Clinical Trial Protocol Development

Developed by Center for Cancer Research, National Cancer Institute
Endorsed by the CTN SIG Leadership Group
Objectives

The clinical trial protocol is the heart of any research project. It is a “recipe” for ensuring that the procedures/measures outlined in the research study are carried out in a consistent, reproducible manner. One of the major roles of the clinical trials nurse (CTN) is to ensure that protocols are adhered to, which requires an in-depth knowledge of all components included in the protocol document. This module will review how to plan a protocol, describe the essential elements of a protocol, and briefly review important parts of a protocol.

At the conclusion of this module, you will be able to:

• Describe characteristics of a good research question
• Describe measurement tools specific to oncology clinical trial endpoints
• Discuss the purpose of a written protocol in clinical trials
Planning a Clinical Trial

- Formulate the Research Question
- Develop the Study Design
- Define the Study Population
- Select the Measurement Tools/Endpoints
- Determine Sample Size and Statistical Analysis
- Data Collection and Storage
Formulate the Research Question

- Define Objective(s) clearly and precisely
- Objective(s) need to be tied to measurable study endpoints
- Primary objective of the study must be identified
- May have several secondary objectives
Characteristics of a Good Research Question – “FINER”¹

- Feasible
  - Adequate number of subjects
  - Adequate technical expertise
  - Affordable in time and money
  - Manageable in scope
- Interesting
- Novel
  - Confirms or refutes previous findings
  - Extends previous findings
  - Provides new findings
- Ethical
- Relevant
  - To scientific knowledge
  - To clinical and health policy
  - To future research directions

Select the Study Design

Selection of the study design is based on:

• study question
• ethical considerations
• resources

See Trial Design Module for details
Study Subject Selection

- Subjects who may benefit
- Subjects who may be at greater risk
- Subject’s ability to comply
- Subject’s concurrent conditions
- Inclusion criteria
- Exclusion criteria
Measurement Tools/Endpoints

- Toxicity
  - Common Terminology Criteria for Adverse Events (CTCAE v.4.0)
- Response
  - May use standard disease specific response criteria (e.g., Response Evaluation Criteria In Solid Tumors – RECIST 1.1)
- Time to Progression (TTP)
- Survival
- QOL/Patient Reported Outcomes (PRO)
  - Various survey tools (e.g.: FACT)
  - Biological Endpoints and Surrogate Markers
Determine Sample Size

- Get statistician involved early
- Estimate the appropriate number of subjects for a given study design
- Test the hypothesis
- How to handle dropouts/withdrawals?
- For interventional studies:
  - How large a difference between treatment groups is medically important
  - Include enough participants to get a statistically significant results
Determine Statistical Analysis

- Get statistician involved early
- Analysis plan appropriate for objectives and design
- How endpoints will be measured
- Statistical methods to be used
- How will common problems be addressed
- Management of safety data
Data Collection & Storage

• Identify critical data elements to be collected
• Develop case report forms (may be required for IRB or FDA submission)
• Safe and secure mechanism for data storage
• Anticipate audits of clinical data
• Length of time for storage
  • Know FDA regulations
  • Know institutional policies as appropriate
THE PROTOCOL

Recipe for: A Successfully Conducted Study

From:
Clinical Research Protocol

A written, detailed action plan that:

• Provides background about the trial
• Specifies trial objectives
• Describes trial’s design and organization

• **Ensures that trial procedures are consistently carried out**

*Please note: Each IRB or Sponsor will have their own Protocol template. The follow slides are an example of 1 IRB template requirement.*
Sample: Protocol Format

- Title page
- Precis
- Table of contents
- Introduction
- Eligibility assessment and enrollment
- Study implementation
- Supportive care
- Data collection and evaluation
- Human subjects protection
- Data reporting
- Pharmaceutical information
- References
- Appendices
Protocol Format

Title page
Precis
Table of contents
Introduction
Eligibility assessment and enrollment
Study implementation
Supportive care
Data collection and evaluation
Human subjects protection
Data reporting
Pharmaceutical information
References
Appendices

Date (version), Protocol #’s, Title, PI, Chair, AI’s, Affiliations, Trial sponsor, IND #’s
Protocol Format

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Summary (~400 words) of trial
Protocol Format

Title page
Precis
Table of contents
Introduction
Eligibility assessment and enrollment
Study implementation
Supportive care
Data collection and evaluation
Human subjects protection
Data reporting
Pharmaceutical information
References
Appendices

Section and subsections matching protocol
Page numbers
Protocol Format

Title page
Precis
Table of contents
Study objectives
Introduction
Study objectives
Eligibility assessment and enrollment
Background and rationale
Study implementation
Supportive care
Data collection and evaluation
Data reporting
Human subjects protection
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Management guidelines for disease- and drug-related complications
Protocol Format

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Study implementation
Supportive care
Data collection and evaluation
Human subjects protection
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Data collection procedures, forms
Response criteria (e.g.: RECIST v1.1)
Toxicity criteria (NCI CTCAE v.4.0)
Statistical section
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Reporting adverse events as specified by IRB, sponsor, other regulatory groups.
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Investigational Drugs
Drug supplier (sponsor)
Formulation (dosage forms)
  Reconstitution
  Dilution
Stability and storage
Administration procedure
  Bolus, infusion, iv push, sc, im
Side effects/toxicities
Dose modification

Commercial Drugs
Drug supplier (sponsored or not)
Formulation, stability and storage
Administration procedure
Side effects/toxicities
Dose modifications
Protocol Format

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Treatment schema
Evaluation roadmaps
Pharmacokinetic worksheet
Detailed surgical/radiation guidelines
Procedures for handling/shipping samples
Data collection/Reporting forms
Reading a Protocol

How you read a protocol and where you begin will depend on your role on the research team.

Examples:
Research Nurse may begin with Informed Consent Document (ICD) to familiarize him/herself to protocol and then begin with the eligibility section, study implementation, appendices, etc.

Data manager may begin with ICD and then focus on study implementation and the data/time points to be collected including the case report forms to be used.

Pharmacist may begin with the Pharmaceutical section.

Treatment nurse may begin with Pharmaceutical section to see how drug(s) will need to be administered.
References


Module Evaluation

The CTN SIG would greatly appreciate your feedback on this learning module. Please complete the evaluation form and fax to Elizabeth Ness at 301-496-9020.