

An Overview of the Research Protocol





Course Objectives

- ★ This seminar is designed for staff that are new to working with research
- ★ Provide an overview structure and content of a clinical research protocol
 - Review study designs including benefits and weaknesses
 - Explain key terms and concepts
 - Provide guidelines for evaluating the feasibility of completing a study in Children's environment





Protocol: What It Is

- ★ The main document for a study
- ★ A written plan of the study
 - Helps organize research in a logical, focused, and efficient way
 - Content differs depending on the following:
 - Type of study
 - The sponsor
 - The audience





Protocol: Industry Sponsor Outline

- ★ Protocol Synopsis
- ★ Introduction
- ★ Study Methodology
- ★ Study Procedures
- ★ Adverse Events
- ★ Statistical Considerations
- ★ Administrative Procedures
- ★ Risk/Benefit Analysis
- ★ Appendices





Protocol Synopsis

[Name] Protocol Synopsis

Title	[Name]
Overview	[Name] is a registry designed to collect and quantify outcomes for patients with chronic pain who receive a [device] by collecting the following: pain, functional restoration, quality of life, and patient satisfaction.
Registry Design	Multi-center cohort registry
Objectives	<p>The objectives of [name] are the following:</p> <ol style="list-style-type: none"> 1. To collect baseline outcomes information for these patients. 2. To collect outcomes information for patients with [device] every 6 months after baseline. 3. To identify conditions associated with better outcomes.
Size	At least 30 centers. [Name] is designed to continue indefinitely. The expectation is that 100% of eligible and consented patients are enrolled at each participating center.
Patient Eligibility	<p>Patients have the following characteristics:</p> <ol style="list-style-type: none"> 1. Scheduled to receive [device] 2. Have pain 3. 18 years or age or older
Registry Procedures	Potential patients are identified by center physicians. After providing informed consent, the baseline assessments are completed (the center staff queries the patient) and submitted to the registry. Follow up assessments are collected every 6 months thereafter.
Appendix A	Data Collection Schedule
Appendix B	Outcome Assessments





Introduction: Background/Significance

- ★ The introduction always includes a “Background” section
 - Sets the study in context and gives rationale
 - What is currently known about the topic?
 - Cites previous research and indicates remaining questions
 - Makes clear how this study will answer these questions
- ★ The introduction often includes a “Significance” section
 - Why is the research question important? Locally? Globally?
 - What is the impact of answering this question?
- ★ The sponsor will name any drug or device included in the study and how they will be used
 - Cites previous research and why the investigators decided to use the drug/device in this way



Study Methodology: Research Question

- ★ Research idea = a general question or concern
- ★ In the methodology section, the primary research question is defined
 - The idea narrowed down into a concrete, researchable issue
 - What will the study answer?
 - What is the purpose of the study?
 - A question that can be answered
- ★ A good research question allows the following:
 - Draw *inferences* from results about population
 - Encourages proper study design
 - Enhances the credibility of the findings





Study Methodology: Research Question

★ When reviewing a protocol, ask yourself,
“Is the Research Question FINER?”

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



Study Methodology: Study Design

- ★ Ecological Study
- ★ Case Study
- ★ Case Series
- ★ Cross-Sectional Study
- ★ Case Control Study
- ★ Cohort
- ★ Clinical Trial

Least Scientifically Valid



Most Scientifically Valid





Study Methodology: Study Design



★ Ecologic Study

- Uses aggregate or population data
 - Information that is available for groups of subjects
 - Usually secondary data sources
- Measure associations by comparing group information on a risk factor with the rate of an outcome
- Utility: hypothesis generation
- Strengths:
 - Inexpensive
 - Quick
 - Simple
- Weaknesses:
 - Population information may not apply to individual = ecologic fallacy
 - No control for confounders
 - Data may not be accurate

• **Only use aggregate data when you don't have individual data**





Study Methodology: Study Design

★ Case Report and Series

- Uses individual or series group selected on disease status
- Retrospectively review patient's chart(s) to create story
- Describe new or interesting clinical observations
- Utility: hypothesis generation, report shared clinical experience
- Strengths:
 - Communicate information
 - Inexpensive and quick
- Weaknesses:
 - Does not reflect the general population = selection bias
 - Exposure is difficult to measure retrospectively
 - Inadequate data collection methods
 - No control over measurements





Study Methodology: Study Design

★ Cross-Sectional Study

- Uses a pre-defined population of subjects
- All measurements are made at one time with no follow-up period
- Describe disease status, exposures, and other characteristics at a specific point in time
- Utility: finding disease and exposure associations
- Strengths:
 - May study several outcomes at once
 - Yields prevalence
 - $\text{Prevalence} = \# \text{ of people who have the disease at 1 point in time} / \# \text{ people at risk}$
 - Inexpensive and quick
- Weaknesses:
 - Not useful with rare diseases or diseases with short duration
 - Does not yield incidence
 - $\text{Incidence} = \# \text{ of people who get the disease over a period of time} / \# \text{ people at risk}$
 - Difficult to determine temporal relationship between exposure and disease (sequence of events)





Study Methodology: Study Design



Cohort Study

- Uses a pre-defined population with follow-up
- Cohort studies have 2 primary purposes:
 1. To describe the incidence of certain outcomes over time
 2. To analyze associations between predictors and those outcomes
- Observe population from health to disease, or disease to event
 - Determine the incidence and investigate the potential cause of a condition
- Utility: characterize relationships risk/treatment and disease outcome
- Strengths:
 - Direct determination of risk
 - Strong evidence of disease relationship
 - Generalizable
- Weaknesses
 - Long duration, expensive, loss to follow-up
 - Observation bias
 - Poor for rare diseases





Study Methodology: Study Design

Case Study – Cohort Study

- ★ The research question is: “Does mild vitamin D deficiency cause hip fractures in the elderly?”
 - How would you develop a cohort study to answer this research question?





Study Methodology: Study Design

★ Case Control Study

- Select diseased (cases) and healthy (controls)
- Look back in time to find differences in predictor variables that explain why the cases got the disease and the controls did not
- Determine cause and effect
- Utility: evaluate relative risk (RR)
- Strengths:
 - Quick and easy, inexpensive
 - Repeatable
 - Useful in rare diseases
- Weaknesses:
 - Only one outcome may be evaluated
 - Selection (sampling) bias
 - Recall bias





Study Methodology: Study Design

Case Study – Case Control Study

- ★ The research question is: “how much does a family history of ovarian cancer increase the risk of ovarian cancer?”
- ★ You plan a case control study to answer this question
 - How would you pick the cases?
 - How would you pick the controls?
 - Are there any potential sources of bias?
 - Do you think the case-control method is an appropriate approach to this research question? Are there other possible study designs?





Study Methodology: Study Design



Clinical Trial

- Uses a clinically defined population
- Compares the effect and value of an intervention(s) against a control
- Demonstrate an intervention effect

- Utility: proof
- Strengths:
 - Control
 - Reduces confounding through randomization
- Weaknesses:
 - Artificial setting → non-generalizable
 - Participant adherence
 - Expense

- Phases:
 - I : Tolerance, laboratory
 - II : Biologic activity, adverse effects
 - III : Effectiveness, benefits and risks
 - IV : Long-term monitoring (post-FDA approval)





Study Methodology: Study Design



Case Study

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- The research question is: “Does maternal height or weight predict infant birth weight?” During a 12-month period an investigator assembles data on consecutive newborns in a large maternity hospital. The study is limited to term newborns as defined by delivery 38 to 42 weeks after the mother’s last menstrual period. In the maternity ward, the investigator measures each infant’s birth weight and the mother’s height and weight. Based on the data obtained, the investigator concludes that birth weight is strongly dependent on both maternal height and weight.
- What kind of study is this?
 - Do you agree or disagree with the investigator’s conclusions?





Study Methodology: Scope

- ★ The scope section of a protocol will define:
 - The length and projected end date of the study
 - Who will be included in the study
 - Choosing study participants are extremely important!!
 - Target population = the people to generalize the results to
 - Study sample = the subset of target population available for the study
 - Sample size = the number of subjects needed to observe an outcome difference between study groups
 - Need an adequate sample size and power to detect clinically important differences
 - The smaller the anticipated difference between the groups, the larger the required sample size



Study Methodology: Inclusion/Exclusion Criteria

- ★ The protocol will define the eligibility criteria
 - This may include permitted and not permitted medication and/or treatment
- ★ Inclusion Criteria
 - Defines the main characteristics of the target population
 - Demographic characteristics
 - Clinical characteristics
 - Geographic/administrative characteristics
- ★ Exclusion Criteria
 - Indicates characteristics that might interfere with the quality or generalizability of the data
 - High likelihood of being lost to follow-up
 - Inability to provide good data
 - High risk for side effects
 - Characteristics that make it unethical to withhold the study treatment





Study Procedures: Informed Consent

- ★ The protocol will highlight the importance of the informed consent process
- ★ All subjects must sign a consent form as a condition of participation
 - The investigator or coordinator describes (in simple language):
 - The nature and objectives of the study
 - The treatments being investigated
 - Tasks, procedures, and tests required of participants
 - Method of treatment assignment
 - Data to be collected
 - Likely benefits and risks of participation
 - Personal information will be kept confidential
 - Withdrawal from the study does not jeopardize medical care





Study Procedures: Recruitment/Enrollment

- ★ The protocol will define the method and procedures for recruitment
 - The goal is to recruit a sample that adequately represents the target population
 - Ultimately, you want to meet the number your site agreed to recruit
 - You will never get the numbers you anticipate!!
 - Telemarketers get a 1.5% response rate
 - Assume you'll get approximately a 20% response rate
- ★ The protocol will also specify any registration and/or enrollment procedure(s)
 - Often completed electronically or by phone
 - Make sure these requirements are practical in the clinical setting





Study Procedures: Description of Procedures

- ★ The protocol will define exactly when research activities will take place
 - Screening
 - Baseline
 - Each study visit
 - Follow-up
- ★ It will also define research activities, which may include the following:
 - Medication administration
 - Blood draw
 - Lab tests
 - H&P
 - Questionnaires
 - CTs, X-rays, MRIs
 - Audiology & ocular exams
 - Neuropsychological tests
 - Specimen collection
 - Etc...

Study Procedures: Study Schedule

Table 3-1 Evaluation and visit schedule

Visit	0	1	2	3	4	5	6	7
Week	SCR	BL	4	8	12	16	20	24
Informed consent	X							
Incl/Excl criteria		X						
Disease history		X						
Height		X						
Weight		X	X	X	X	X	X	X
CBC ¹	X	X	X	X	X	X	X	X
Serum creatinine ¹	X	X	X	X	X	X	X	X
Serum ALT (SGPT) and AST (SGOT) ¹	X	X	X	X	X	X	X	X
Serum ferritin ¹	X	X	X	X	X	X	X	X
Pregnancy test ²	X	As required						
Ocular exam ³	X							X
Auditory exam ³	X							X
Dosage administration		X	X	X	X	X	X	X
Adverse Events ⁴	As required (See # 4 below)							
Serious Adverse events	Reported once subject signs Informed Consent and continuously during trial on CRF and SAE forms							
Study Completion								X

SCR = Screening visit may be conducted up to 4 weeks prior to baseline visit
 BL = baseline visit prior to administration of study drug. Please note that labs do not need to be repeated at baseline if the baseline visit happens within 7 days of the screening visit.
 1 Studies to be performed at the local laboratory for all visits and noted in source documentation (SAE to be entered, if applicable). Please note that serum ferritin at baseline and serum ferritin at the end of study (visit 7 or later, if applicable) should be recorded on the CRF
 2 Pregnancy test only to be performed in females of childbearing potential at local lab; Pregnancy test may be given during study, if required, and results should be noted in source documentation
 3 The first ocular and auditory exams can be performed within 4 weeks prior to the baseline visit. The second ocular and auditory exams can be performed within 4 weeks prior to week 24 visit. The results should be noted in source documentation (and SAE to be entered, if applicable)

Study Procedures: Study Schedule

Table 1. Study Schedule

Patient Research Charges:	Screening					
	Month 0	Month 1	Month 3	Month 4	Month 5	Month 7
Consent Patient	X					
Emla	X		X		X	X
Blood Draw	X		X		X	X
Cholesterol (fasting LDL only)	X		X		X	X
Creatine Kinase	X		X		X	X
ALT	X		X		X	X
AST	X		X		X	X
Billirubin (total and indirect)	X		X		X	X
Pregnancy Test (blood)	X		X		X	X
History and Physical (new patients only)	X					
Drug Administration		10mg	20mg		40mg	
Conner's Continuous Performance Test	X	X				X
WISC-IV Letter-Number Sequencing	X	X				X
Stanford-Binet Intelligence Scale-V Block Span	X	X				X
Hopkins Verbal Learning Test	X	X				X
Grooved Pegboard	X	X				X



Study Procedures: Sampling Method



- ★ The protocol will define the sampling method for the study
- ★ Sampling design = the plan for how you will acquire subjects
 - Non-random method
 - A systematic assignment method that is based on the order of enrollment
 - Probability sample
 - No way to predict the order of future assignments from that of past ones
 - “Randomization”
- ★ Treatment design = the plan for how you will administer intervention
 - Parallel design
 - Group 1 – Treatment A → Follow-up and outcome assessment
 - Group 2 – Treatment B → Follow-up and outcome assessment
 - Crossover design
 - Group 1 – Treatment A → Washout → Treatment B → Follow-up and outcome
 - Group 2 – Treatment B → Washout → Treatment A → Follow-up and outcome





Study Procedures: Sampling Method



- ★ Blinding = study group assignment is unknown
 - In a randomized trial, blinding is as important as randomization
 - Prevents biased assessment of outcome
 - “Co-intervention” – PI gives extra attention to treatment group
 - Difficult to carry out
 - Have the exact same procedure for all study groups
 - After study, assess subjects and investigators to see if unblinded
 - Have a 24-hour mechanism for unblinding





Study Procedures: Sampling Method

Case Study

- ★ A sampling design called for listing all the adult residents of a town and then asking every second person to participate. Unfortunately, one-third of the population refused to participate, and in their place, the PI accepted other respondents who had heard about the study and wanted to participate.

What is the potential problem with this scenario?





Study Procedures

★ Patient Withdrawal

- Clarifies what happens to the patient's data when they do not complete the study
- Think about possible ways to reduce patient withdrawal

★ Patient Study Completion

★ Patient Death

★ Drug / Device Handling / Storage

- Specifies how to dispense the medication, what documentation is required, and what to do with any left-overs





Adverse Events

- ★ Determining whether the beneficial effects of an intervention outweigh adverse effects is a major goal of clinical research
- ★ Adverse events (AEs) range from relatively minor symptoms such as a rash or flu to serious and fatal complications
- ★ The protocol should include a well defined list of minor and serious AEs
- ★ It should also include how these events will be reported to the sponsor and/or the FDA
 - Make sure the reporting timeline is reasonable





Statistical Considerations: Hypothesis

- ★ The hypothesis is a version of the research question that provides the basis for testing the statistical significance
- ★ The hypothesis is included in the statistics section
- ★ A hypothesis can be framed in one of two ways:
 1. Demonstrate no difference: the outcome is the same for the intervention and control or between two interventions
 - Called the “null hypothesis” (H_0)
 2. Test a hypothesis: an intervention group have an outcome that is different from the control group
 - Called the “alternate hypothesis” (H_a)



Statistical Considerations: Hypothesis

★ Example:

- Research question: What are the effects of treatment with estrogen plus progestin on Lp(a) levels in postmenopausal women?
 - H_0 : Postmenopausal women in the hormone-treated group will have the same Lp(a) levels as the women who receive the placebo
 - H_a : There will be a difference (decrease) in Lp(a) levels in the hormone-treated group than the placebo group
- ★ Come up with a research question of interest to you
- ★ What is the hypothesis (specify null or alternate) for this research question?



Statistical Considerations: Hypothesis

★ Is the hypothesis specific?

- The “effect size” should be very clear
 - This is the size of outcome that is clinically important
 - Example: Alcohol consumption (in mg/day) is associated with an increased risk of proteinuria (>30 mg/dL) in patients with diabetes

★ A study may include primary and secondary hypotheses based on the research question(s) / objective(s)





Administrative Procedures

★ Investigational Sites

★ Case Report Forms (CRFs) / Data Requirements

- Get copies of the CRFs as soon as possible
- Evaluate the clinical relevance and benefit to the patient and our institution to participate in terms of feasibility and cost
 - Is the study collecting enough data?
 - Are the subject requirements reasonable?
 - Are the staff requirements reasonable?
 - Will the budget cover the costs to complete these requirements?
 - Is the timeline for data submission reasonable?

★ Source Documentation

★ Study Monitoring





★ Administrative Procedures

- ★ Protocol Deviations
- ★ Protocol Amendments
- ★ Document Retention and Availability
- ★ Regulatory/Ethical Obligations
- ★ Institutional Review Board (IRB)
- ★ Patient Confidentiality
 - What steps have been taken to ensure patient confidentiality?
- ★ Records and Reports
 - Will the results of the study be reported to anyone? Published?
- ★ Data Management
 - Who is responsible for maintaining the data?



Risk/Benefit Analysis

★ Potential Risks

- What are the risks to participating?

★ Methods to Minimize Risk

- How has the study been designed to minimize risk?

★ Potential Benefits

- What are the benefits, compared to standard of care?

★ This section of the protocol is very useful as a reference during the informed consent process

- Make sure the information present here is in alignment with the consent/assent form(s)

