

From “Proof-of-Principle” Trials Through Phase 3: The Process

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Regulatory Issues

- Stages of Drug Development
 - Protocol Design Issues
- Evidence of Effectiveness
- Endpoint Selection
- Accelerated Approval

Stages of Drug Development

- In-vitro studies
- Preclinical animal studies
- Clinical Trials
 - Phase 1
 - Phase 2
 - Phase 3
- Marketing Approval
- Phase 4 Clinical Trials

Protocol Design Issues - Preclinical

Mimic proposed human administration

Dose

Route

Regimen

Duration

Provide “Proof-of-Principle”

Predict toxicity

– guide monitoring program

Phase 1

- Includes initial introduction of the study agent into humans
- Small (usually <100) sample size
- Often dose-escalation design
- Primary goals are usually safety and pharmacokinetic assessments
 - Define common side effects
- Demonstrate activity of the treatment in the disease

Protocol Design Issues – Phase 1

- Starting dose
- Rate of Dose-escalation
- Regimen

Protocol Design Issues – Phase 1

- Parallel vs. Sequential cohorts
- Staggering (time interval)
 - Between cohorts
 - Within cohorts
- Stopping rules – incidence of adverse events that will lead to discontinuation of enrollment and treatment

Phase 2

- Moderate size (up to a few hundred)
- Define activity of the drug
 - Define optimal dose and regimen
 - Assess population (and subgroup) response
 - Evaluate various endpoints
 - Magnitude of effect
- Additional safety information
 - Define moderately common adverse events

Protocol Design Issues – Phase 2

- Dose, route, and regimen exploration
- Population
- Endpoints

Phase 3

- Definitively establish safety and efficacy; lead to assessment of Risk : Benefit Relationship
- Usually large (hundreds to thousands)
- Success depends on design
 - Dose and regimen
 - Target population
 - Endpoints

Protocol Design Issues – Phase 3

- Evidence of Effectiveness
 - 2 Trials vs. 1 Trial
- Endpoint Selection

Protocol Design Issues – Phase 3

Evidence of Effectiveness

FDA requires substantial evidence of effectiveness to support marketing approval

Protocol Design Issues – Phase 3

Evidence of Effectiveness

- FDA requires substantial evidence of effectiveness to support marketing approval
- What is substantial evidence? : usually requires two well-designed (well-controlled) clinical trials, each one positive, to establish that a drug is effective.

Protocol Design Issues – Phase 3

Evidence of Effectiveness

A single positive study, especially if there are multiple centers, consistency across centers, a large sample, consistency across study subsets, good rationale, multiple endpoints, and a statistically persuasive result, may be sufficient for marketing approval.

(see FDA Guidance on “Providing Clinical Evidence of Effectiveness”)

Protocol Design Issues – Phase 3

- Evidence of Effectiveness
- Endpoint Selection
 - Types: Measures vs. Events
 - Roles: Primary vs. Secondary
 - Qualifications: Valid vs. Ideal

Endpoint – Definition

- Measure or event that occurs during the course of a clinical trial
- A specific outcome, at a specific timepoint, using a specific analysis plan

Measurements vs. Events

- Often continuous
 - Examples:
FVC, MVIC
 - Many potential values over time
 - Relatively high sensitivity to detect an effect
 - May detect unimportant changes
- Binary - yes / no
 - Examples: death, progression to a specified landmark
 - Occur at specific time
 - Relatively low sensitivity to detect an effect
 - may be more clinically meaningful and interpretable than measurements

Primary vs. Secondary Endpoints

- Primary endpoint
 - the endpoint which is the single best indication of the treatment effect
- Secondary endpoint(s)
 - Supportive of primary endpoint
 - Especially important when primary endpoint is subjective
 - Multiple endpoints may improve confidence

Endpoint – Qualifications

Valid vs. Ideal

- Valid Endpoint
 - Required for the primary efficacy endpoint in a Phase 3 trial
- Ideal Endpoint

Endpoint - Qualifications

- Valid Endpoint
 - Reliable
 - Clinically Meaningful (how much of a change?)
 - Varies with individual trial
- Ideal Endpoint
 - Reliable
 - Clinically Meaningful
 - Feasible
 - Objective
 - Sensitive
 - Clinically Interpretable (e.g., MVIC slope?)

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Relationships of Clinical Trial Phases to Endpoints

- Choice of endpoint(s) should reflect the trial objectives
- Different endpoints may be appropriate for different phases of drug development
- Primary and secondary endpoints should be complementary

Relationships of Clinical Trial Phases to Endpoints

No single endpoint is
ideal for all phases
of all clinical trials in
a specific disorder

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Accelerated Approval

- For serious or life-threatening diseases
- May use surrogate endpoint which is reasonably likely to predict clinical benefit
- Requires adequate well-designed trials
- Requires meaningful therapeutic benefit over existing treatments
- Marketing approval includes a requirement of further studies to determine the true clinical benefit

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References

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