CLINICAL TRIALS

John M. Kane, M.D.
Professor of Psychiatry, Neurology & Neuroscience
Albert Einstein College of Medicine

Thomas Laughren*, M.D.
FDA

Larry Alphs, M.D.
Janssen

*FDA/Laughren/2008

Basic Components of Typical Protocol

- Background (Rationale)
- Objectives
- Statement of “the Question/Hypothesis”
- Definition of primary and secondary measures
- Definition of endpoint
- Definition of population to be studied
  - Selection criteria
- Trial design
  - Procedures
  - Schedule
- Statistical analysis plan
- Consent procedures
- Other logistical issues
  - Drug Supply
  - Monitoring
  - Training

Step 1

Identify the customer for the study.

Matching the Information to the Customer

Regulators	Meet necessary regulatory requirements in US and ex-US • Manage ever shifting demands by customer • Clarify issues that are unclear
Physicians, Patients, Advocacy Groups Professional Societies	• Establish efficacy of drug in relevant areas • Establish safety of drug in relevant areas • "Drivers Manual" issues: Dosing, titration, Drug-Drug Interactions; acute and maintenance effects • Demonstrate value in particular subpopulations - pediatric, geriatric populations - Effects by gender, race, etc
Payers National/ Federal/State Gov't Managed Care	• Establish "value proposition," i. e, identify patient populations where drug might bring particular value

Customer: Regulators

- Package Insert—governs promotable information about the drug
- Elements
  - Clinical pharmacology -- Clinical Indications
  - Pharmacodynamics -- Dosage range
  - PK -- Contraindications
    - Special Populations -- Warnings
    - Gender -- Precautions
    - Age
    - Ethnicity
    - Liver Disease
    - Renal Disease

Customer: Regulators

- Package Insert—Elements (cont)
  - Drug-drug interactions
  - Side Effects
    - Clinical Trials
    - Post Marketing
  - Pediatric Use
  - Geriatric Use
  - Drug abuse/dependence
  - Safety in Pregnancy/Nursing
  - Discontinuation effects
  - Overdose

Customer: Payers

- “Value proposition”
  - Differentiation from existing compounds
    - New indications
    - Special populations
    - Long term outcomes
    - Disease modification
    - Functioning
    - Adherence

Step 2

Identify the question to be address for customer(s).

Step 3

Identify appropriate methodology.

Trial Design
Study Population

- Rarely identical to ‘target population’
- How generalizable are results of study?
- Need for efficacy studies—knowledge of molecule– and ‘effectiveness’ studies—knowledge of value of molecule in target population

Trial Design
Sources of Information

- Often interpretation of patient experiences via a second party
- Issues
  - Quality of information gathering
  - Ability to interpret information
  - Poor communication/insight from many patients
  - Cultural difference
  - Validity of instruments (diagnostic or rating scales)
  - Reliability of raters
  - Blinding

Trial Design
Comparators

- Choice is dependent on the nature of the question being asked
- Possibilities
  - Across time (historical controls)
  - Between Studies (‘virtual head to head’)
  - Among treatment groups
    - Placebo
      - FDA requires demonstration of superiority to some comparator that does not worsen the patient’s condition.
    - Active…which active comparator?
      - Often desired by clinicians
      - Appropriate use

Trial Design
Randomization

- Random treatment assignment offers many benefits (especially to avoid confounding)
  - Still requires adequate sample size
  - Must be ethical/practical
- Alternatives must be considered where not ethical/practical
- Don’t underestimate the intelligence of the patient or the investigator
- Possibilities include: “patient preference” trials, adaptive randomization
- Randomization can be blocked or stratified

Trial Design
Blinding

- Offers reduction of several sources of bias
- Must consider effect on treatment pattern, external validity and pragmatic complications
- At least three levels of blinding possible in large clinical trials
  - Patient
  - Health care provider (physician)
  - Rater
  - Sponsor

Trial Design
Increasing ‘Signal to Noise’ Ratio

- Exclude confounding concomitant medications
- Exclude confounding psychotherapies
- Control/minimize non-specific interventions
- Dosing schedules (fixed or flexible)
- Trial duration: long enough to see meaningful effect
- Ensure treatment occurs
  - Compliance checks; medication diaries; blood levels
- Site Selection
  - Investigator/Staff/Staff Training/Incentives
  - Mechanisms for follow-up and drop-out control

Trial Design
Patient Selection

- Define eligible population (selection criteria)
  - Varies by phase of development
  - Safety and generalizability are competing factors
- Ensure entry of eligible patients
  - SCID interview/structured interview
  - Review investigator/staff
  - Effects of incentives
  - http://www.soyouwanna.com/site/syws/guineapig/guineapig.html

Trial Design
Measures of Outcome

- Choose appropriate secondary efficacy measures and safety/tolerability outcomes
- Efficacy:
  - "Sensitivity analysis"
    - Supports/extends understanding of primary hypothesis
    - Generates new hypotheses
    - May add to causal inference reasoning
    - May help understand confounding issues (e.g., country)
- Safety/Tolerability
  - Ethically required
  - Crucial context for interpreting risk:benefit
  - May be primary outcome measures
- PK and pharmacogenomic information
  - May multiply value of study

Clinical Trial
Evaluation and Analysis of Scales

- Quantification
  - Numerical treatment of typically non numerical reality or theoretical constructs
  - Issues
    - Within a construct, does 2 = 2?
    - Within a construct, does 3 – 2 = 3 – 2?
    - Within a construct, does 2 – 1 = 4 – 3?
    - (Is a change from moderate to severe, the same as a change for mild to moderate?)

Clinical Trial
The Primary Inferential Test

- A classical test intending to find difference (null hypothesis of equivalence) or a test intending to find equivalence (non-inferiority)?
  - Because of great variability across populations with respect to response to any treatment (active or placebo) a “difference test” is necessary
  - Equivalence / non-inferiority to an active drug may be equivalence to placebo
- Placebo response is a problem
  - Even when compared to drugs that work well and immediately (e.g. benzodiazepines)
  - Even in severe chronic psychiatric disorders (e.g. schizophrenia)

Trial Design
Sample Size

- What is the right size?
  - What is the question?
    - Proof of Concept
    - Regulatory Grade
- What is the variability of the measure? What is absolute size of difference sought?
  - Ethical considerations of underexposure/overexposure
- Additional considerations
  - Need for co-variates
  - Need for stratification
  - Need to address potential confounders (country/culture)
  - Noise in Phase 3, based on results of Phase 2
  - Need to exclude sites/data

Clinical Trials

Achieving a Statistically Significant Difference

- Increase the power
  - Increasing number of subjects may increase variance
- Decrease the variance
  - Reduce the number of investigators
    - Reduces number of subjects recruited/unit time
    - Decreases power or increases time to completion
  - Reduce the proportions of “refractory patients” and “placebo responsive patients”
    - Entry criteria
    - Enrichment strategies
      - Affects generalizability of findings
    - Reduce speed of enrollment pressures
  - Training on Clinical Trial measures
  - Better inter-rater reliability, less variance

Clinical Trials: Developing the Report "How to Read a Research Paper"

- Identify the main question or hypothesis.
- Determine to what extent the methodology allows you to answer that question?
- Be familiar with statistical approaches and their limitations.
- Review the results
  - Be skeptical of p values
  - Are results supported by secondary measures
  - Consider generalizability of data
- Read discussion

FDA Role in Psychopharmacological Drug Treatment Development

Thomas Laughren, M.D.

Director,

Division of Psychiatry Products

Food and Drug Administration

Topics Covered

- Ideal knowledge base for new drug
- Phases of drug development
- FDA’s role in drug development
- Key regulatory issues for the development of psychiatric drugs

Ideal Knowledge Base for New Psychotropic (Part I)

- Identify population(s) that will benefit (and how)
- Understand how to use the drug
- Understand drug interactions
- Know comparative efficacy and safety

Ideal Knowledge Base for New Psychotropic (Part II)

- Identify population (s) that will benefit (and how)
  - Adequately characterize population
  - Predictive value of illness subtypes, etc
    - Role of biomarkers
  - What features of illness do and do not respond?
  - Management of nonresponders
    - Note: Re-randomization design

Ideal Knowledge Base for New Psychotropic (Part III)

- Understand how to use the drug
  - Dose response curve (same for plasma level)
    - Effectiveness range
      - Minimum Effective Dose
      - Plateau for effectiveness
      - Maximum Tolerated Dose
    - Safety: D/R for important adverse events
  - Optimal titration
    - Daily dosing schedule
    - Titration schedule (increments/intervals)
  - Timing of efficacy and safety
    - Time of onset
    - Duration of effect (both short-term and long-term)
      - Note: Randomized withdrawal design
  - How to stop the drug

Ideal Knowledge Base for New Psychotropic (Part IV)

- Understand drug interactions
  - Both for efficacy and safety
  - Both PK and PD
  - General Types of Drug Interactions to Explore
    - Drug-drug
    - Drug-disease
    - Drug-demographic

Safety: Requirements for Approval [Food, Drug, and Cosmetic Act (Sec. 505)]

- “include all tests reasonably applicable to show...drug is safe...under...proposed labeling”
- “results of such tests show...drug is safe under such conditions”

Phases of Drug Development

- Phase 1: Initial human trials--Tolerability and pharmacokinetics
- Phase 2: Early patient studies
- Phase 3: Definitive clinical safety and efficacy trials
- Phase 4: Postmarketing development

Efficacy: Requirement for Approval [Food, Drug, and Cosmetic Act (Sec. 505)]

- "Substantial evidence" of effectiveness from "adequate and well-controlled investigations"

ICH Guidance Regarding Population Exposure to Assess Safety

- For drugs intended for long-term treatment of non-life-threatening conditions
- General expectations for exposure
  - 1500 overall
  - 300-600 for $\geq$ 6 months
  - 100 for $\geq$ 1 year
- These numbers refer to exposure at relevant doses

Labeling: Requirement for Approval [Food, Drug, and Cosmetic Act (Sec. 505)]

- Labeling must not be "...false or misleading in any particular."

FDA's Role in Psychiatric Drug Development
(with focus on clinical aspects)

- Oversight of IND process
- NDA review and action
- Drug labeling (package insert)
- Drug promotion and advertising

FDA Oversight of IND Process

- Initial IND review (may proceed/hold)
- Ongoing protocol review
- Review of adverse event reports
  - Note: Reflected in Clinical Investigator Brochure
- Review of annual reports

NDA Review and Action

- Different levels of review
- Decision-making authority (division vs office)
- Actions:
  - Complete Response
  - Approval

Interactions of FDA with Sponsors

- Formal Meetings
  - PreIND
  - End-of-Phase 2 (EOP2)
  - PreNDA
  - Often other meetings as well
- Formal correspondence (letters)
- Informal contacts (telcon, fax, e-mail)

Key Regulatory Issues in Discussions with Sponsors

- Identifying acceptable clinical targets for drug claims
- Identifying populations to study
- Identifying acceptable trial designs
- Specifying primary and secondary endpoints in clinical trials

Evolution in Psychiatric Drug Claims over Past 20 Years

- Previous approach: Broad claims (mostly anxiety, depression, psychosis)
- Current approach: Specific diseases or syndromes (and possibly specific symptoms or symptom clusters)

Specific Psychiatric Diseases/Syndromes for which Psychotropics Now Approved

- Generalized Anxiety Disorder
- Obsessive Compulsive Disorder
- Panic Disorder
- Social Anxiety Disorder
- Posttraumatic Stress Disorder
- Major Depressive Disorder
- Bipolar Depression
- Seasonal affective disorder
- Schizophrenia
- Mania
- Bulimia
- Premenstrual Dysphoric Disorder
- ADHD

Specific Psychiatric Symptoms or Symptom Clusters for which Psychotropics Now Approved

- Agitation in schizophrenia
- Agitation in mania
- Suicidality in schizophrenia

Specific Psychiatric Diseases/Syndromes and Symptom Clusters for which Psychotropics are Being Developed

- Psychosis of Alzheimer's Disease
- Psychotic depression
- Treatment resistant depression
- Cognitive deficits in schizophrenia
- Negative symptoms of schizophrenia

Evolution in Psychiatric Populations Studied over Past 20 Years

- Previous approach: Limited diversity in demographics and comorbidity
- Current approach: More diverse demographics and more comorbidity
  - Especially pediatric and elderly populations
- Future: Need greater diversity in Phase 3 (demographics, comorbidity, co-administered drugs)

Evolution in Trial Designs for Psychiatric Drug Studies over Past 20 Years

- Previous approach: Mostly acute (3-6 weeks), flexible dose vs placebo
- Current approach:
  - Longer acute studies (up to 12 weeks)
  - More fixed dose studies
  - More 3-way studies (active control and placebo)
  - More long-term studies (randomized withdrawal)
  - Add-on studies
  - Fixed combination trials
  - Large simple trials

Primary vs Secondary Outcomes

- Primary Outcome
  - Primary hypothesis being tested
  - Needed for “win”
  - Usually change from baseline, drug vs placebo, on disease specific measure
  - If more than one, need to make it at $p \leq 0.05$ on all
- Secondary Outcomes
  - Clinical questions of interest, but may not be considered essential for win (e.g., CGI or functional status)

Labeling Implications of Secondary Outcomes

- In past, generally not considered acceptable to include in labeling
- Alternative approach:
  - Prior agreement with division on certain “key” secondary outcomes
  - Declaration in protocol of these secondary outcomes
  - New drug need not “win” on these for study to be considered “positive”
  - If primary outcome is positive, distribute alpha=0.05 over declared secondary outcomes (or test sequentially)
  - Positive results included in labeling, if replicated

Other Regulatory Issues Under Active Discussion

- Comparative claims (superiority or noninferiority)
- Time of onset
- Optimal designs for longer-term efficacy trials
- Critical Path Initiative