

**CLINICAL
PROTOCOL
DEVELOPMENT**

Clinical Protocol (1)

- **Background/Justification**
 - Where we are in the field
 - What the study will add that is important
- **Objectives**
 - Primary hypothesis
 - Secondary hypotheses
 - Other

Clinical Protocol (2)

- **Study Design and Methods**
 - Type of study, comparison
 - Inclusion and exclusion criteria
 - Description of intervention (what, how)
 - Concomitant therapy
 - Examination procedures (baseline, follow-up, outcome assessment)
 - Intervention assignment procedure

Clinical Protocol (3)

- **Monitoring and Management**
 - Data and safety monitoring
 - Adverse event assessment, reporting
 - Contingency procedures
 - Withdrawal criteria

Clinical Protocol (4)

- **Statistics**
 - Sample size
 - Stopping guidelines
 - Analysis plans
- **Participant protection issues**

Summary

- **Protocol lays out who, what, why, when, where, how**
- **Safeguards participants**
- **Safeguards study integrity**
- **Midcourse changes are often appropriate (even necessary)**

What's The Question?

What is the study hypothesis?

What's The Question?

- **What's the outcome?**
- **What's the intervention?**
- **When and for how long?**
- **Who and for whom?**
- **How many?**
- **How can we optimize potential benefit (and what we learn) while minimizing potential harm?**

Answering the Question

- **Endpoint (response variable) selection and measurement**
- **Defining the intervention**
- **Study design**
- **Eligibility criteria**
- **Sample size estimate**
- **Patient management procedures**
- **Monitoring for safety and benefit**
- **Data analysis approaches**

Response Variable Selection

- **“Dose ranging”**
- **Biologic activity**
- **Biomarker**
 - **Understand mechanism**
 - **Surrogate outcome**
- **Toxicity**
- **Gene interaction**
- **Feasibility for larger study**
- **Clinical outcome**

Endpoint choice

- **Well defined**
- **Stable**
- **Reproducible**
- **Unbiased**
- **Ascertainable in all participants**
- **Adequately address study hypothesis**

Defining the Intervention

- **Dose/dosing schedule**
- **Route of delivery**
- **Method of preparation**

Study Design

- **Uncontrolled**
- **Controlled**
 - **Before/after**
 - **Historical**
 - **Concurrent, not randomized**
 - **Randomized**

Comparing Treatments

- **Fundamental principle**
 - **Groups must be alike in all important aspects and only differ in the intervention each group receives**
 - **In practical terms, “comparable treatment groups” means “alike on the average”**
- **Randomization**
 - **Each participant has the same chance of receiving any of the interventions under study**
 - **Allocation is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned**
- **Blinding**
 - **Avoidance of conscious or subconscious influence**
 - **Fair evaluation of outcomes**

Study Population

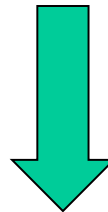
Subset of the general population determined by the eligibility criteria

General population



Eligibility criteria

Study population



Enrollment

Study sample

Observed

Eligibility Criteria

- **State in advance**
- **Consider**
 - **Potential for effect of intervention**
 - **Ability to detect that effect**
 - **Safety**
 - **Ability for true informed consent**

Sample Size (1)

- **The study is an experiment in people**
- **Need enough participants to answer the question**
- **Should not enroll more than needed to answer the question**
- **Sample size is an estimate, using guidelines and assumptions**

Sample Size (2)

- **Assumptions depend on**
 - **Nature of condition**
 - **Desired precision of answer**
 - **Availability of alternative treatments**
 - **Knowledge of intervention being studied**
 - **Availability of participants**

Regular Follow-up

- **Routine Procedures (report forms)**
 - **Interviews**
 - **Examinations**
 - **Laboratory Tests**
- **Adverse Event Detection/Reporting**
- **Quality Assurance**

Contingency Plans

- **Patient management**
- **Evaluation and reporting to all relevant persons and groups**
- **Data monitoring plans**
- **Protocol amendment or study termination**

Data Analysis (1)

- **Occurrence of event**
- **Time to event**
- **Mean level of response**
- **Duration of response**

Data Analysis (2)

- **Intention-to-treat**
- **Explanatory**
- **Subgroups**
- **Adjusted vs. Unadjusted**

Data Analysis (3)

- **Specify in advance**
 - **Primary**
 - **Secondary**
 - **Other**
 - **Statistical approach**
- **Exploratory**

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