MEDICAL COLLEGE OF WISCONSIN

Writing A Protocol

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What is a Protocol?

- A document that describes the
- objective(s),
- design,
- methodology,
- statistical considerations and
- organization of a study

What Does a Protocol Do

- Instructs study team on exactly what to do
- Explains the study to the outside world
- Provides a scientific basis for studies
- Provides a reviewable document for necessary approvals

What is in a Protocol

- *Some of the key elements are:*
  - Study objectives - Study design
  - Rationale – Eligibility requirements
  - Endpoints - Treatment regimen
  - Safety Reporting –
  - Analysis methods
  - Oversight Responsibilities

Basics of Protocol design

All Studies Have Same Basic Outline

1. Objectives and Specific Aims
2. Background and Significance
3. Study Design/Plan
4. Outcomes
5. Other Variables
6. Statistical Considerations
7. Study Specific Considerations
8. References

Study Process

Choose the research question

↓

Develop the concept

↓

Write the protocol

↓

Revise/finalize the protocol

↓

Conduct the study

↓

Choose the research question

Start with the Scientific Question

- Clear idea of the primary research question being asked

- Clearly stated primary objective:

not necessarily the same as specific aim

Begin Concept Development

- How can the hypothesis be tested?
  - literature review
- Generate measures of exposure and outcome
  - how have other researchers defined /measured the exposure and/or outcome?
- Choose the right control group

Types of Study

- Each Type of Study Modifies the Basic Protocol design
- Retrospective versus Prospective studies
- Observational versus Experimental studies

Retrospective Studies

- Examples:
  - Chart Reviews,
  - Data base studies
  - Large US data bases such as SEER, Social Security
- Protocol Focus on
  - Sample Selection
  - Variable Selection and Definition
  - Outcome definitions
  - For fixed known sample size, power or detectable difference or precision of estimators
  - Protocols usually have demographic tables

Prospective Studies

- Examples
  - Randomized Phase III trials
  - Phase I II TRIALS
  - Cohort trials, Case Control Studies

In a prospective study, you can choose how to measure factors of interest, whereas in a retrospective study you will need to rely on measures obtained in the past, or the subjects' recall

Observational Studies

- Here you observe patient behavior and make no attempt to modify behavior
- Can be retrospective or prospective
- Typically have shorter simpler protocols

Experimental Studies

- Study dictates treatment for each patient
- Prospective in nature
- More detailed protocols with discussions of treatment modalities, adverse effects, supplemental care, etc.

Writing The Protocol

- Collaboration between
  - –Statistician
  - Data manager
  - Clinician or epidemiologist
  - Study coordinator/implementation expert
  - Community representative
- Facilitated by a template
- Content depends on study design

Advantages of Templates:

- Organizes essential information
- Prompts for items otherwise forgotten
- Eliminates non-essential information, ambiguity, redundancy, conflicting statements
- Facilitates review (by institution, IRB, Sponsor, DMC)
- Facilitates study implementation
  - protocol specifics readily located
  - enhances compliance

Potential Disadvantages of Templates:

- Can include inappropriate ‘boilerplate’
- Sometimes retains vestiges from other studies
- May seem too complex for a simple study
- Driven by emphasis on process rather than science

Writing the Protocol: Section by Section

1. Objectives/ Specific Aims

Objectives

- Clearly and concisely list what the goals of the study are.

- What you want to study?
- What question you want to answer?
- Who do you want to answer the question for?

1. Objectives/ Specific Aims

Specific Aims

Specific Aims translate the objectives into testable hypotheses.

Specific Aims for both primary and secondary hypotheses

Specific Aims must relate to the hypothesis present in the rationale and should be consistent with the objectives..

2. Background and Rationale

- Briefly sketch the background to the current proposal, critically evaluating the existing knowledge and specifically identify the gaps that the project is intended to fill.
- Briefly sketch the rationale for selection of the study dosage

2. Background and Rationale

- Give a brief description of the drug/device to be studied. Their mechanism of action, whether currently in use and approved for use. Include a description and justification for the route of administration, dosage, dosage regimen, intervention periods, and selection of study population.

2. Background and Rationale

- Justify selection of target population.
- State the rationale behind the proposed study design (e.g. two period cross over, case control etc.)
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3. Patient Selection

- **List the number of subjects to be enrolled.**
- Indicate from where the study population will be drawn from. The study design.
- Discuss evaluations/procedures necessary to confirm eligibility.
- List **Inclusion Criteria**
- **List Exclusion Criteria**

3. Patient Selection

- **For retrospective studies discuss demographics of available sample**

4*: Trial Schedule

- **Primarily needed in prospective interventional studies**
- Information outlined in this section should be consistent with the information in the schedule of study visits and procedures.

5. Study Design

- Discuss experimental design
  - Two period crossover, case control
  - placebo control, blinding
  - randomization number of study arms
  - phase of trial
  - approximate time to complete recruitment
  - expected duration of subject participation,
  - sequence and duration of all trial periods
  - single or multi centre
  - healthy or sick population, in or outpatient
- Use diagrams to explain designs.
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6. METHODS AND ASSESSMENTS

Outcomes

- Provide definitions of all outcome value
  - Include type of variable
  - Appropriate parameter to represent value
  - How to deal with missing values, censoring, competing risks
  - provide for primary and secondary hypothesis
- Crucial for observational Studies

6. METHODS AND ASSESSMENTS

Variables to be Analyzed

- Provide list of other variables to be considered. Most often these are variables to be adjusted for in Study
- Provide information on how variable is to be treated (eg. Age continuous, categorical)
- Particularly important in observational studies

6. METHODS AND ASSESSMENTS

- Discuss the procedures to be used to accomplish the specific aims of the project.
- Describe randomisation and blinding procedures
- For females of childbearing age included in the trial describe methods of pregnancy testing and contraception if pregnancy is to be avoided during the trial.

6. METHODS AND ASSESSMENTS

- Provide a brief outline of the all the study visits, procedures to be done during the study, follow up after the study and discontinuation visit.

7*. Trial Materials

- Describe placebo or control product
- Provide background information on the trial product, its safety issues and duration of exposure. For drugs also include information on dosage.
- Describe product's storage needs.
- Define terms e.g. what would be regarded as serious adverse events etc..

8* Treatment

- Clearly explain the rationale for the dose used during the study.
- Describe in what form the study drug will be dispensed to the subjects.
- Describe the drug regimen to be used.
- Indicate any limitations on medications, herbs, vitamins and mineral supplements while participating in the study. Include time periods if applicable.

8* Treatment

- Describe the measures that will be undertaken to blind the study. State when unblinding is expected. Note plans to handle early unblinding when needed
- All medications (prescription and over the counter), vitamin and mineral supplements, and / or herbs taken by the participant should be documented.
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9*. Safety Measurements

- Define terms e.g. what would be regarded as serious adverse events etc..
- Include details of the protocol specific reporting, procedures, including the individual responsible for each step.
- Include specific details of reporting
  - Deaths and life threatening events
  - other SAEs
  - Other adverse events

9*. Safety Measurements

- **Safety Monitoring Plan**
  - **D**iscuss the plans in place to ensure the safety and well being of subjects, and integrity of data collected.
- **Complaint Handling**
  - Briefly discuss how complaints will be handled and how the data obtained will be managed.

10. Data Management

- Discuss the measures undertaken to ensure that the data obtained from this research is accurate, complete and reliable.
- Briefly discuss where data will be entered (i.e. will these entries be on paper or electronically), stored and handled.
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11. Size and Statistical Methods

Determination of Sample Size

- Details on sample size calculation and the means by which data will be analysed and interpreted.
- In particular, specify all of the following:
  - Null and alternate hypothesis
  - Type I error rate P[Reject H_o| H_o True]
  - Type II error rate (Power)

    P[Reject H_o| H_o False]

11. Size and Statistical Methods

Type of Study	Sample Size	Detectable Difference	Power Type II Error
Retrospective	Fixed known	fixed Clinically Important Delta	computed
Retrospective	Fixed known	computed	fixed (90, 80)%
Prospective	computed	fixed Clinically Important Delta	fixed (90, 80)%

11. Size and Statistical Methods

- For exploratory studies base calculations of estimating key quantity to within some limit by standard error or 4 standard errors (confidence interval weight)

11. Size and Statistical Methods

Statistical and Analytical Plans

- **Game plan for data analyst**
- **Contains**
  - *General Considerations*
  - *Safety Analyses*
  - *Interim Analyses*

12. Ethical Considerations

- **Informed Consent--** Describe the procedures for obtaining and documenting informed consent of study subjects. Make provision for special populations e.g. non English speakers, children, illiterate or non writing individuals, vulnerable populations. Specify when consent will be taken and who will take consent.

- Identify different consent forms that are needed for the study(e.g. screening, study participation, HIV screening, future use specimens, assent from minors)

12. Ethical Considerations

- **IRB review**
- Include procedures for maintaining subject confidentiality, any special data security requirements, and record retention. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to the participating subjects.

13. Publications

- State publication policy for study findings.
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14. Plan for retention of study documents

- Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation should be retained by the PI in a secure storage facility. The records should be accessible for inspection and copying by authorized authorities. Describe the retention plans for study documents.
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15. References

- List references relative to proposal

Appendices

- Optional vs required:
  - Sample informed consent
  - Schedule of events/visits
  - Product use directions
  - Other special procedures
  - Data collection forms
  - Summary Statistics

Protocol Writing Tips

- Spell out abbreviations and acronyms at first use
- Version number and date are required;
- Use bulleted lists where helpful
- Footer: pagination; version number; short title; date

Final Hints

- Clear, concise protocol critical to study success
- Start early—protocol development takes time
- Early input facilitates review
- Expect multiple reviews as IRBs and scientific committees send comments

References

- Pocock Clinical Trials: A Practical Approach. Wiley 1983.
- http://ctep.cancer.gov/protocolDevelopment/templates_applications.htm (Collection of templates for prospective cancer trials)
- http://www.nidcr.nih.gov/ClinicalTrials/ToolkitClinicalResearchers/ClinicalTrialsProtocolTemplate/ (Collection of templates. Includes template for minimal risk study)
- http://www.cibmtr.org/Studies/Observational/StudyManagement/index.html#protocol (Discussion of protocol development for CIBMTR observational studies)