Writing a Protocol: From Proposal to IRB-Ready

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What is a Protocol?

- ICH Guidelines **E6, Section 1.44**:
  
  “A document that describes the objectives, design, methodology, statistical considerations and organization of a trial”--

- Written by sponsor, investigator or team
- It’s required!
- It takes a lot of time!
What is the purpose?

- Instructs study team on exactly what to do
- Explains the study to the outside world
- Provides a reviewable document for necessary approvals
What is the difference between a **Grant Proposal** and a **Protocol**?

<table>
<thead>
<tr>
<th>Grant proposal</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Purpose:</strong></td>
<td>Obtain funding</td>
</tr>
<tr>
<td><strong>Focus:</strong></td>
<td>Describes broad aims and hypotheses</td>
</tr>
<tr>
<td><strong>Feasibility:</strong></td>
<td>Costs, staffing, equipment</td>
</tr>
<tr>
<td><strong>Review by:</strong></td>
<td>Scientific review committee, funders</td>
</tr>
<tr>
<td><strong>Tone:</strong></td>
<td>Persuasive</td>
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</tbody>
</table>
What is the difference between a **Grant Proposal** and a **Protocol**?

<table>
<thead>
<tr>
<th>Protocol:</th>
<th>A regulatory document</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose:</td>
<td>Describes a single study in detail</td>
</tr>
<tr>
<td>Focus:</td>
<td>Organized around specific objectives</td>
</tr>
<tr>
<td>Feasibility:</td>
<td>Specifics of enrolling, implementation details</td>
</tr>
<tr>
<td>Reviewed by:</td>
<td>Scientists, Sponsor, IRBs</td>
</tr>
<tr>
<td>Tone:</td>
<td>Informative; focused on details</td>
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</table>
What is in a Protocol?
ICH E6, Section 6

Some of the key elements are:
- Study objectives
- Main endpoints
- Study design
- Eligibility requirements
- Treatment regimen
- Statistical Considerations
- Ethics
Start with the Scientific Question

- Clear idea of the primary research question being asked
- Clearly stated **objective(s)** that will answer this question:
  - Specific
  - Measurable
  - Relevant
  - Feasible
  - Ethical
## Objectives

**ICH E6, Section 6.3**

- Common error – Sinking ship: Avoid overloading the study with too many objectives and too much data collection.

- A single primary question around which to focus the development of the protocol and sample size estimates.

- Secondary research questions: can be related to the primary question or to other hypotheses.
Objectives
ICH E6, Section 6.3

- Use “action” word, such as assess, measure, compare, etc.
  - Example: To determine the effectiveness and safety of male circumcision on the acquisition of HIV by young men
Write a protocol concept

- Objectives and Rationale
- Main Endpoints
- Study Population
- Study Design
- Feasibility Issues
- Preliminary Sample Size

Time to involve a statistician
Other Sections

- Background and Rationale
- Safety Assessment
- Subject Confidentiality
- Informed Consent Process
- Quality Control and Assurance
- Data Management
- Publication Policy
Appendices

- Sample informed consents
- Schedule of events/visits
Other Related Documents

- Detailed Data Management Plan
- CRFs
- Site Monitoring Plan
- Manual of Procedures
- Detailed Analysis Plans
- DSMB Charter

Consistent with the protocol
Protocol Writing Tips

- Recommended co-authors or reviewers include:
  - Statisticians
  - Data managers
  - Clinicians or epidemiologists
  - Study coordinator/implementation experts
  - Regulatory, GCP, sponsor requirements experts (terms of award)
Protocol Writing Tips

- Use of a template is highly recommended
- Assign writing tasks to others, especially statistician, data manager, lab expert
- Manage review process, inform reviewers and authors of key changes
- Expect multiple reviews from sponsor and IRBs
Protocol Writing Tips

- Spell out abbreviations and acronyms at first use
  - add to the list in the front of the protocol
- Use bulleted lists where helpful
- Make it easy to update/amend:
  - Minimize duplication
  - Refer to positions instead of names
  - Keep it vague, but accurate
- Header/Footer: page number, version number, short title, date.
Version numbering system

Version numbering example:
- 0.1 = 1st draft
- 0.2 to 0.xx = the next sequence of drafts
- 1.0 = the 1st approved version
- 1.1 = the 1st draft of an amended version
- 1.2 to 1.xx = the next sequence of drafts of the amended version
- 2.0 = the 2nd approved version (i.e., the 1st amended version that has been approved)
Back it up!

“You caught a virus from your computer and we had to erase your brain. I hope you kept a back-up copy.”
Summary

- Writing a study protocol is a team effort
- Clear objectives and endpoints are essential
- All procedures/data must contribute to answer research question
- Check for consistency
- Templates ensure sponsor’s needs are met and all pieces are included
- Manage versions, amendments, and approvals especially if multi-site
- Think ahead to implementation—Time, Effort and Money
6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator’s Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design
The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:
   (a) Randomization.
   (b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
   (a) When and how to withdraw subjects from the trial/ investigational product treatment.
   (b) The type and timing of the data to be collected for withdrawn subjects.
   (c) Whether and how subjects are to be replaced.
   (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects
6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring,
audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics
Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance
Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy
Publication policy, if not addressed in a separate agreement.

6.16 Supplements
(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)