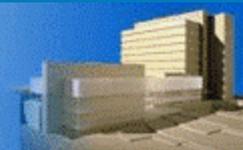


Key Elements of a Successful Phase III Study

W R Parulekar

NCIC Clinical Trials Group

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NCIC Groupe des essais cliniques



Learning Objectives

At the end of the session, the participants should be able to:

- ✓ List the characteristics of a phase III study
- ✓ Understand the components of a phase III study
- ✓ List and understand the multiple roles of the study protocol and describe its general content
- ✓ List useful web resources that relate to clinical trial design, conduct and reporting

Phase III Study Characteristics

- Pivotal: regulatory and/or practice perspective, knowledge of the therapeutic impact of an intervention
- Comparative: two or more therapeutic interventions (usually new treatment compared to standard therapy)
- Randomized: to minimize bias and assure comparability of test groups
- Predefined outcome measures and analyses: formal hypothesis testing, estimation of treatment effect(s) and precision
- Multi-institutional: feasibility and generalizability

Components of a Clinical Study

- Study concept and design
- Protocol document
- Study conduct
- Analysis and manuscript preparation

Study Concept

- Trial question
 - Single most important aspect of study design
 - *Rationale:*
 - Current therapeutic gap(s), ‘extent of the problem’
 - Sufficient background and preliminary data
 - Ability of the study to advance the health of a population and scientific agenda
 - *Feasible:* protocol interventions, accrual, available resources

Study Design

- A good trial design will be simple, measure important clinical parameters, be precise (reduce errors of chance), eliminate bias and provide external validity¹
- *Simple*: design versus logistics of conducting a study

Study Design

- Planned interventions: experimental and control
- Masking: Open label or blinded
- Method of treatment allocation: e.g. minimization; use of stratification factors
- Study population criteria
 - *Disease or health state of interest*: histology, molecular markers, stage, treatment history
 - *Safety*: organ function, other morbidities
 - Ability to comply with interventions

Study Design

- Analyses
 - Outcome measures: Primary and secondary
 - Unambiguous, accurately measured, clinically meaningful: overall survival (or intermediate or surrogate endpoint) or improvement in quality of life or disease related symptoms.
 - *Intent*: test superiority or equivalence or non inferiority
 - *Sample size and final analysis* (time to event analysis): effect size, Type I and II error rates, event rate, duration of accrual and follow-up

Study Design

- Analyses
 - *Interim analyses*: how many, when, intent (futility or efficacy), associated statistical adjustments
 - *Planned subgroup analyses*: associated power calculations
 - International guidelines on statistical principles for clinical trials ICH E9 (www.ich.org)

Study Design

- Explanatory (ideal setting) versus pragmatic (real world) studies^{2,3}
 - Subtle differences in today's research environment
 - Many shared characteristics
 - Terminology relates to interpretation and application of trial results rather than a specific characteristic in either study design

	Explanatory	Pragmatic
Eligibility	<ul style="list-style-type: none"> Selected population e.g. Central review of histology or biomarker 	<ul style="list-style-type: none"> Broad criteria
Interventions	<ul style="list-style-type: none"> Highly prescribed interventions Centralized review of entry criteria, outcome measurements Rigorous monitoring 	<ul style="list-style-type: none"> Less rigid guidelines for treatment delivery and outcome assessment
Outcome	<p><i>May emphasize biological activity (i.e. PFS or clinical benefit) in addition to clinically meaningful outcome measures</i></p>	<p>Clinically meaningful – live longer or better</p>
Analysis	<p>Use of censoring and sensitivity analyses to isolate, estimate the efficacy of a particular therapy</p>	

Protocol Document

- Provides quality control
 - Specifies overall research plan
 - Provides guidance for management of the individual study subject
 - Basis for publications
- *Legal / ethical properties:* Regulators, Ethics Boards
- Thus it must be a structured and accessible document

Study Protocol

- Non adherence to a protocol: design versus biological validity
 - Rigid adherence to a protocol (design validity) does not guarantee clinically relevant data

Generic Protocol

DRAFT

PROTOCOL DATE: 2011-APR-25
NCIC CTG TRIAL: **XXX**

When protocol is "final" &, if you are submitting to NCI U.S., please note: NCI U.S. SUBMISSION

If you are re-submitting the protocol to NCI U.S., please note: NCI U.S. RE-SUBMISSION

When protocol is "final" &, ready for submission to Health Canada, please note: HEALTH CANADA SUBMISSION

Please leave "DRAFT" on this protocol until ready for submission to NCI U.S. or Health Canada

NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A PHASE [] STUDY OF []

NCIC CTG Protocol Number: XX.X

STUDY CHAIR:

TRIAL COMMITTEE:

PHYSICIAN COORDINATOR:

BIostatistician:

QUALITY OF LIFE COORDINATOR

STUDY COORDINATOR:

SPONSOR: **Print NCIC CTG here unless pharmaceutical company is making Health Canada submission**

NCIC CTG "**WORKING**" GENERIC PROTOCOL (for phase I/II/III trials)

This "**Working**" generic protocol may be used as a starting base for the development of a new protocol. A **reference document** "**With Examples**" Generic is available giving full details of protocol development. All information given in **normal typeface** is part of the generic content of the protocol and must be included. All information given in *italic typeface and highlighted* is provided as guidelines for the writer. When sections are not applicable to the protocol you are writing (e.g. central radiology review) leave them out and renumber the subsequent sections.

(For contact information of study personnel see Final Page.)

Note to Writer: Use the following statement when submitting an **Amendment** or **Administrative Update** to CTEP: **(See CTEP Amendment Request Submission Policy at: <http://ctep.cancer.gov/guidelines/templates.html> (click on: CTEP Amendment Request Submission Policy))**

(for NCI CTEP Use ONLY: VERSION DATE: 200X-XXX-XX, UPDATE DATE: 200X-XXX-XX)

CONFIDENTIAL

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Protocol Content

- Study schema
- Background and rationale
- Objectives
- Patient population
- Trial design
- Treatment
- Trial procedures

Protocol Content

- Endpoint and evaluation criteria
- Statistical considerations
- Correlative studies
- Serious adverse event reporting
- Data collection
- Administrative issues
- Informed consent
- Appendices

Protocol Content

- Spirit Initiative⁴
 - International collaborative effort launched in 2007
 - *Standard Protocol Items: Recommendations for Interventional Trials*
 - Aims to improve the quality of trial protocols by producing evidence-based recommendations for a minimum set of standard items that protocols should address
 - Soon to be published Statement, 33 Item Checklist and Explanation and Elaboration document.

Study Conduct

- Study conduct is dynamic and requires multiple levels of oversight to ensure that the safety, ethical and scientific standards are met.
- Amendments to the protocol are part of trial conduct and should not be viewed as indicators of a flawed study

Study Conduct

- Attentive to internal data
 - Adverse and serious adverse event data, laboratory data
 - Adherence to protocol therapy and interventions
 - Accrual
 - Event rate
- Attentive to external data
 - Safety
 - Efficacy - validity of statistical assumptions, continued relevance of the ongoing study

Study Conduct

- Transparent and collaborative
 - Mandatory oversight of independent Data Safety Monitoring Committee
 - Interactive / informative with study participants, ethics boards, scientific community, funders
- Compliant with ethical/ regulatory / scientific standards

Analysis

- The analysis preparation begins at the concept development stage and the process continues until the publication of results
- Fidelity with the protocol
- *Database compilation*: transparent and consistent processes of data management
- Analysis plans and details prospectively defined in the statistical analysis plan

Publication

- Manuscript requirements
 - Uniform requirements for manuscripts submitted to biomedical journals (ICMJE): Writing and editing for biomedical publications (www.icjme.org)
 - Ethical considerations (including authorship and contributorship, COI, privacy...)
 - Publishing and editorial issues (including obligations to publish negative studies, registration of studies...)
 - Manuscript preparation and submission

Web Resources: Regulatory

- E6. ICH Guideline on Good Clinical Practice
 - <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php>
 - Force of law (2001); research conducted under Clinical Trials Application (CTA) with Health Canada (HC)
- Division 5 of the Food and Drug Regulations
 - <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024-eng.php>
 - Trials conducted under a CTA with HC

Web Resources: Regulatory

- Guidance 0068 - Guidance for Records Related to Clinical Trials
 - http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_68_tc-tm-eng.php
 - Describes record retention requirements for trials conducted under a CTA with HC
- Guidance for Clinical Trial Sponsors
 - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php
 - HC requirements and regulations

Web Resources: Regulatory

- OHRP website - Policy and Guidance webpage
 - <http://www.hhs.gov/ohrp/policy/index.html>
 - Includes information related to trials receiving US federal funds
- Clinical Trials Registries
 - <http://www.ClinicalTrials.gov>
 - <http://www.who.int/ictrp/en>

Web Resources: Ethics

- Tri-Council Policy Statement Version 2
 - <http://www.hc-sc.gc.ca/index-eng.php>
 - Not formally adopted by HC; basis of ethical principles in most academic institutions
- Declaration of Helsinki from the World Medical Association
 - <http://www.wma.net/en/30publications/10policies/b3/>
- Belmont Report
 - <http://ohsr.od.nih.gov/guidelines/belmont.html>

Web Resources: Protocol Content

- TNM Staging Criteria
 - www.cancerstaging.org
- Response Criteria
 - RECIST 1.1⁵
 - <http://ctep.cancer.gov/protocolDevelopment>
- Toxicity Criteria
 - Common Terminology Criteria for Adverse Events (CTCAE)
 - <http://ctep.cancer.gov/forms>

References

1. Piantadosi S. Clinical Trials: A Methodologic Perspective. New York NY: John Wiley & Sons; 1997
2. Meyer RM. Generalizing the results of cancer clinical trials. J Clin Oncol. 2010;28:187-189
3. Meyer RM. Contrasting Explanatory and Pragmatic Randomized Controlled Trials In Oncology. ASCO 2011 Educational Book 72-75.
4. Strengthening the Credibility of Clinical Research. Lancet, 2010; 375: 1225
5. **Eisenhauer** EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47

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