Writing a Great Protocol: Opportunities and Pitfalls

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Everyone should do a clinical trial – once!
Bill Clarke, University of Iowa
Different Perceptions of Reality in Research

Diferent Perceptions of Reality in Research

The glass is half full!

The glass is half empty.

The glass is too big.

(Protocol)

How much water did the other PIs get?

Is that placebo or the drug?

The glass is vulnerable, and must be provided special protection.

What glass?

Let me assure our stockholders that the glass is definitely full!

Public

ACCOUNTING

GLASS BROKEN!
Details at eleven.

MEDIA

Do I have to report this to the IRB?!!

COORDINATOR

The glass is not regulation.
It must be resubmitted with a handle.

FDA

IRB

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Operationalizing a Clinical Trial

- Begin thinking about the logistical considerations early in the grant process
- The goal is no surprises with the budget
- And no surprises with trial implementation
Step 1

- Develop good teams
  - Lead Protocol Coordinator/Project Manager is crucial
  - Sponsor
  - Co-Investigators
  - Patient Representative(s)
  - Coordinating Centers
  - Vendors
  - Steering Committee
  - DSMB
Step 2

- Glue the teams together with
  - A well-written protocol
  - Well-written study materials for training and education
  - Well-designed data collection systems
  - Well thought-out data and safety monitoring plans
  - SOPs
  - Adequate funding😊
Develop (realistic) timelines

- Study planning and start-up
- Study execution
- Data cleaning and database lock
- Analysis and Reporting
- Keep track of your timelines!
Writing the grant is the first step

NINDS generally requires a protocol, in addition to the research strategy of the grant

Protocol templates are available on the NINDS website

http://www.ninds.nih.gov/research/clinical_research/toolkit/protocoltemplate.htm

The protocol helps describe how the science will be operationalized
IND or non-IND Study?

- Reach out to FDA to determine if an IND would be required
- If re-purposing a marketed drug for new indication, can often request IND exemption
- If submitting an IND study, NINDS generally requires that an IND is submitted to the FDA >31 days prior to grant submission
Synopsis

1. Study Objectives
2. Background
3. Study Design
4. Selection and Enrollment of Subjects
5. Study Interventions
6. Clinical and Laboratory Evaluations
7. Management of Adverse Experiences
8. Criteria for Intervention Discontinuation
9. Statistical Considerations
10. Data Collection, Site Monitoring, and AE Reporting
11. Human Subjects
12. Publication of Research Findings
13. References
The primary objective should always be to address a specific hypothesis.

State the hypothesis in quantifiable terms: e.g., “the experimental treatment will result in 12 months of additional survival compared to the control treatment.”

Secondary objectives may or may not be hypothesis-driven, may include secondary outcomes, and may include more general non-experimental objectives (e.g. to develop a registry, to collect natural history data).
Background

Study Rationale

- Provide historical background, patient population to be studied, state the need, relevance and priority for the study

Supporting Data

- Describe previous pre-clinical studies that support the proposed research, and results of prior clinical studies that help to justify the study, its design and the intervention groups
Briefly describe the design and indicate how the design will fulfill the intent of the study

Use diagrams to explain design complexities

Study Design

- Screening Phase
  - Up to 4 weeks
- Treatment Phase
  - MN-166
    - Day 1a through 14
    - 30 mg BID
    - Day 15b through Week 96
    - 50 mg BID
- Follow-up
  - 96 weeks
  - 4 weeks post
Selection and Enrollment of Subjects

- Inclusion criteria
- Exclusion criteria
- Criteria for subject withdrawal
- Study enrollment procedures
  - Recruitment/Retention
  - Screening logs
  - Informed consent
  - Randomization/Treatment assignment
Study Interventions

- What is your intervention?
  - Study medication?
  - Device?
  - Other?
Study Interventions

- How are you handling your intervention?
- Handling of study medication
  - Storage, preparation, labeling, dispensing
  - Site pharmacist requirements
  - Procedures for unmasking, dose changes, etc
- Are there required or prohibited medications?
- How will compliance be assessed?
# Schedule of Activities

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<th>Tests and Evaluations</th>
<th>Screening Visit</th>
<th>Baseline Visit</th>
<th>Week 4 ± 5 days</th>
<th>Week 8 ± 5 days</th>
<th>Week 12 ± 14 days</th>
<th>Week 24 ± 14 days</th>
<th>Week 36 ± 8 days</th>
<th>Week 48 ± 14 days</th>
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Clinical and Lab Evaluations

- Describe procedures that will occur at each of the study visits
  - Screening
  - Randomization
  - Each study visit
Management of Adverse Events

- List all expected adverse experiences for the study medication/intervention, based on previous studies
- Describe procedures for study management and modification of study intervention regimen
Criteria for Study Discontinuation

- Define stopping rules or discontinuation criteria for individual subjects (pregnancy, SAE, etc) and for the entire trial (more than x# of AE of interest, etc)
- If subject discontinues intervention will they continue to be followed off treatment?
Statistical Considerations

- Describe primary and secondary hypotheses and how they relate to the choice of primary and secondary outcome measures
- Provide details of why certain design features were chosen (crossover, washout, etc)
- Describe randomization plan (criteria for stratification, etc)
- Details of sample size calculations
Data Collection, Site Monitoring and AE Reporting

- How will your data be collected?
- How will your data be monitored?
  - Quality
  - Accuracy
  - Compliance
  - Safety
Human Subjects

- IRB review
  - Initial Review
  - Continuing Review
  - Reporting
- Subject confidentiality
- Study modification/discontinuation
Publication of Research Findings

- Data Sharing
  - Other investigators
  - Scientific community
- Manuscript plan
  - Methodology/protocol manuscript
  - Baseline
  - Primary
  - Secondary
- Clinicaltrials.gov
Provide citations for all publications referenced in the protocol
Writing the protocol will help better define study logistics
Drug supply?

- Will you need to purchase or will it be donated from manufacturer?
- Do you need a matching placebo?
- Setting up vendor contracts
- How much drug preparation is required?
- Should you budget for site pharmacy fees?
- What are the adverse events associated with the drug?
Drug Distribution?

- Do you need a central pharmacy?
- How will drug be packaged/ labeled?
- Shipping requirements
- Storage temperature requirements
- Just –in-time shipping
- Chain of custody
Central Laboratory?

- Specimen kit assembly (tube expirations)
- Bar code scanners
- Requisitions
- Laboratory manuals
- Shipping materials and manifests
- Chain of custody for samples
- Reporting results
Other Vendors?

- Will you have a central imaging reading center?
  - Comparable scanners at sites
  - QC of scanners
    - Dummy scans
    - Phantom scans
- Reporting Incidental Findings
- Reporting results
Make sure you are collecting data in a usable way (limit open text boxes)
Don’t collect data that you are not going to use in analysis
NINDS Common Data Elements
Data Management Plan
Recruitment Plans and Materials?

- Start thinking about this in the grant-writing phase – understand your population
- Partner with patient advocacy groups
  - Have them read your draft protocol and provide feedback
- IRB approval of brochures, advertisements
- Clinical trials.gov
- Pre-screening logs
Everybody should do a clinical trial

- More than once...
- And have some fun along the way!
Questions?