source Data

- Study investigators or institutions will permit study–related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/ documents
- In protocol or other written agreement

Quality Assurance

- usually submitted as a separate document
- The protocol should provide a general description of the quality assurance methods.

Ethics

- Ethical considerations relating to the study
- Measures taken to protect human participants and to maintain confidentiality of study data

Data Management

- A detailed data management plan
  - how study data will be gathered, documented, submitted, verified and archived
- usually as a separate document
- The protocol should provide a general description of the data management activities

Financing and Insurance

- How the study will be financed and insured
- Can be addressed in a separate agreement

Publication Plan

- Institutional and sponsor requirements/ policies for publication
- Public website (ClinicalTrials.gov) – a resource for clinical trial participants

Supplements

- Informed consent form
- Patient information handbook
- Quality assurance plan
- Training plan etc.

Protocol Amendment

- a written description of a change to some aspect of the study as described in research protocol
- must be approved by the IRB
- Exceptions:
  - immediate hazards to the participants
  - only administrative aspects (change of monitor, telephone number)
- FDA

Protocol Amendment

- Study participants informed of protocol amendments
- ICF may be revised and participants will need to sign a new ICF

Protocol Violation

- Whenever any study staff member performs any action that does not adhere to the description in research protocol
- An omission/ an addition/ a change in any procedure
- Each violation and the action taken to correct the situation – documented and reported to IRB
- Repeated protocol violations – a need for
  - additional staff training
  - a protocol amendment

Summary of Key Points

- Standardization is critical in a clinical research study. Research that is not conducted in a standardized manner is unethical because it may put research *participants at risk* while yielding *invalid data*.
- All research staff involved in a clinical study must be familiar with, and must strictly adhere to, the procedures described in the research protocol.

Summary of Key Points

- The research protocol – one of the main documents that must be approved by a designated IRB before a research study can begin
- ICH GCP guidelines – a research protocol for any study that involves human participants

Sources

- ICH Harmonised Guideline. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), March 2018
- Key Elements of a Clinical Research Protocol (9/2010) Compiled from NIH Guidelines and ICH/GCP Guidelines
- The Research Protocol. Good Clinical Practice. National Drug Abuse Treatment Clinical Trials Network (https://gcp.nidatraining.org/modules/6)
- Tips on clinical trials. Maha Al-Farhan. Association of Clinical Research Professionals, USA

THANK YOU