Protocol, CRF, ICF, IB

Protocol

- A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study.

Parts of the Protocol

- Introduction/Abstract
- Objectives (including study schema)
- Background/Rationale
- Eligibility criteria
- Study design/methods (including drug/device info)
- Safety/adverse events
- Regulatory guidance
- Statistical section (including analysis and monitoring)
- Human subjects protection/informed consent

Protomechanics: Chapter 1 (http://www.cc.nih.gov/ccc/protomechanics/),

CTEP Investigators' Handbook, 2002 (http://ctep.cancer.gov/forms/Hndbk.pdf)

Elements

- Title: identifying number, version and date, amendments if any
- Name , title and contact details as applicable for
  - sponsor and monitor
  - person authorized to sign the protocol and amendments- sponsor's medical expert
  - investigator responsible for conducting the trial
  - physician responsible for trial site related decisions.
  - clinical laboratory involved
  - Statement assuring compliance with ICH – GCP and applicable regulatory requirements

Background and Rationale

- All protocols require a section detailing the scientific rationale for a protocol and the justification in medical and scientific literature for the hypothesis being proposed.
- Introductory section should be as succinct as possible and should be organized in a logical, sequential flow.
- Double check all citations:
  - "Bibliographic inaccuracies harm the citing author and may cast doubt on the quality of the research being reported…"

Wyles DF, Behavioral and Social Sciences Librarian, 2004

Objectives

- Objectives should be stated clearly as hypotheses to be tested.
- Each objective should have a corresponding discussion in the statistical section.

CTEP Investigators' Handbook, 2002 (http://ctep.cancer.gov/handbook/index.html)

Writing Eligibility Criteria

- Eligibility criteria—stated as either exclusion or inclusion criteria—define and limit the kinds of patients that can participate in a clinical trial.
- Reasons for imposing eligibility criteria can include scientific rationales, safety concerns, regulatory issues, and practical considerations.[3]
- Eligibility criteria are the largest barrier to accrual to clinical trials.[1]
- Poorly written or poorly conceived criteria may undermine a trial's generalizability and scientific validity.[2]

[1]Fuks A, J Clin Epidemiol, 1998
[2]George SL, J Clin Oncol, 1996

3 George SL, J Clin Oncol, 1996

Writing Eligibility Criteria

- Problems with restrictive criteria:
  - Limitations of generalizability
  - Failure to mimic clinical practice
  - Increased study complexity
  - Increased costs
  - Decreased patient accrual
- Recommendations:
  - Keep # of eligibility criteria to a minimum.
  - Include only those absolutely necessary to ensure scientific validity and patient safety.
  - Eligibility criteria should be clearly defined and verifiable by an external auditor.

George SL, J Clin Oncol, 1996, Fuks A, J Clin Epidemiol, 1998

Writing Eligibility Criteria

- Eligibility criteria should be straightforward and unambiguous. Which of these criteria would you choose?
  - Pregnant and/or nursing women are not eligible.
  - All women of childbearing age are required to have a serum pregnancy test.
  - Pregnant and/or nursing women are not eligible for this study. All women of childbearing potential (defined as…) must have a negative pregnancy test (serum or urine) within 2 weeks of study enrollment.

Writing Eligibility Criteria

- However, be aware of the consequences of highly specific criteria:
  - For example: consider the issues that will follow from mandating a particular serum concentration of some marker, rather than building the definition around institutional upper limits of normal.

Trial Design

- Scientific integrity and credibility of the trial depend upon the trial design. This should include:
- Primary and secondary endpoints to measured during the trial
- A description of the type/design of the trial to be conducted. Schematic diagram of trial design, procedures and stages
- Methods of :
  - Randomization
  - Blinding

Trial Design

- Trial treatment, dosages, schedules, dosage form, packing and labeling
- Expected duration of the subject participation, with visit schedules etc.
- Inclusion/eligibility criteria
- Exclusion criteria
- Withdrawal criteria including reasons, and replacement and follow up of withdrawn subjects
- Stopping rules for individual subjects, parts or the entire trial

Trial Design

- Accountability procedures for the investigational product, comparator and placebo
- Maintenance of trial treatment randomization codes and procedures for code break
- Identification of any data written directly into the CRF (absence of source documents)

Treatment

- Dose, dosing schedules, etc for the treatment and control groups
- Medications permitted (other than the ones under test) and those not permitted during the trial
- Procedures for monitoring subject compliance

Efficacy and Safety

- Efficacy parameters and methods of assessing the same.
- Safety parameters and methods of assessing the same.
- Procedures for recording and reporting Adverse events
- Type and duration of follow up of adverse events
- Should also include:
  - Detailed information for reporting adverse events, including reporting to the FDA and/or the sponsor
  - Unblinding processes (if applicable)
  - Lists of expected adverse events

Human Subjects Protection

- This section includes discussion of:
  - Subject selection and exclusion
  - Proposed methods of patient recruitment
  - Minority representation
  - Recruitment (or exclusion) of special subjects, including vulnerable subjects
  - Lists of potential risks and benefits, including justification for risks

OHSR Information Sheet 5: Guidelines for Writing Research Protocols (ohsr.od.nih.gov/info/sheet5.html)

Statistics

- Selection of subjects for analysis
- Statistical methods to be employed
- Statistical calculation for number of subjects reasons of choice and power.
- Level of significance
- Criteria for termination of trial
- Procedures for missing data
- Reporting deviation from original statistical plan

Other elements

- Quality control and assurance procedures
- Ethics
- Data Handling and record keeping
- Financing and Insurance
- Publication policy
- Supplements

Conclusion

- Protocol is the most important of all clinical trial documents
- It is also the first to be prepared and discussed with the investigators.
- It is a confidential document since it contains most useful information on an investigational drug.

NIH Guidance on Protocol Writing

- Protomechanics:

http://www.cc.nih.gov/ccc/protomechanics/

- The Office of Human Subjects Research:

http://ohsr.od.nih.gov/info/info.html

- The NCI Investigators' Handbook:

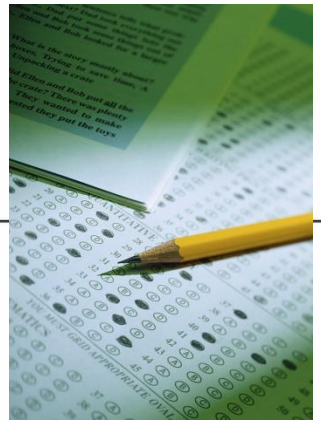
http://ctep.cancer.gov/handbook/index.html

- The International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals

  http://www.icmje.org/

Case Record Form (CRF)

Data recording



- Case Record Form - A document used to record data on which eventual analysis and reporting of clinical trial will be based
- The CRF is a main day-to-day tool that enables the correct information to be captured at correct time.
- The CRF design must therefore reflect two principal uses of the document in the trial…..***collection*** and ***extraction*** of data

Contents of the CRF

- Must be protocol driven
- Must contain sections on
  - Study Number, Center Code, Patient Number
  - Name, signature of Investigator
  - Version, Date, Page numbers
  - Emergency Numbers
  - Instructions for filling the CRF
  - Study Flow Chart
  - Inclusion /Non-inclusion criteria
  - Demography of Patients
  - Medical History of Patients
  - Concomitant Medications/ Previous therapy
  - Current Illness (Signs and Symptoms/ Diagnosis)

Contents of the CRF (contd)

- Must contain sections on (contd)
  - Study Medication dosing details
  - General Examination
  - Laboratory Examination
  - Special Examination
  - Adverse Event Reporting
  - Serious Adverse Event Reporting
  - Compliance Check
  - Efficacy Parameters
  - Safety Parameters
  - Global Evaluation of Efficacy and Tolerability
  - End of Study Information

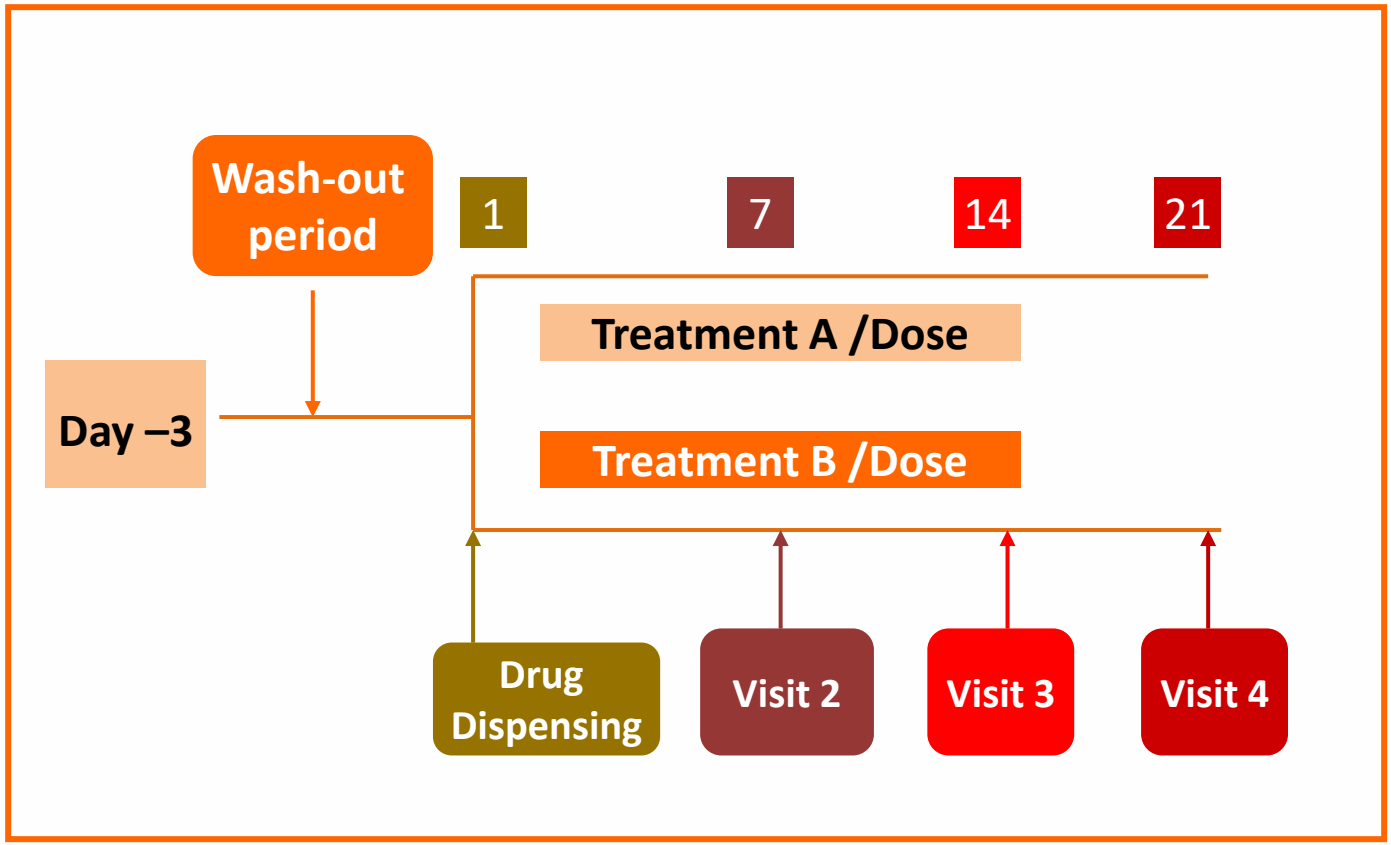
Instructions for Filling the CRF

- Enter Patient Number in CRF
- Ensure Patient Number in the CRF corresponds to the study medication packing
- Use only standard abbreviations
- For correction of any entries, strike out the incorrect entry with one line and enter correct entry alongside, initial and date it
- Enter data in black ball-point pen only

Designing a CRF….

- A skeleton plan showing the visits and each associated assessment is generated
- The assessments are reviewed to determine whether they are visit specific or global, based on this the number of pages are determined and content of each page is defined.
- Clear, simple and unambiguous questions are scripted and appropriate areas are created for data to be recorded.
- After subsequent reviews and incorporation of inputs from the study team the CRF is finalized

Study Flow Chart



Schedule of Observations

Parameter	Day – 3	Day 1	Day 7	Day 14	Day 21
Informed Consent	✓	-	-	-	-
Inclusion/ Exclusion	✓	Review	-	-	-
Lab Investigations	✓	-	-	-	✓
Compliance Check	-	-	✓	✓	✓
General Examination	✓	✓	✓	✓	✓

Inclusion Criteria

Please Check all statements and tick (✓) the appropriate box

- Morning stiffness in and around joints lasting 1 hour

  Y ☐ N ☐

If the answer is “No” to any of the above, please do not enroll the patient

Exclusion Criteria

Please Check all statements and tick (✓) the appropriate box

- Pregnant/ Lactating woman and woman of child bearing potential not following adequate contraceptive measures

  Y ☐ N ☐

If the answer is "YES" to any of the above, please do not enroll the patient

Demography of Patients

Patient's Initials	
Age (in years)	
Sex	M☐ F ☐
Weight (in Kg)	
Height (in cm)	

Concomitant Illness and Medications

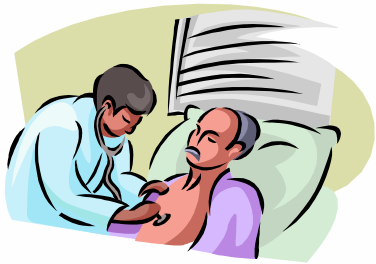
Condition	Name of The Drug (Generic)	Dosage Strength/ Frequency	Started on	Remarks
Hypertension	Atenolol	50mg OD	Date	

STUDY MEDICATION DOSING DETAILS

- Treatment A/B
- Dose: ____mg
- Frequency: OD/BID

General Examination

- VITAL SIGNS
  - Body Temperature
  - Pulse Rate
  - Blood Pressure



Laboratory Examination

- Complete Blood Count: **Hb, WBC, RBC, ESR, Platelets etc.**
- Enzymes: **Alkaline phosphatase, SGPT, SGOT etc.**
- Blood Sugar: **Fasting, PP, HbA1C**
- Urine Analysis
- ECG findings
- Other Investigations

Normal Lab values must be given either in the CRF or separately

Special Examination

- Depends on the type of the study
  - For Pain, pain VAS score is analysed
  - For Inflammation, swelling, redness, local temperature, pain are analysed
  - For RA, HAQ score is determined
  - For hypertension, DBP, SBP average of 3-6 readings are taken into consideration

Adverse Event Reporting

- Did the patient experience any of the following?

Event	**Yes/ No**	**Severity** Mild/Moderate/ Severe	**Treatment** If given Drug, Dose	**Outcome** Continued/ resolved
Nausea				
Abdominal Discomfort				

Efficacy Parameters

- By Investigator

- By Patients
- Appropriate tables with spaces to enter relevant data

Open Ended Questions

- Give Details of Patient's Medical History

Close Ended Questions

- Does patient have any clinically significant medical history?

  Y ☐ N ☐

- If yes, fill the following details

Body System	Normal	Abnormal	Comments What? Since when?
CVS			
Respiratory System			
CNS			
Eyes/ Ear			

Questionnaires and Dairy cards

- These are a part of the CRFs which are intended for completion by the subjects, rather than by the investigators….

- The following points in particular should be borne in mind

-

- Medical jargons to be avoided
- Full example of each entry should be given
- Attractive and easy to use format
- Text entry should be minimized

.....e - CRF

- The design of e-CRF still incorporates the traditional CRF skills but also needs technical IT support to design the data entry screens, to provide the electronic data collecting scheduling, validation checks, data base interaction and to maintain the overall system security….

Merits and demerits of e- CRF

- Merits:

  Inclusion of validation checks for the compliance with the protocol and data management validation checks , should reduce the number and frequency of data query forms.

  If the data are being entered directly into a centralised database, the monitors and data managers will be able to review the data more quickly

Merits and demerits of e- CRF

- Demerits

- Currently it takes longer to design, deploy the e-CRF with the supporting database and IT infrastructure, compared with designing, printing and distribution of traditional CRF.

- Adequate support is required to ensure continuity of data collection whenever access of e-CRF is unavailable.

Informed Consent Form

Informed Consent

As defined by ICH GCP guidelines:

- ‘Informed consent is a process by which a subject ***voluntarily confirms*** his/her willingness to participate in a particular trial, after ***having been informed*** of all aspects of trial that are relevant to the subject’s decision to participate.’

Informed Consent Document

- This ICD is generally in two parts :

- Subject Information Sheet (SIS) : Written Information describing the trial

- Informed Consent Document (ICD) : A form which the subjects sign to document that he/she has given consent to take part in the trial.

Subject Information Sheet

- Purpose
- Description of the Procedure
- Duration
- Benefits and Risks
- Compensation and /or treatment available to the subject in the event of trial related injury

Subject Information Sheet

- Consent withdrawal
- Alternative treatment
- Confidentiality
- Informed Consent Form

Elements of Informed Consent

Necessary information to be provided to subjects

- That the trial involves research
- Purpose: that the trial is experimental
- Trial treatment and probability of random assignment to treatment
- Trial procedures, alternative procedures/ treatments; everything that will happen to them
- Risks and anticipated benefits
- Subject's responsibilities
- Confidentiality, voluntariness, access to subjects' records

Informed Consent Form (ICF)

- Approved by Ethics Committee
- Language best understood by the subject
- Signed & Dated by the subject
- Signed and dated by person conducting the informed consent process
- Copy to Subject along with the information sheet and a copy at site

Informed Consent

- Office of Human Subjects Research http://ohsr.od.nih.gov/info/info.html
- The Office for Human Research Protections (OHRP):

  http://www.hhs.gov/ohrp/policy/index.html#informed

Investigator’s Brochure

Investigator's Brochure

- The Investigator's Brochure is an axis document in a new drug's clinical development programme. Crucial to various processes that regulate clinical research into new drugs, its content is well defined
- The ICH E6 guideline specifies that an Investigator's Brochure should include information on the drug product to be investigated and its performance in non-clinical studies along with specific guidance to investigators on the drugs use
- The Investigator's Brochure is a multidisciplinary document, summarising information from each of the teams involved in a drug's development

IB-Purpose

- To provide information to the Investigator and others involved in a clinical study on such issues the appropriateness of dose, dose frequency/interval and the characteristics of the investigational medicinal product (IMP) – so that it can inform safety considerations and clinical management of study subjects during a clinical trial

Structure of an Investigator's Brochure

- The structure is defined within ICH E6 (Section 7) [2]:
- Summary
- Introduction
- Physical, chemical, and pharmaceutical properties and formulation
- Non-clinical studies
- Effects in humans
- Summary of data and guidance for the Investigator

Introduction

- Introduction should be 1–2 pages in length and provide a high-level overview of the IMP and the setting of its proposed use
- Should provide a background on the therapeutic rationale behind an IMPs use and its target indication
- The generic name ,tradename , active ingredient(s) and the pharmacological class and a summary of its position within this class
- The content should reference the scientific literature and incorporate aspects of the IMPs clinical development plan and associated briefing packages

Physical, chemical, and pharmaceutical properties and formulation

- Product code names, information relating to the chemical structure and physical form/solubility of the drug substance relevant to clinical use/formulation
- Qualitative list of all excipients without excipient grades and justification for inclusion of the excipients in the formulation if clinically relevant
- Details of any matching placebos if relevant
- Recommendations on storage and handling of the dosage form. This may be by reference to the product label

Non-clinical studies

- Report on all relevant non-clinical pharmacology, toxicology, pharmacokinetic and metabolism studies, reporting on the nature and frequency of effects/AEs.
- In addition to summarising the time of onset and duration of any effects and any dose response findings the reports should summarise information:
- Species tested
- Number of sex in each group
- Unit dose (e.g., mg/kg)
- Dosing intervals
- Route of administration
- Duration of dosing

Effects in Humans

For a first-time-in-human study this section should be left blank.

- Where clinical studies have been conducted this section should start by noting the stage of development for the IMP and summarise the studies that have been conducted
- A description of each completed clinical trial should be provided; ICH E6 states that available information on pharmacokinetics, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities should be included [2]

Marketing experience

When not marketed this section is left blank.

- Countries where marketed or approved and information of any relevant history of use and, if possible, an estimate of patient exposure
- Countries where the investigational product failed to achieve marketing approval/registration or was withdrawn should also be recorded with reasons
- Any post-marketing safety information available to the sponsor will also need to be summarized along with information from any pharmacovigilance databases

Summary of data and guidance for the investigator

- This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible
- Where appropriate, the published reports on related products should be discussed
- Practical information is provided for the management of subjects being treated with the investigational product
- Information may also be drawn from published knowledge on other drugs in the same class

References, Supplements and Appendices

- References may be provided at the end of each section of the document or be given in a combined list at the end of the Investigator's Brochure
- References should not be made to Sponsor documents (as these may not be readily available to an investigator)
- A supplement should be considered as a separate, standalone document and not a revision or an appendix