The Fundamentals of International Clinical Research

Writing a Protocol: From Proposal to IRB-Ready

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Family Health International
What is a Protocol?

ICH Guidelines:

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

Written by sponsor, investigator or team
What is the difference between a **Grant Proposal** and a **Protocol**?

<table>
<thead>
<tr>
<th>Grant proposal:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose:</strong></td>
<td>Obtain funding</td>
</tr>
<tr>
<td><strong>Focus:</strong></td>
<td>Describes Aims, methods, 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>
</tr>
</tbody>
</table>
What is the difference between a Grant Proposal and a Protocol?

Protocol: a regulatory document
Purpose: Describes a single study in detail
Focus: Organized around specific objectives
Feasibility: Specifics of enrolling, implementation details
Reviewed by: Scientists, Sponsor, IRBs
Tone: Informative; focused on details
Start with the Scientific Question

- Clear idea of the primary research question being asked
- Clearly stated objective(s):
  - Specific
  - Measurable
  - Relevant
  - Feasible
  - Ethical
- Everything in protocol relates back to research question
General Information
ICH E6, Section 6.1

Protocol title, identifying number, version number and date

Investigator responsible for the study

TITLE
A Prospective Study of Dengue Virus Infections during Infancy to Define Correlates of Protective Immunity

DMID Protocol Number: 06-0013

Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)

DMID Funding Mechanism:
U01-AI-05654-01

Principal Investigator:
Daniel H. Liberty, M.D.

DMID Protocol Champion:
Walla Dempsey, PhD.

Draft or Version Number:
3.0

Day Month Year
28 March 2006
Statement of Compliance

Signed statement by Principal Investigator that study will be conducted in compliance with protocol, GCP, and applicable regulatory requirement(s).

ICH E6, Section 6.2.5
Protocol Summary/Schema

Last section actually written:

- Concise overview—population, duration, number of sites
- Briefly describe design
- List objectives—clear and specific
- Provide schematic
Background/Rationale

- Review findings of other research
- Rationale—why your study needs to be done
- Describe design—observational, randomized
- Known or potential risks and benefits—applies to any type of study
- If using intervention, describe

E6, Section 6.2
Objectives

- Clearly state primary and secondary objectives—the fewer the better!

- Typically include “action” word, such as assess, measure, compare, etc.
  - Example: To define levels of serotype-specific neutralizingAbs associated with protective immunity against dengue

- Method by which objective is met, outcome measures
  - Example: Neutralizing Ab titers in blood samples collected from infants before DV infection, and predicted neutralizing Ab titers at time of illness, will be correlated with disease severity and peak viremia levels. Neutralizing Ab titers at which infants developed symptomatic dengue will be determined.

ICH E6, Section 6.3
Design

- Type of study, e.g., observational, case-control
- Specific outcomes/endpoints to be measured and methods of data collection
- How many participants, in which groups
- Time to complete enrollment
- Describe study groups/arms
- Expected duration of trial periods including follow-up

ICH E6, Section 6.4
Study Population: Selection and Withdrawal

- Define population from which participants will be drawn
- Describe recruitment strategies
- State estimated number of participants needed in each group/arm
- Define age, gender, ethnicity
- Example: 1050 male and female patients at ______ Hospital, age 6 months through 15 years, who are DV-RT-PCR positive

ICH E6, Section 6.5
Study Population

- Vulnerable populations require special considerations:
  - Children
  - Pregnant women
  - Prisoners
  - Other vulnerable populations

- http://www.hhs.gov/ohrp/humansubjects/guidance
Study Population

- List inclusion criteria
  - describe characteristics and conditions necessary for eligible persons to be included
  - Include willingness to provide consent

- List exclusion criteria
  - describe characteristics that would disqualify otherwise eligible participants
  - Include exclusionary concomitant medications

- Risks of study should structure in/ex criteria
  - Example: if intervention is risky for pregnant women, ensure that women who are enrolled are not pregnant and use effective contraceptive during study

ICH E6, Section 6.5
Study Procedures/Evaluations at Each Contact

- Obtain consent
- Medical history, physical exam, specimen collection
- Interview/questionnaire
- Environmental survey, e.g., water sample, insect collection, etc.
- Counseling procedures
- Medications/treatments permitted and not permitted

ICH E6, Section 6.6
Study Procedures/Evaluations

- Screening: what happens to participant at first contact, including consent
- Enrollment: baseline assessment, randomization procedures, etc.
- Follow-up Visits: plan for retention
- What and how data are collected at each visit
Study Procedures/Evaluations

- **Laboratory Evaluations**
  - *Include specific test components and estimated volume and type of specimens needed for each test*
  - *Specify laboratory methods*

- **List special assays or procedures required** (e.g., immunology assays, sputum specimens, photographs)

- **Instructions for specimen preparation, handling, storage, and shipment**
## Schedule of Events -- required

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screen</th>
<th>Enroll/ Baseline</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign Consent</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>update</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review Con Meds</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td>Symptom directed</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Chemistry</td>
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<td>X</td>
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<tr>
<td>Hematology</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Intervention</td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>Assess AE</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Safety Assessment (other than minimal risk protocol)

- Define adverse events (AEs) and serious adverse events (SAEs)
- Describe types of AEs that may occur, including lab values
- Procedures to follow if AE occurs
- Describe methods used to track AEs
- Report pregnancies
- Halting rules

ICH E6, Section 6.8
Statistical Considerations

- Written as “self-contained” section
- Clearly linked to study objectives
- Assumed number of drop-outs, withdrawals, missing data, etc.
- Criteria for terminating study/participants
- Procedures for deviations
- Participants to be analyzed

ICH E6, Section 6.9
Analysis Plan Summary

- Adequate for reviewers to decide if planned primary analyses are appropriate for the study
- Include the way in which anticipated analysis problems will be handled
- Describe how safety measures monitored
- Full plan done *prior to* any analyses
Data Management

- Describe source documents
  - Refer to DMID Source Documentation Standards
- Indicate schedule for data reports, and final study reports
- Describe how documents/data maintained
- Statement about who will have access
- Specify length of time for retention of study records
Ethics/Protection of Participants

- Discuss
  - ethical review
  - risks/benefits
  - participant compensation
  - confidentiality, especially limits of
    - include any communicable disease reporting requirements
  - study discontinuation

ICH E6, Section 6.12
Informed Consent Process

- Refer to ICH E6, Section 4.8
- Describe process of obtaining consent
  - Special attention for minors, different languages, and low literacy
- Identify if more than one consent used, i.e., for screening, for enrollment, for specimen storage
- Must be approved by IRB(s) prior to use
Other Sections (if required by DMID)

- Quality Control and Assurance
- Financing and Insurance
- Publication Policy
- Supplements/Appendices

ICH E6, Section 6.11-6.16
Appendices

- Sample informed consents—required
- Schedule of events/visits—required
- Data Management Plan
- Site Monitoring Plan
- Manual of Procedures
Protocol Writing Tips: Getting Started

- Writing a protocol is
  - a team effort, not individual
  - takes *time*, with many drafts
- Recommended co-authors or reviewers include:
  - Statistician(s)
  - Data manager
  - Clinicians or epidemiologist
  - Study coordinator/implementation expert(s)
  - Community representative(s)
Protocol Writing: Getting Started

- Use of a template is recommended by DMID
- Assign writing tasks to others, especially statistician, data manager, lab expert
- Expect multiple reviews from sponsor and IRBs
Protocol Writing Tips

- Spell out abbreviations and acronyms at first use
  - Abbreviations should be added to the list in the front of the protocol

- Version number and date are required;
  - Follow DMID version control guidelines
  - Posted on the ICSSC website
    (http://www.icssc.org/templates_resources.htm/)

- Use bulleted lists where helpful

- Header/Footer: pagination; version number; short title; date.
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

- Clear objectives and endpoints are essential
- All procedures/data contribute to answer primary question
- Templates ensure sponsor’s needs are met and all pieces are included
- Writing a study protocol is a team effort
- Think ahead to the implementation
Finally, remember why we do research