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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