Efficacy (Explanatory) and Effectiveness (Pragmatic) Trials in Psychiatry: US Regulatory Perspective

Ni A. Khin, M.D.

Medical Team Leader
Division of Psychiatry Products (DPP)
Office of Drug Evaluation I/Office of New Drugs
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

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Statistical, Clinical, Payer and Regulatory Perspectives on Dimensions that Define the Spectrum of Efficacy and Effectiveness Trials

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Outline of Presentation

- Efficacy and Effectiveness Trials in Drug Approval
- Examples of Effectiveness Studies in Psychiatry
- Trial Design, Population, and Endpoints
- Data Analysis
- Regulatory Issues: Labeling Claim

Effectiveness Requirement for Drug Approval

- To establish a drug's effectiveness by "substantial evidence"
  - Added to the Federal Food, Drug and Cosmetic Act in 1962
  - Impetus: Concern about the misleading and unsupported claim
- Substantial Evidence [section 505(d)][1]
  - Adequate and Well-Controlled Investigations

Efficacy Trials in Psychiatry Drug Approval

- FDA requires positive results from adequate and well-controlled investigations
  - Pre-Approval: 2 Short-term Efficacy & Safety Trials

    - Randomized, Double-Blind, Placebo-controlled is a standard.

    - Active-Control for assay sensitivity is helpful.

  - Post-Approval: Longer-term Maintenance Trial

    - Open-label stabilization followed by double-blind, placebo-controlled, randomized withdrawal phase.

Efficacy Trials in Psychiatry

- Short-term DB, PC, RCT (MDD, n=81 [2]; Schizophrenia, n=32[3])

  - Difference in mean change from baseline between drug and placebo (~2.5 points in HAMD; ~8.5 PANSS)

  - Approx. 50% MDD & 75% schizophrenia trials were successful

- Baseline disease severity and treatment response

  - substantial treatment effect (drug-placebo difference) with higher baseline scores[2,4]

- Maintenance Trials (Randomized Withdrawal Design)[5] (MDD, n=13)

  - 50% reduction in relapse rate with antidepressants

  - Very high trial success rate (~100%)

Efficacy/Effectiveness in Psychiatry

- NICE definition of a threshold for clinical significance[6]
  - an effect size of 0.50 or
  - a drug/placebo difference of 3 points on HAMD

- Number Needed to Treat
  - NNT= 4 (6 MDD trials)[7]
  - NNT= ~5-10 (CATIE phase 1)[8]
  - NNT= 3 (CATIE phase 2 with clozapine)[8]

Effectiveness Studies in Drug Approval

- FDA considers effectiveness trials as part of the efficacy continuum
  - Distinction is not unidimensional, but more complex[9,10]
  - Not unusual to adapt some pragmatic and explanatory features in trial design[10]
- Division of Psychiatry Products (DPP) has yet to develop policy on this, but
  - Considered the effectiveness trial in psychiatry: Clozapine in reducing of the risk of recurrent suicidal behavior in schizophrenia[11]
  - Will consider effectiveness studies if arguments be made by the sponsors

Examples of Effectiveness Trials in Psychiatry

- **A series of publications on large pragmatic trials**
  - **Schizophrenia**
    - **InterSePT** (International Suicide Prevention Trial)[12]
    - **CATIE** (Clinical Antipsychotic Trials of Intervention Effectiveness)[13]
    - **CUtLASS** (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study)[14]
    - **EUFEST** (European First Episode Schizophrenia Trial)[15]
  - **MDD**
    - **STAR*D** (Sequential Treatment Alternatives to Relieve Depression)[16]
    - **CO-MED** (Combining Medications to Enhance Depression Outcomes)[17]

Trial Design Features in Effectiveness Studies

"Prospective, Randomized, Blinded" Trials

- Double-blind RCT with some exceptions
  - CATIE-Phase 2: Open-label clozapine arm
- Single-blind, Randomized
  - CO-MED: Some medication assignments blinded to patients
- Randomized, Open-Label, Blinded Rater
  - InterSePT
    - Type I event (attempt/hospitalization): blinded adjudication external group (SMB)
    - Type II event (worsening): blinded psychiatrist at the site.
  - CUtLASS: patients were randomly assigned to open-label antipsychotic treatment with clinical rater blinded to treatment assignment

Design Feature for Effectiveness Studies in Regulatory Submission

- **Randomized Controlled Trial** 
  - Required feature

- **Non-Randomized Trial** 
  - Generally, not acceptable for labeling claim
  - Exception: Observational Studies may be considered as part of the source of supportive data[11,18,19]

Trial Design Issues in Effectiveness Studies

Patient Selection:

- Eligibility Criteria
  - Broader Inclusion Criteria
  - Minimal Exclusion Criteria

Outcome Measures and Assessment:

- Patient Reported Outcome
  - Self-Report

Endpoint:

- Define Endpoint (e.g., Time to Treatment Failure; Time to Rescue)
  - Use of blinded adjudication
  - Clinician judgment

Effectiveness Studies

Often Comparative Effectiveness

- Dosing
  - More flexible dosing
  - Comparable doses
- Compliance
  - Improve compliance (e.g., IM depot vs. oral)
  - Treatment delivery system related issues should be built into the trial
- Dropouts
  - Follow up plan

Effectiveness Studies

Large sample size

- Site Setting
  - Clinic: mostly represent real world
  - Not typical trial site but may have some experience in conducting clinical trial
- Large numbers of investigator sites
  - Clinician expertise; Prescribing pattern differences
  - Site monitoring

Data Analysis in Effectiveness Studies

- Hypothesis Testing
- Determine acceptability of proposed analysis method

  Example:
  - Using a log-rank test based on the ITT analysis set
  - Cumulative distribution of time to event will be estimated by Kaplan-Meier method
  - Estimate of the hazard ratio and CI will be determined using a Cox proportional hazards model
- SOP

  Prospectively define blinded adjudication process
- SAP

  Submit statistical analysis plan prior to trial completion
  - Composite primary endpoint: analyze sub-components
  - Alternative censoring schemes for sensitivity analyses

Labeling Language in Psychiatry Products

1. Indications and Usage

- Drug X is indicated for the treatment of YY Disorder
  - Efficacy established in 2 short-term RCT
  - Add 1 maintenance trial
  - State in adults and/or pediatrics
  - May consider 1 typical efficacy trial and 1 effectiveness trial at initial approval (depend on claim going after)
  - Additional effectiveness trial conducted post-approval may be noted in the indication section as additional support for approved indication
  - May just simply state as PC or AC trial and refer to section 14 where results could be provided. Exactly what details to provide would be a matter for review.

Labeling Language in Psychiatry Products

14. Clinical Studies

- Description of Clinical Study and Results
  - Trial Design: Randomized, Placebo
  - Study Duration
  - Dosing
  - Patient Population
  - Instruments, Study Endpoints
  - Summary of Results for Primary Endpoint
  - Pre-specified Key Secondary, if any
  - Subgroups (age, gender, race)

Potential Labeling Claim of Effectiveness Trials: DPP Current Thinking

- DPP encourages the sponsors to request for a meeting prior to initiating any effectiveness trial "intended" for potential labeling claim
  - Submit relevant information: description of study design, target patient population, analysis plans, etc.
  - Discuss scientific and regulatory issues: how the information might be described in the labeling
  - Potential to produce useful results to clinicians
- DPP may take the application to Advisory Committee (PDAC) to further discuss any complex issues (interpretation of results)

Potential Promotional Claim of Effectiveness Trials

- DPP Review Division Perspective
  - Any information in the product label may be used for promotion
- FDA CDER Office of Prescription Drug Promotion
  - The Sponsor should request for advisory from OPDP

Conclusion

Efficacy (exploratory) Trials

- Regulatory approval based on results from efficacy trials
- Scientific community is working on study design issues in order to improve signal detection in RCT
- FDA is in support of this effort

Conclusion

Effectiveness (pragmatic) Trials

- Will ask for scientifically valid design (RCT)
- Will likely accept diverse setting, broader population, different endpoint, and trials not necessarily include blinding.
- Payer's perspective: results from comparative effectiveness studies - informative choice among treatment options
- May consider effectiveness study as part of labeling claim but the sponsor should work with DPP on study design and analysis plan prior to initiating such trial

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