ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Challenges and Implications of Use of Active Controls in Risk:Benefit Analysis in CNS Clinical Development Programs: An Industry Perspective

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Disclaimer

- Employee of Ortho-McNeil-Janssen
- Past employee of Novartis, Knoll (Abbott), Pfizer
- Past academic positions at
  - U of Chicago, U of MD, CWRU, Wayne State U
- Past Chair of Scientific Committee/President of ISCTM
- Opinions are NOT those of any employer past or present, ISCTM or any other group with which I am/have been affiliated
  - Believer in the scientific method
  - Dedicated to the patients I serve
  - Fallible

The Question

- **Are the standards for CNS drug development changing?**
- **How?**

Background

- **R Temple (*IOM 2008*)**
  - **"…we would like to find a way to get CATIE into the labeling for all of the antipsychotics"**
  - **"…we have recently turned down antipsychotics because they were less good than the existing drugs, and we did not feel that schizophrenia patients should have less good treatments than they already have."**
  - **"Comparative *effectiveness* is a very thorny problem,…for most drugs their *effectiveness* might be in the range of 20% to 30%, not 100%. …How can research be designed to detect an advantage that may be slight in one drug over another for the same condition? …The methodology that's used depends on what you're trying to detect"**

General Questions

- **Are *effectiveness* trials now a requirement for labeling?**
- **Or are they an opportunity for labeling?**
- **What is the meaning of 'inferiority' in a trial not designed to show inferiority?**

Specific Comparator Questions

- What is the question asked of the active comparator?
- Which active comparator?
- Which doses of active comparator
- For which indications is the active comparator valid?
- In which phase of development?
- Is this statistically valid?
- Are there alternative approaches to addressing these issues?

Effectiveness Trials

- **'Comparative Efficacy' vs 'Comparative Effectiveness'**
  - **'Is the drug safe and effective in a particular population?'**
  - **"Is the drug effective in a particular population using a particular medical treatment paradigm?'**
    - **Labeling issue vs Commercial issue**
  - **Drug…patient selection..medical treatment paradigm cannot be disentangled**
    - **Issues of generalizability**
  - **Is it the domain of regulators of the product label? Do regulators of pharmaceuticals also regulate the treatment system?**
  - **Will comparative efficacy trials also be required?**

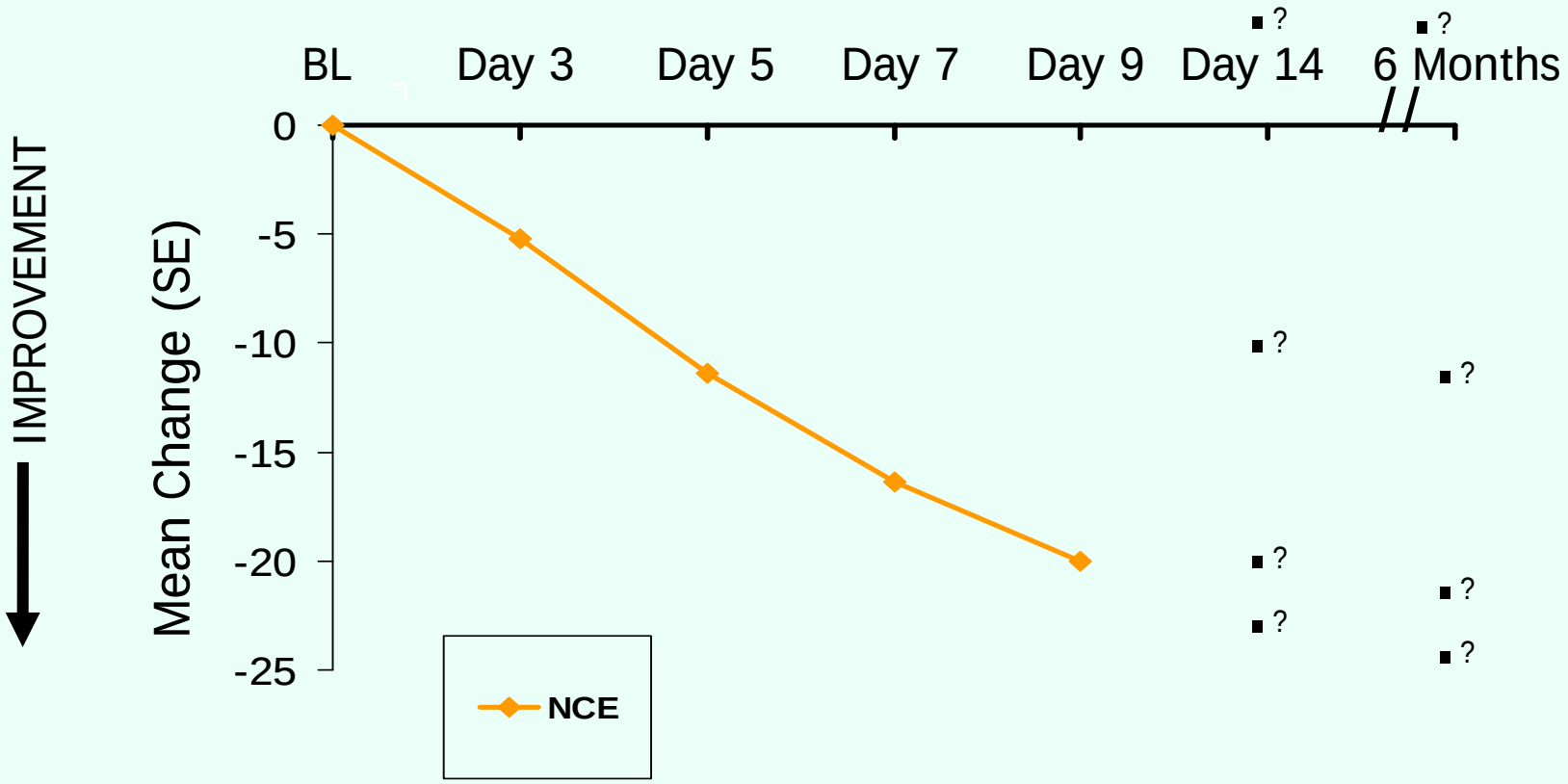
Consequences of Lack of Continuity of Care (Missouri)

18% of patients discharged to full-care facilities.

- **Of the patients discharged to the community**
  - **35% attended first outpatient visit within 30 days**
  - **25% were confirmed as "no shows," and not seen in 30 days.**
- **At Discharge**
  - **50% of patient records had a treatment/recovery plan at discharge.**
  - **62% of patients had evidence of family support and 28% received social work support.**
- **47 patients out of the 120 (39.2%) were re-hospitalized within 6 months of initial discharge.**

Is this a failure of medications or a failure of the treatment system?

Missing Data In Efficacy And Effectiveness Trial



Because of the special issues of effectiveness trials close to 100 % follow up to the last planned observation is essential to success

What is the question asked of the active comparator?

- **Assay sensitivity**
  - **Failed trials vs negative trials**
- **Identify points of potential differentiation**
- **Usually not to show superiority**

Which active comparator?

- **Typical or Atypical? … Specific atypical?… Olanzapine? … Risperidone?**
  - **Assumes one drug represents gold standard across their safety and efficacy profile**
  - **Limits development questions that can be addressed**
  - **Antipsychotic drugs affect many different receptors: the interplay among them produces overall clinical profile**
    - **Efficacy**
      - **Working with syndromes whose symptom domains have different neuropharmacological basis**

Which doses of NCE and active comparator?

- **Phase II and III trials represent limited experience with NCE (new chemical entity)**
  - **Poorer apparent efficacy may be due to underdosing or bad titration schedule**
  - **Dosing must be cautious when safety profile is being evaluated**
  - **Titration is likely to be more cautious with NCE**
  - **Requirements of regulatory bodies may limit use of some dosing and titration alternatives**
    - **QD vs BID vs TID**
- **Choice of dose for active comparator?**
  - **Optimal efficacy? Maximal risk:benefit?**

Comparators for Which Indications?

- **Schizophrenia**
  - **Positive symptoms**
  - **Negative symptoms**
  - **Cognitive symptoms**
  - **Disorganized symptoms**
- **Mood disorders**
  - **Bipolar I vs Bipolar II**
  - **Mania vs depression**
- **Suicidality**
- **Acute vs maintenance**
- **Do we need a separate gold standard for each indication?**

Comparator for Safety and Tolerability?

- **Safety issues are complex**
  - **Frequency of safety concern**
  - **Severity of safety concern**
  - **Seriousness of safety concern**
- **Can safety differences be known with confidence worthy of label differentiation?**
  - **When is a 'signal' for safety differences identified?**
  - **What is a statistically valid approach to establishing inferiority?**
- **How safe is 'safe enough'?**

Which Phase of Development?

- **Driving questions differ at different phases of development**
- **May suggest different comparators depending on issues being addressed**
  - **Safety**
  - **Differentiation**
- **Limiting comparators may limit number of questions addressed**

Implications for Pharma

- **Have the requirements for approval changed?**
- **New Chemical Entities**
  - **Does the NCE have the potential to meet these standards?**
- **Development Program**
  - **How can the NCE's potential be most quickly determined?**
  - **Which questions must be addressed during development?**
  - **How can development resources be optimally focused?**
  - **Can it be done with available resources?**
  - **Is it worth it?**

Is This an Unmet Need?

- **Efficacy risk addressed by other stakeholders**
- **If NCE is less safe than active comparator, risk should be identified in studies in standard comparator trials**
- **Establishing that a safety risk is less than that of an alternative requires special trials**

Summary

- Cannot address all questions prior to approval
- Must select most critical questions necessary for clinicians and patients
- Label is for a population, not for an individual patient
  - Clinician must translate from the label to patient
- Complexity of illness means that some benefit might accrue to some people with drug shown to be ‘inferior’ on some aspect of safety or efficacy
- If “effectiveness studies are included in the label, should go with major caveats
  - address different questions and have confounds that go beyond the efficacy of the drug

Summary

- **A single comparator is unlikely to address complexity of issues**
- **Much is already addressed with existing requirements and by other stakeholders**
- **Partnership is need to select those that must be addressed prior to approval**