CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

PROTOCOLS

Guidance/Regulation References:

- Good Clinical Practice: Consolidated Guidance (ICH-E6), Section 6, Clinical Trial Protocol and Protocol Amendment(s)
- Good Clinical Practice: Consolidated Guidance (ICH-E6), Section 4.5, Compliance with Protocol
- European Regulation on Clinical Trials coming into effect in 2016 Appendix 1 part D §16 and 17

PROTOCOL

GCP DEFINITION OF A PROTOCOL:

"A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial."

(GCP 1.44)

Table 1. Clinical Trial Protocol Contents, adapted from ICH Guideline for Good Clinical Practice[7]

1. Identifying Data
2. Brief Trial Summary
3. Background Information
4. Detailed Statement of Trial Objectives and Purpose
5. Trial Design
6. Selection and Withdrawal of Subjects
7. Assessment of Efficacy
8. Assessment of Safety Including Reporting to Regulatory Bodies
9. Statistical Considerations
10. Data Monitoring Consideration
11. Quality Control and Assurance
12. Ethical Considerations
13. Finance and Liability*
14. Publication Policy
15. Patient Information and Consent Form
16. Relevant Appendices: References, etc.

**Financial details in the form of specific budgets are not uniformly included in protocols. Generally, this may refer to the financial responsibilities of the sponsor.*

In the countries where the GCP is enforced by law, the protocol is a document of mixed nature.

In fact, it contains different elements:

- explanations (study background, choice of the experimental design, etc.)
- instructions (flow-charts, execution of standard clinical examinations, calculation of an index, etc.)
- mandatory declarations (respect of GCP, acceptance of audit and inspections, compliance with Helsinki declaration, etc)

In most countries the protocol is a legal document, because only the respect of the protocol guarantees the coverage of study insurance in case of incident for the patient.

PROTOCOL CONTENTS

A trial protocol should include:

- General Information
- Background Information
- Trial Objectives and Purpose
- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects

PROTOCOL CONTENTS

- Assessment of Efficacy
- Assessment of Safety
- Statistics
- Direct Access to Source Data/Documents
- Quality Control and Quality Assurance
- Ethics

PROTOCOL CONTENTS

- Data Handling and Record Keeping
- Financing and Insurance (if not addressed in a separate agreement)
- Publication Policy (if not addressed in a separate agreement)
- Supplements

GENERAL INFORMATION

The general information that should be included in a trial protocol are:

- Protocol title

  "A Phase I, Dose-Escalating, and Pharmacokinetic, Single-Center Study of ABC123, Administered Intravenously Twice Weekly for 4 Weeks, Followed by a 2-Week Rest, to Patients With All Advanced Solid Tumor Malignancies"

GENERAL INFORMATION

- Protocol Identifying Number
- Date (and version)

- **Names, titles, and addresses of**
  - Sponsor and monitors, if different.
  - Person authorized to sign protocol and protocol amendments for sponsor.
  - Sponsor's medical expert.

GENERAL INFORMATION

- **Names, titles, and addresses of (cont):**
  - Investigator(s) responsible for conducting the trial.
  - Trial site(s).
  - Qualified physician who is responsible for all trial-related medical decisions, if different than investigator.
  - Clinical lab(s) and other medical and/or technical department(s).

BACKGROUND INFORMATION

The background information that should be included in a trial protocol are:

- Name and description of the investigational product(s).
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

BACKGROUND INFORMATION

- Summary of the known and potential risks and benefits, if any, to human subjects.
- Description of and justification for, the route of administration, dosage, dosage regimen, and treatment period(s)
- Statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s)
- Description of the population to be studied.

TRIAL DESIGN

The description of the trial design should include:

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted.

TRIAL DESIGN

- A schematic diagram of trial design, procedures, and stages.
- A description of the measures taken to minimize/avoid bias.
- A description of the trial treatment(s)/intervention(s).
- A description of the dosage and dosage regimen of the investigational product(s).

TRIAL DESIGN

- The expected duration of subject participation.
- A description of the “stopping rules” or “discontinuation criteria”.

- Accountability procedures for the investigational product(s).
- Maintenance of trial treatment randomization codes and procedures for breaking codes.

STUDY POPULATION

The trial protocol should include:

- Subject inclusion criteria
- Subject exclusion criteria
- Subject withdrawal criteria

STUDY POPULATION

Procedures for subject withdrawal should specify:

- When and how to withdraw subjects?
- What is the type and timing of the data to be collected for withdrawn subjects?
- Are subjects replaced? If so, how?
- What is the follow-up, if any, for subjects withdrawn?

TREATMENT OF SUBJECTS

The trial protocol should include:

- The treatment(s) to be administered.

- Medication(s)/treatment(s) permitted and not permitted before and/or during the trial.
- Procedures for monitoring subject compliance.

EFFICACY

The trial protocol should include:

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

SAFETY

The trial protocol should include:

- Specification of safety parameters.
- Procedures for eliciting reports and for recording and reporting adverse event and intercurrent illnesses.
- Methods and timing for assessing, recording and analyzing safety parameters
- Type and duration of the follow-up of subjects after adverse events

STATISTICS

The trial protocol should include:

- The statistical methods to be employed.
- The number of subjects planned to be enrolled.
- The selection of subjects to be included in the analyses.
- The level of significance to be used.

STATISTICS

- Criteria for the termination of the trial.
- Procedure for accounting for missing, and unused data.
- Procedure for reporting any deviation(s) from the original statistical plan.

CONTENTS

The trial protocol should include:

- QC and QA procedures.
- Ethical considerations relating to the trial.
- Data handling and recordkeeping.
- Supplements, if applicable.
- Financing and insurance.
- Publication policy.

PROTOCOL AMENDMENTS

A protocol cannot be changed without a formal amendment.

GCP DEFINITION OF A PROTOCOL AMENDMENT:

A written description of a change(s) to or

formal clarification of a protocol.

(GCP 1.45)

CASE REPORT FORM (CRF)

Document prepared to record all information required by the protocol and related to each subject included in the clinical study to be transmitted to the Sponsor

It’s the investigator (principal and/or co-investigator) to enter the data into the CRF (either paper or electronic).

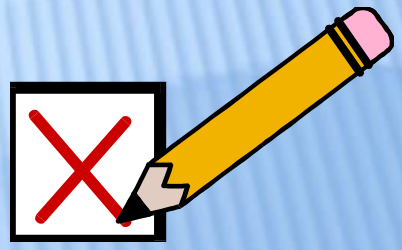
In every clinical study, these data can be the results of instrumental examinations, laboratory analyses, instant measures taken from instruments like blood pressure, weight, subjective assessments given by patients (severity of pain, general conditions), diaries filled in by patients …

CRFs provide data for the statistical analysis

- this analysis describes the results of the study
- these results are correct only if generated from the “right” data, that is data without errors and inconsistencies

CARACTERISTICS

- The CRF should perfectly reflect the approved protocol



- It is generally prepared and provided by the Sponsor

- The instructions for the correct way to enter the data should be available

CONTENTS 1/4

CRF is organised by sections.

1. Identification of the study and of the patient

The 1st section is generally the description of patient's medical history, the confirmation of inclusion/exclusion criteria, the diagnosis of the disease subject of the study, the date of giving informed consent.

After this, there are as many sections as many visits are foreseen by the protocol.

CONTENTS 2/4

CRF is organised by sections.

2. Identification of the study visits and data to be recorded

The section containing the information collected at each study visit has all the spaces required to record primary and secondary end-points, safety elements such as laboratory and presence/absence of adverse events, other information as drug compliance, diaries returned by patients, etc.

CONTENTS 3/4

CRF is organised by sections.

3. Study termination

The last section is organised to record study conclusion or premature interruption with relevant reason and all information regarding the end of the study as foreseen by the protocol.

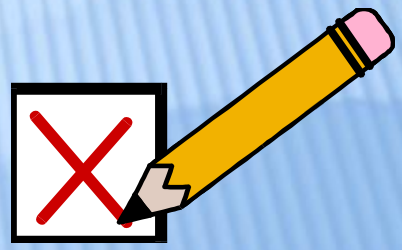
CONTENTS 4/4

CRF is organised by sections.

4. All pages

All pages are marked with code or name of the study, patient's initials or code and all the other identification elements permitting to identify each single page (or screen in case of eCRF) and to attribute it to a given patient at a given date of visit.

The right way to enter data into the CRF:



- ✓ Just after having visited the subject
- ✓ If on paper, data must be legible and complete
- ✓ Data must be taken by source document

CRF:

CORRECTION OF DATA

Corrections must not obscure previous data, must be explained, dated and signed (**audit trail concept**)