The Clinical Trial Protocol Guide

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THE CLINICAL TRIAL PROTOCOL

The clinical trial protocol to test one's product, to confirm or reject a specific hypothesis, is key in the clinical development plan and in the overall development of the product with the goal of moving the science forward and preparing a product for market acceptance.

The clinical trial protocol is the experimental blueprint for a clinical study, and every activity and procedure it specifies should contribute to the efficient testing of the central hypothesis being examined.

A DETAILED GUIDE TO THE CLINICAL TRIAL PROTOCOL

KEY PROTOCOL ELEMENTS	PROTOCOL GUIDANCE
1. Key Roles	Define institutions Sponsor Principal investigator Investigators Key responsible individuals
2. Product rationale; potential risks and benefits	Name of drug Summary of preclinical data Summary of clinical data Relevant background literature Potential risks and benefits Importance of the study
3. Study objectives	Definition of the goals of the study. Should define the gathering of data that are absolutely required building blocks of the total registration dossier of the new drug. Several major categories of clinical trial objectives exist: • Dose-dependent objectives: o Safety and tolerability o Biological effect, pharmacodynamics, surrogate end points o Absolute efficacy (i.e., versus no treatment or placebo control) o Relative efficacy (i.e., versus an established comparative agent) o Pharmacokinetic behavior o Pharmacoeconomic outcomes o Effects in special populations (e.g., pediatric or renal impaired patients)

	• Non-drug-dependent objectives o Natural history of disease o Pilot data to guide the design of subsequent trials
4. Primary and secondary clinical end points	Define primary and secondary clinical trial end points. Phase 1: The end points for first in human studies are usually safety and are conducted in human volunteers. The safety outcomes are assessed after single and multiple dose administrations. Phase 2: These studies are usually exploratory studies in each candidate indication to determine which are most suitable for further development. Phase 2 studies often explore the most appropriate dose of drug to use too, looking for the best efficacy without causing undue safety risks. Phase 3: The FDA and the market place requires the demonstration of clinical relevance and benefit. Typically, the end point should reduce mortality, extend longevity or some other clinical benefit and would require the study to follow patients for a longer period of time. Key commercial questions to consider: 1. What is it your drug really does? How do you define it? What is the benefit it offers over existing treatments? For example, do you know or suspect you have an advantage over the standard of care treatment? If so, how do you articulate it? More critically, how to you define it in a way that translates into a clinical trial end point? 2. Exactly what is the market your drug addresses? Which patients does your drug help most? How can this segment be optimally defined for the purposes of clinical trial conduct and, ultimately, the product label? 3. What information would a doctor want to see to convince them to change their prescribing habits? For example, would a comparison study with the standard of care treatment have great influence, even if not necessary for regulatory approval? If so, what is the magnitude of advantage that must be shown to make your drug a relevant competitor? 4. What product profile would convince a patient to "demand" this drug from their physician? How can the more "technical" clinical benefit shown in trials be communicated on a "lay" level? 5. What information would insurance carriers need to convince them to include this drug in their formularies? Could it reduce overall healthcare costs? Can it replace

	more expensive therapy? Or show such greater benefit that it becomes the new standard of care?
5. Study population; inclusion and exclusion criteria.	Study population description • Inclusion criteria • Exclusion criteria Strategies for Recruitment and Retention
6. Study design	Description of Study Design • Type of design: placebo-controlled, double-blind, open label, dose escalation, dose-ranging • Phase of the trial • The number of study groups/arms • Single or multi-center • Healthy of sick population • In-patient or out-patient • Description of study groups/arms including sample size • Approximate time to complete study enrollment • Expected duration of subject participation • Description of the sequence and duration of all trial periods, including follow up • Name of study agents/interventions • Changes in scheduling such as dose escalations • Stratifications
7. Investigational product	• Define the formulation, packaging and labeling • Product storage and stability • Dose, preparation and administration of the investigational product • Concomitant medications and procedures • Precautionary and prohibited medications and procedures • Prophylactic medications and procedures • Rescue medications • Accountability procedures; Assessment of subject compliance; concomitant medications allowed
8. Study schedule	Subject screening prior to enrollment Enrollment/baseline visit Follow up and follow up visits Final study visit Early termination visit Pregnancy visit Unscheduled visits
9. Study Procedures and Evaluations	Clinical evaluations Laboratory evaluations; specimen preparation; biohazard containment Substudies

10. Safety assessments	• Specification of safety assessments • Definition of an Adverse Events (AE); severity; relationship to study products • Definition of a Serious Adverse Event (SAE) • Method and timing of assessing, recording, analyzing and managing safety parameters • Reporting procedures • Reporting of pregnancy • Type and duration of monitoring of subjects after adverse events • Modification of study agent(s) and intervention(s) for a participant. • Halting rules for the protocol • Stopping rules for an individual participant or cohort • Premature withdrawal of a participant • Replacement of a participant who discontinues study treatment • Expected adverse events • Serious adverse events • Unanticipated events • Procedures of abnormal laboratory test values and abnormal clinical findings • Halting rules • Safety oversight – Data Safety Monitoring Board.
11. Clinical monitoring plan	Site monitoring plan Safety monitoring plan
12. Statistical analysis	Overview and study objectives Study population Description of the analyses Measures to minimize bias Appropriate methods and timing for analyzing outcome measures Study hypothesis Sample size considerations Maintenance of trial treatment randomization codes Participant enrollment and follow up Planned interim analysis (if planned) Safety review Efficacy review Final analysis plan
13. Quality control and assurance	Define local quality assurance and quality control processes, along with relevant SOPs
14. Ethics protection	Ethical principles being followed Institutional Review Board Informed consent process

	Exclusion of women, minorities and children (special populations) Subject confidentiality Study discontinuation Future use of stored specimens
15. Data handling and record keeping	Data management responsibilities Data capture methods Types of data Source documents and access to source data and documents Timing of reports Study records retention Protocol deviations
16. Financing and insurance	Ensure financing is available to complete the study and follow up of patients as defined in the protocol. Ensure adequate insurance is obtained to cover the clinical study
17. Publication policy	Funding body may require interventional studies to be registered with Clinicaltrials.gov If funding body requires it: state publication intent

Sources:

- http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
- http://www.niaid.nih.gov/labsandresources/resources/toolkit/protocol/Pages/protocol.aspx
- http://www.nidcr.nih.gov/ClinicalTrials/ToolkitClinicalResearchers/ClinicalTrialsProtocolTemplate/InterventionProtocolTemplate.htm
- http://www.hhs.gov/ohrp/assurances/
- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50
- http://www.fda.gov/ICECI/EnforcementActions/default.htm
- http://prsinfo.clinicaltrials.gov/