International Society for CNS Clinical Trials and Methodology

FDA
Advisory Committee Meeting

Proposed Requirement for Long-Term Data to Support Initial Approval of CNS Drug Indications

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International Society for CNS Clinical Trials and Methodology

- **Society Membership: CNS methodologists from academia, industry, regulatory agencies**
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  - -- Steven Potkin (Scientific Com.)
  - -- Mark Rapaport (Scientific Com.)
  - -- Larry Alphs (Program Com.)
  - -- Munaf Ali (Regulatory Liaison)
- **Mission**
  - **To evaluate current concepts of CNS drug development:**
    - **indications**
    - **trial methods**
    - **regulatory guidelines**
    - **modes of usage**
    - **clinical methods**
  - **To address potential conflicts between research objectives & regulatory requirements**

CNS Efficacy Data: Current Status

- ***ISCTM supports:*** FDA requirements & approved indications where the objective is demonstrating control of symptoms over 4–6 wks (schizophrenia, depression, anxiety disorders, and bipolar disorder)

- ***ISCTM questions:*** proposed FDA requirements & labels for continuation/maintenance treatment based on preventing relapse of index episode or recurrence of new episodes in remitted/stable patients

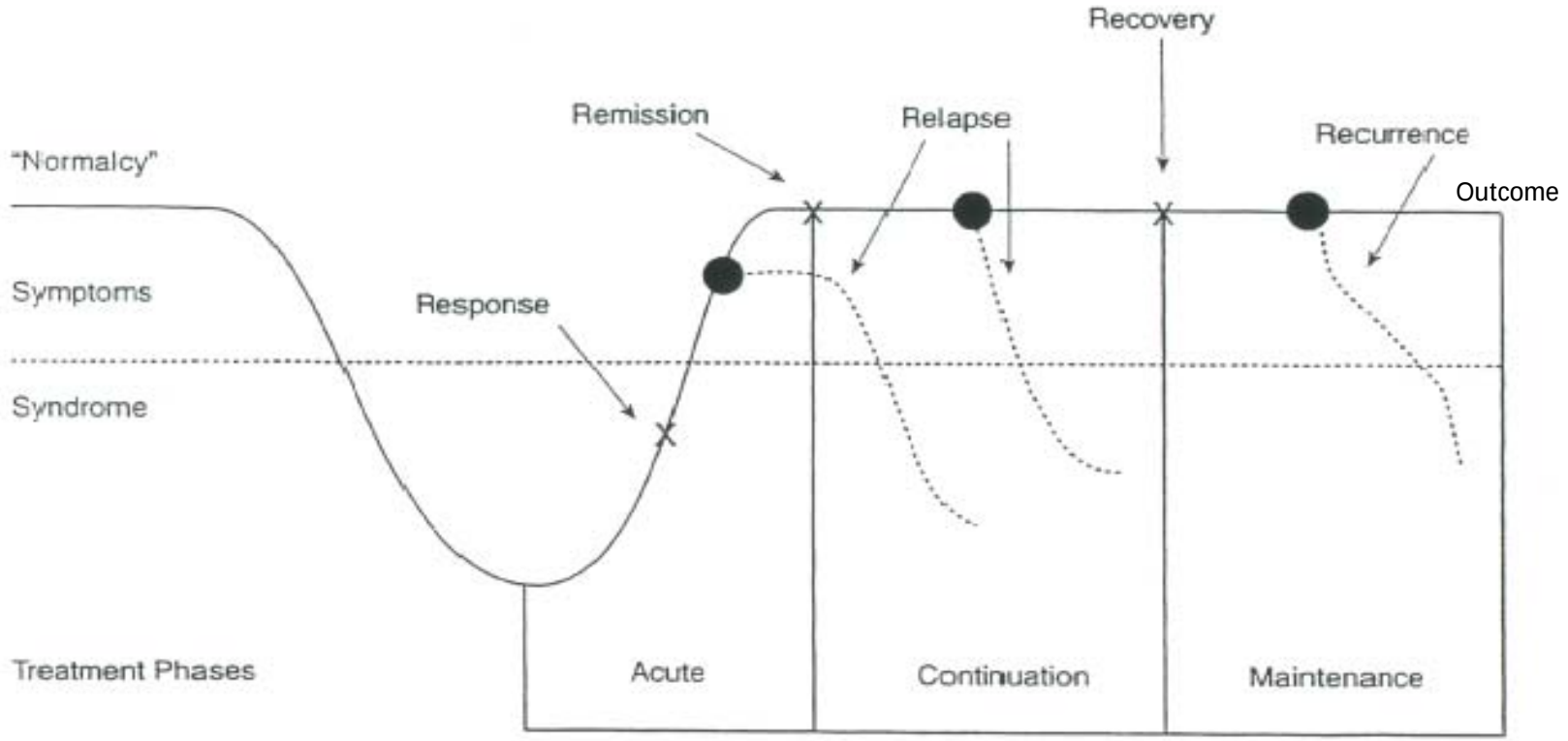
Study Design Determinates

Key Issues:

- Disease Characteristics
- Stakeholder Needs
- “The Question”

Need for Long-Term Data Varies by Disease Course

Generalized Course for Depression

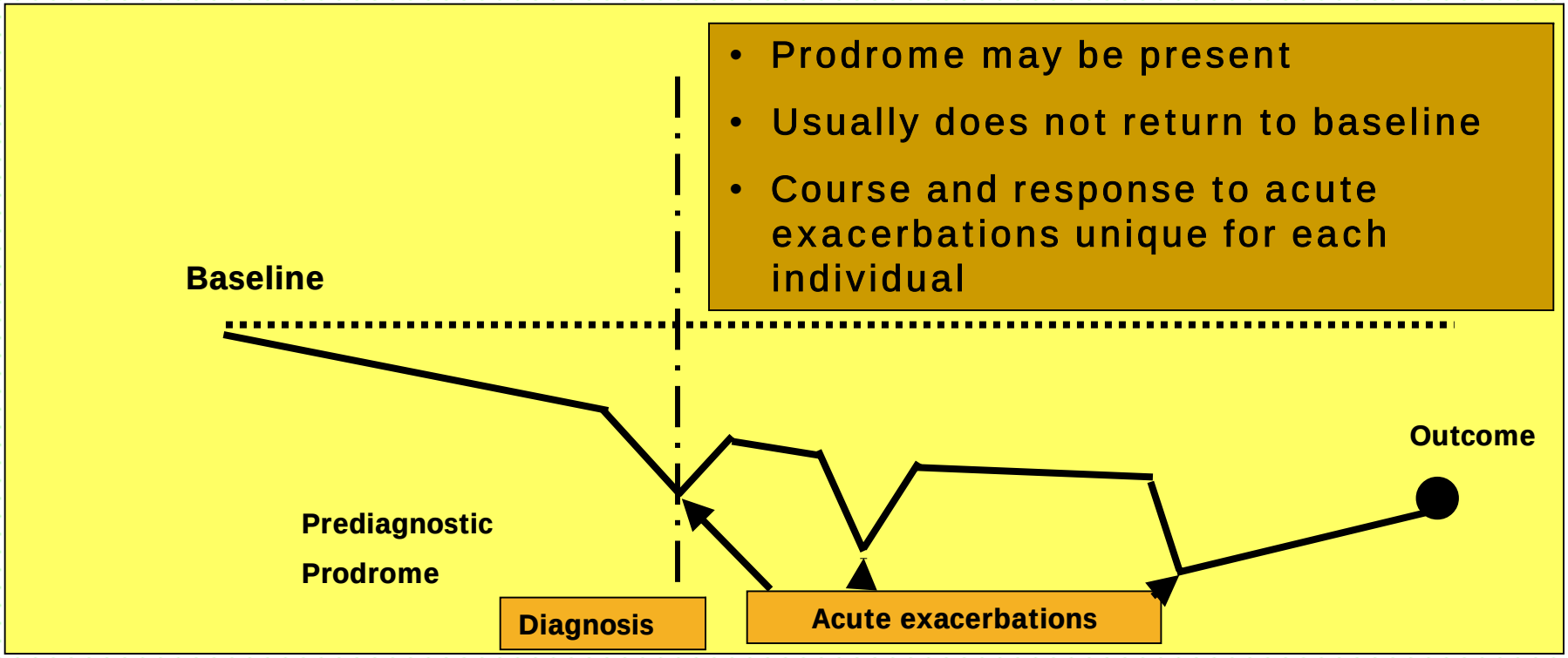


Kupfer DJ (1991): Long-term treatment of depression. *J Clin Psychiatry* 52:28 –34

- Broadly similar course for most persons with disorder
- Frequently returns to baseline

Need for Long-Term Data Varies by Disease Course

Variable Course of Schizophrenia



Conclusion: Different study designs are needed to address differences in diseases and treatment needs.

Vocabulary of Long-Term Efficacy

- **Terminology for long-term data in depression**
  - **Response** **-- Relapse**
  - **Maintenance of effect** **-- Recurrence**
  - **Remission** **-- Prophylaxis**
  - **Recovery**
- **Similar terminology is required for other CNS disorders:**
  - ***Schizophrenia*—chronic; may not return to baseline; irregular exacerbations**
  - ***Bipolar disorder*—recurrent disorder with manic and depression phases, highly variable in timing & duration**
  - ***Anxiety disorders*—shorter treatment often is adequate**

Vocabulary is emerging to describe various aspects of long-term maintenance considerations, but must be adapted for major disease entities

Stakeholders' Needs

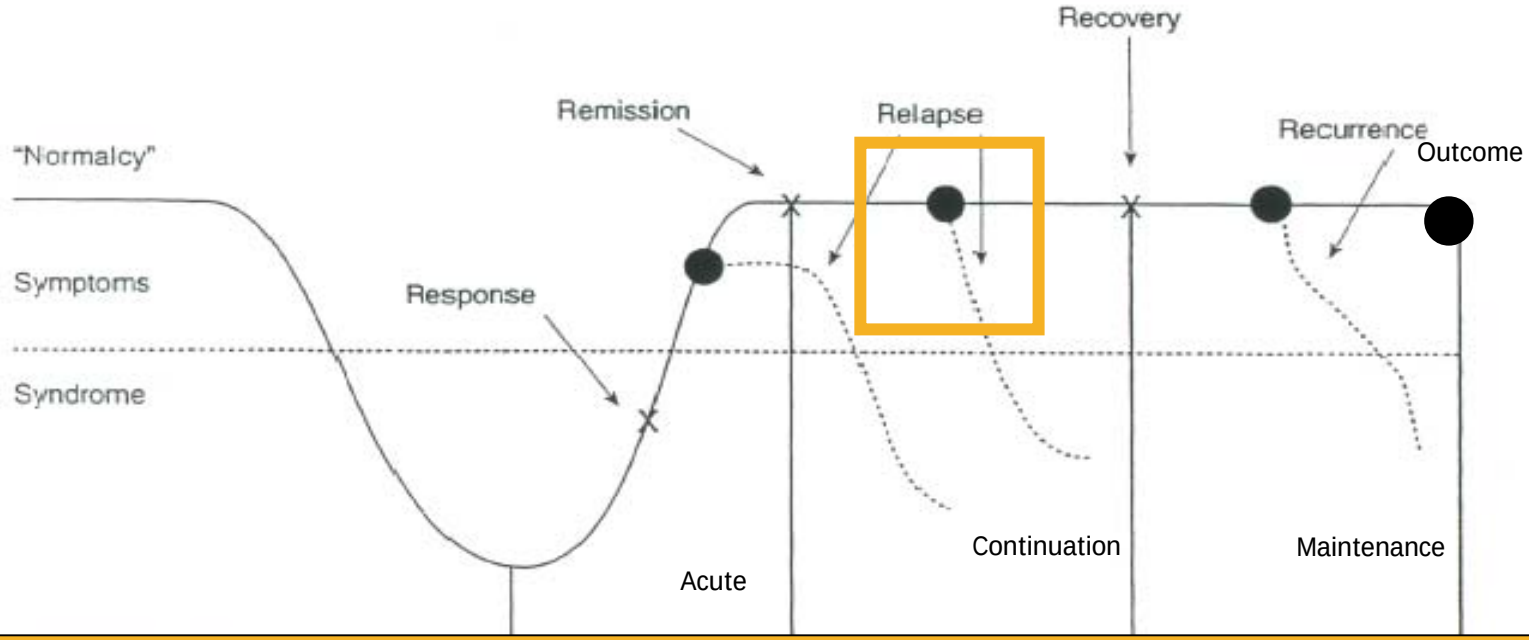
- **Needs for evidence of long-term efficacy vary for different stakeholders depending on their perspective**
  - **Patient:** "Will I continue to do well if I take this medication?" or "Do I need to continue to take this medication?"
  - **Clinician:** "Will the drug/dose that effectively treated symptoms in my patient continue to have an adequate effect long term and will it be safe?"
  - **Society:** "Does this drug improve functioning, quality of life and outcome during long-term treatment in a population of persons with the index disease in treatment trials?"
  - **Regulators:** "Is the drug which demonstrated an acute effect still providing risk: benefit when its use is continued for long periods?"
  - **Developers:** (identical to above)"Is the drug which demonstrated an acute effect still providing risk: benefit when its use is continued for long periods?"

Trial Designs

- **The clinical question should be the primary driver of clinical trial designs**
- **Alternative trial designs are available for long-term trials**
  - **Randomized withdrawal designs are of limited value, based on unsound scientific principles, and ethically questionable**
  - **Double-blind, long-term treatment studies are an alternative approach**
    - **Differs from typical extension study**
    - **Assesses long-term effectiveness**
    - **Analyses based on all randomized patients**

Possible Questions, Design and Label for Long-Term Efficacy

Question: During continued treatment with medication will time to relapse or incidence of relapse be reduced?

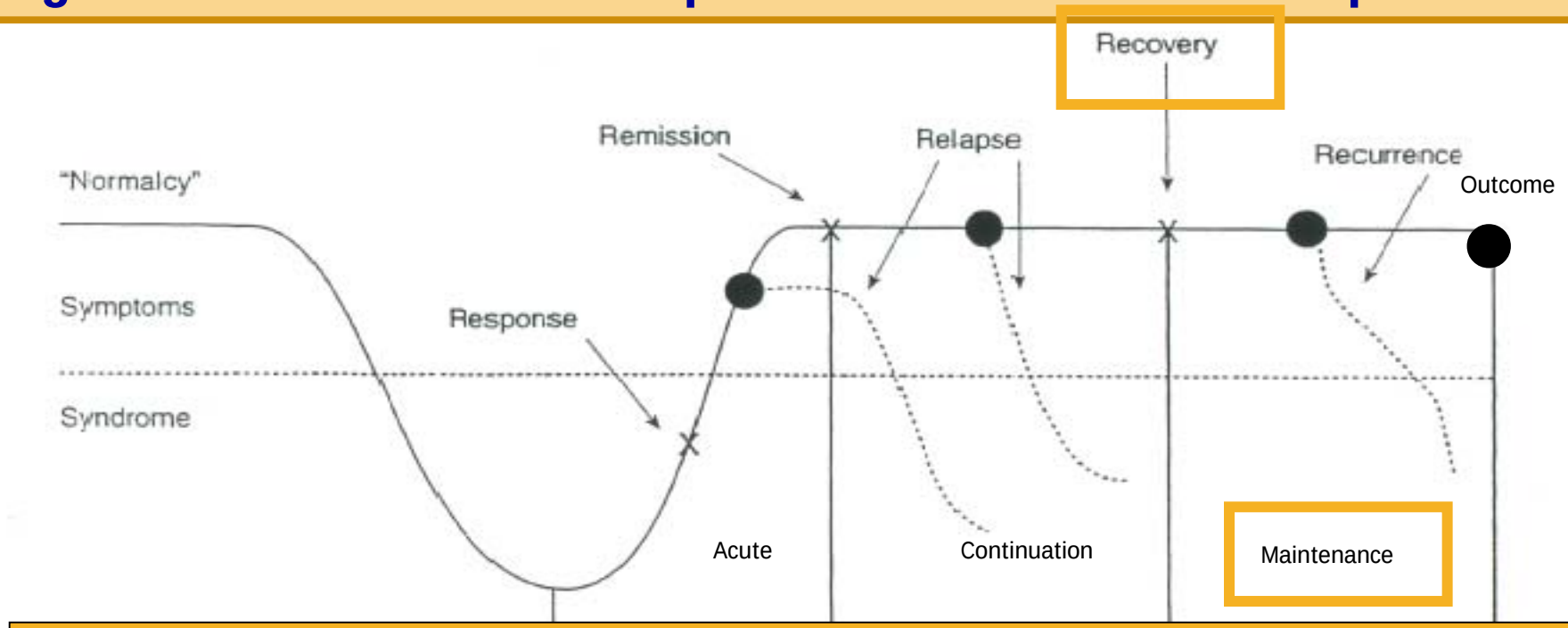


Possible Design: Randomized Withdrawal

Possible Indication: "Compound X has been demonstrated to increase the time to relapse (or decrease incidence of relapse) in patients who had previously responded to treatment as compared to a control during 26 weeks of continuation treatment."

Possible Questions, Design and Label for Long-Term Efficacy

Question: If a patient has responded to medication, will continued long-term treatment result in persistence of the initial response?



Possible Design: Double Blind Long-Term

Possible Indication: "Compound X has been demonstrated to be effective in maintaining an initial treatment response compared to a control for up to 52 weeks."

ISCTM Consensus Points

- **Recent change in guidance requiring extended stabilization followed by randomization with treatment discontinuation paradigms risks:**
  - **ethically questionable trials**
  - **scientifically questionable outcomes**
  - **logistically prohibitive protocols**
- **Proof of long-term efficacy requires *specific* definitions, outcomes, and protocols for each disorder**

ISCTM Consensus Points

- **Definitions of "long-term" are specific to each disorder and treatment**
  - **They differ greatly, e.g., for:**
    - **new antipsychotics or mood-stabilizers**
    - **short-term treatment for acute panic attacks**
- **Stakeholders still need to clarify**
  - **definitions of long-term efficacy**
  - **appropriate timing of approvals of new agents for short, intermediate, and long-term applications**
  - **what data are required when (e.g., at initial regulatory submission vs. in post-marketing commitments)**
  - **whether the current process of acute followed by long-term indication is sufficient**

The Way Forward

- **Re-evaluate current concepts of long-term efficacy of psychotropic drugs**
- **Prioritize needs by specific disorders**
- **Redefine objectives & designs of clinical trials adequate to assess long-term effects**
- **FDA sponsored workshops can help:**
  - **Expert consensus workgroups to develop guidelines for appropriate designs for long-term effectiveness trials for specific indications**
  - **Include representatives key stakeholders: regulatory, academic, clinical, industrial & statistical**