



International Society for CNS Clinical Trials and Methodology

MAINTENANCE OF EFFECT

Industry Perspective: Goals and Hurdles

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Goal of Pharmaceutical Industry

- **Provide safe and effective medications that are cost effective both for the patient who takes them and for the industry that manufactures them**

Who are our customers?

- **Patient**
 - **Effective, safe, tolerable and affordable medications to treat clinical disorders**
- **Clinician**
 - **Medications that meet patients needs**
 - **Knowledge of how to use compound short-term and long-term**
- **Regulators**
 - **Provide scientifically credible evidence to support evidence for efficacy, safety, tolerability and appropriate use of compound**
- **Society**
 - **Demonstrate improved functioning and quality of life such that the medication is cost effective**

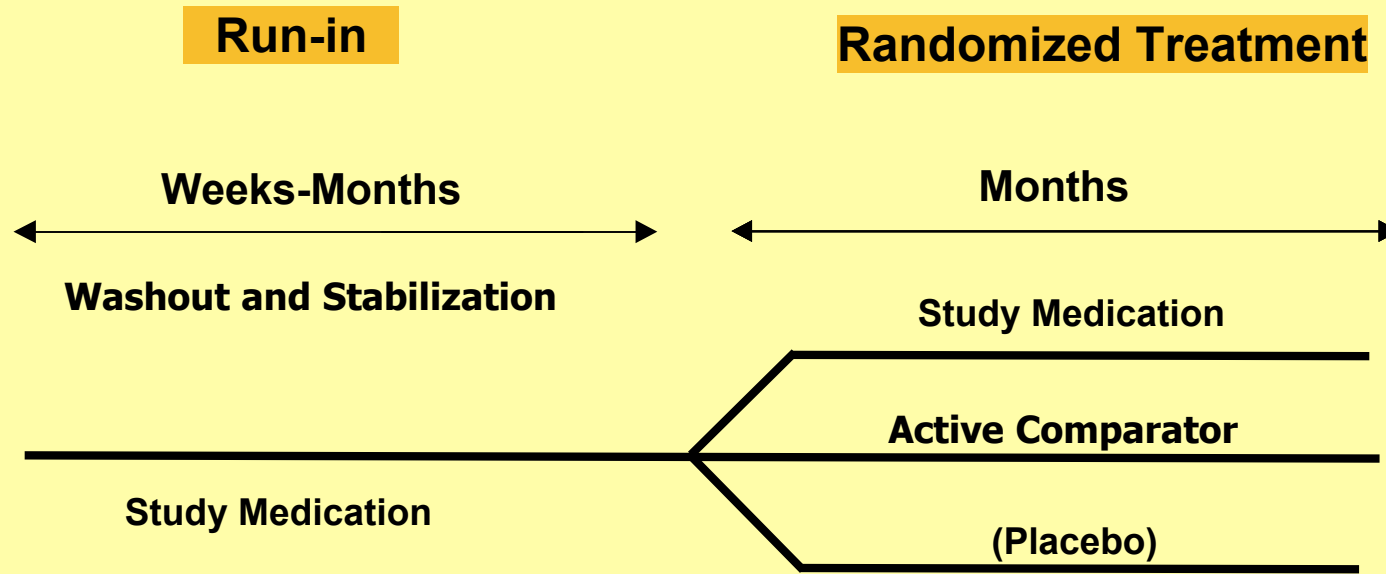
What needs must we satisfy?

- **Clinical**
 - Getting the question right: clear, best of alternatives
 - Performing clinically acceptable studies
- **Scientific**
 - Performing studies with valid, meaningful designs
 - Correct endpoints, valid scales and appropriate analyses
- **Logistical**
 - Doing studies that are clinical feasible in timeframe and with acceptable budgets
 - Performing studies in all parts of the world with various languages, cultures and medical practices
- **Regulatory**
 - Meet requirements of different cultures and health care systems around the world
- **Business**
 - Must be economically viable product

What are the important clinical questions for long-term efficacy?

- **Past:**
 - No clear understanding of what “long-term efficacy” represent as a clinical question
 - Similar labels for very different trials
- **Current:**
 - **US:** After a period of stabilization, will patient’s condition relapse if the index medication is discontinued?
 - **EU:** Are recurrences of symptoms minimized during long term treatment with the index medication?

A General Study Schematic for Long-Term Treatment



- In most relapse studies have a pbo comparator
- Maintenance of effect studies have an active comparator



Example: Current Regulatory Claims for Bipolar Disorder

FDA

- **xx is indicated for maintenance monotherapy of Bipolar I Disorder. The benefit of maintaining bipolar patients on monotherapy with xx after achieving remission of an acute manic or mixed episode was demonstrated in a controlled trial.**

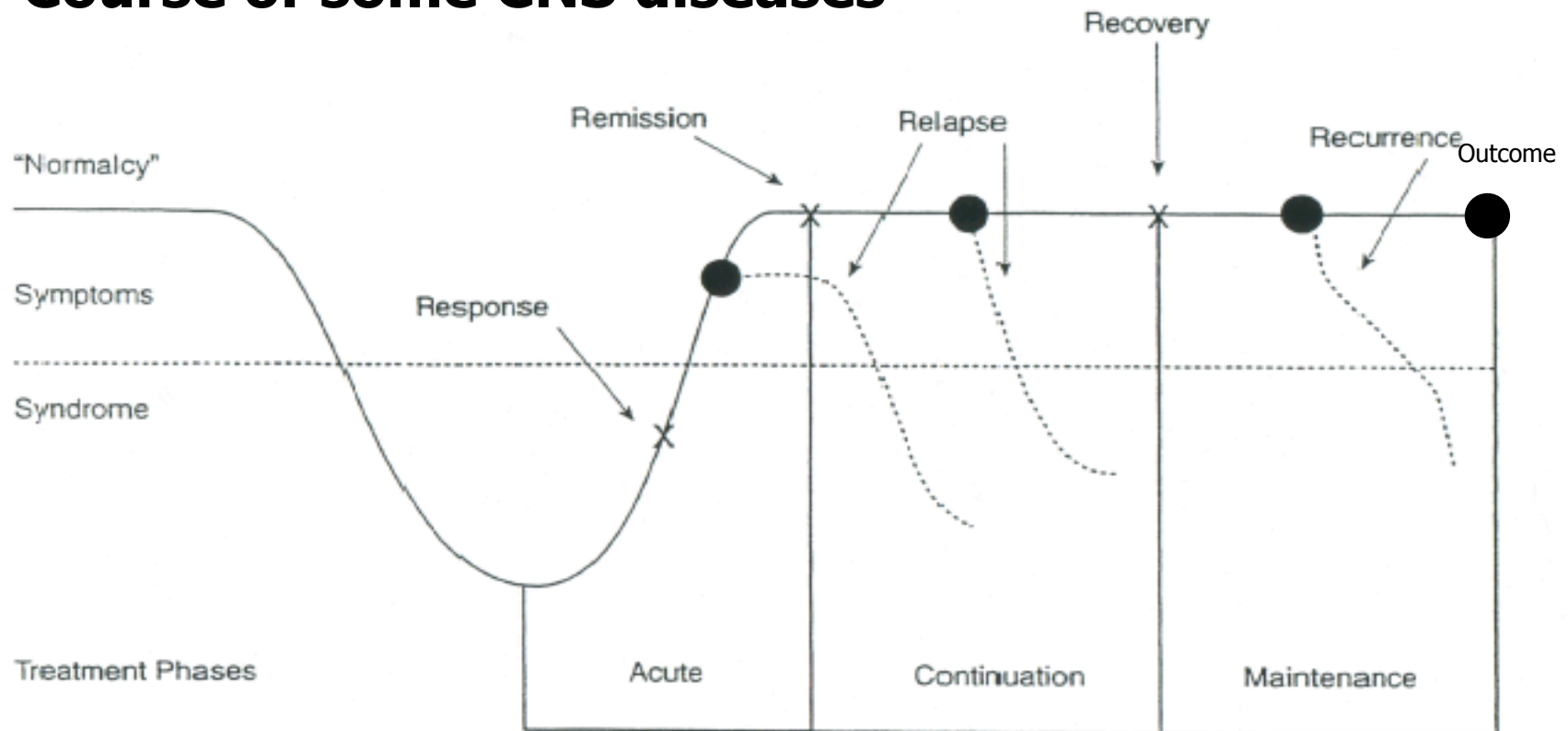
EU

- **xx is indicated for the prevention of recurrence in patients with bipolar disorder in patients whose manic episode has responded to xx treatment**

Critique of Current Approaches to Long-Term Efficacy

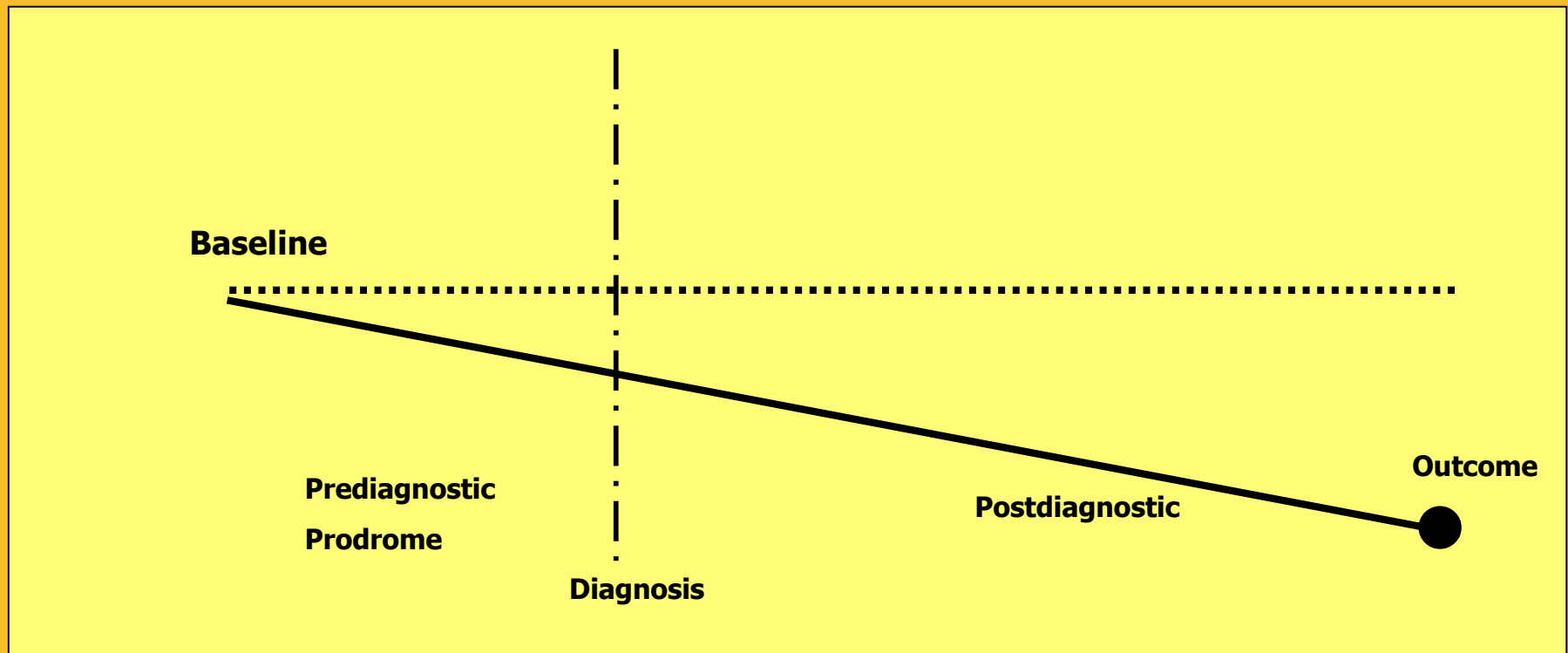
- **Current view is too simplistic**
 - **Multiple dimensions of long-term efficacy need to be considered**
 - **Key issues for long-term efficacy may be different for different CNS diseases**
 - **Epilepsy**
 - **Schizophrenia**
 - **Alzheimer's dementia**
 - **Bipolar disorder**
 - **Anxiety disorders**
 - **Priority is different for different diseases**

Course of some CNS diseases



Clinical questions for long-term efficacy

Course of other CNS diseases (Alzheimer's)

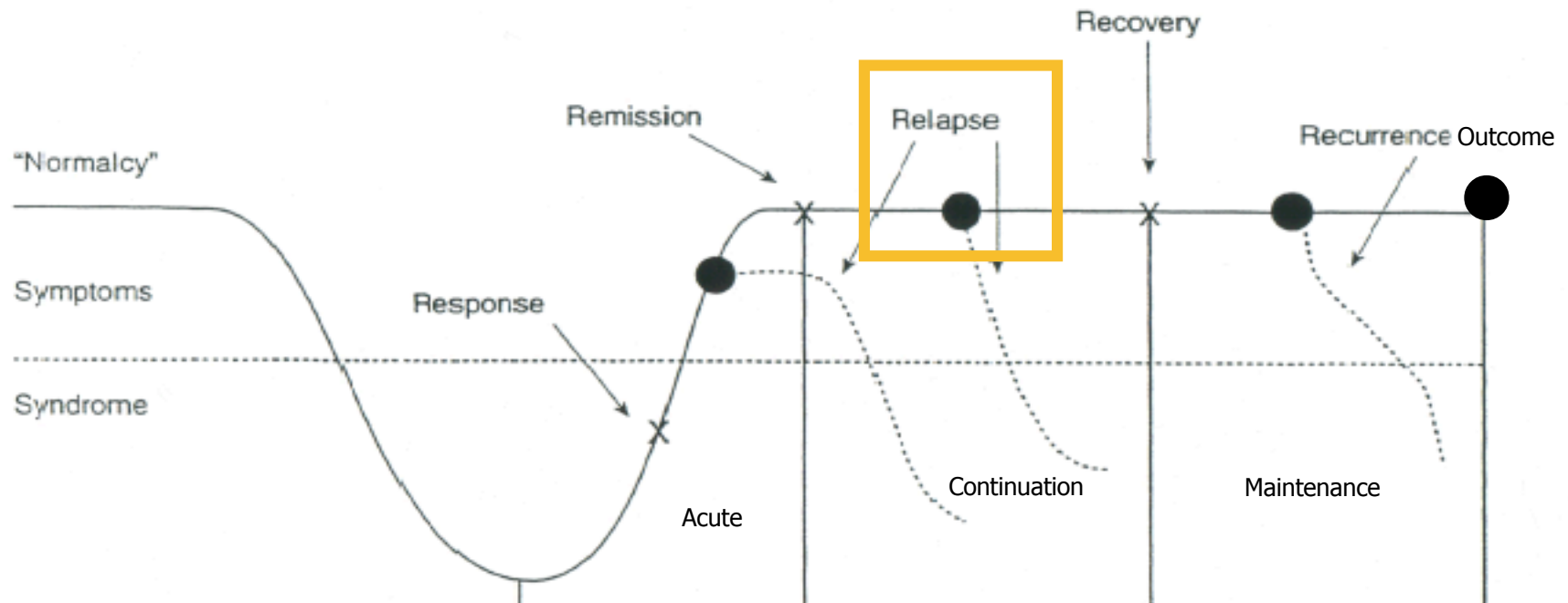


A Possible Vocabulary of Long-Term Efficacy

- **Response**—reduction of symptoms of acute episode not necessarily complete
- **Maintenance of effect**—demonstration of the persistence of a treatment effect
- **Remission**—complete or nearly complete response of acute symptoms (implies underlying disease may still be present, but not expressed)
- **Recovery**—underlying disease has been treated and clinical symptoms absent
- **Relapse**—return of symptoms within same episode
- **Recurrence**—occurrence of new episode after an extended period of remission
- **Prophylaxis**—treatment to prevent some adverse outcome associated with disease state

Clinical questions for long-term efficacy

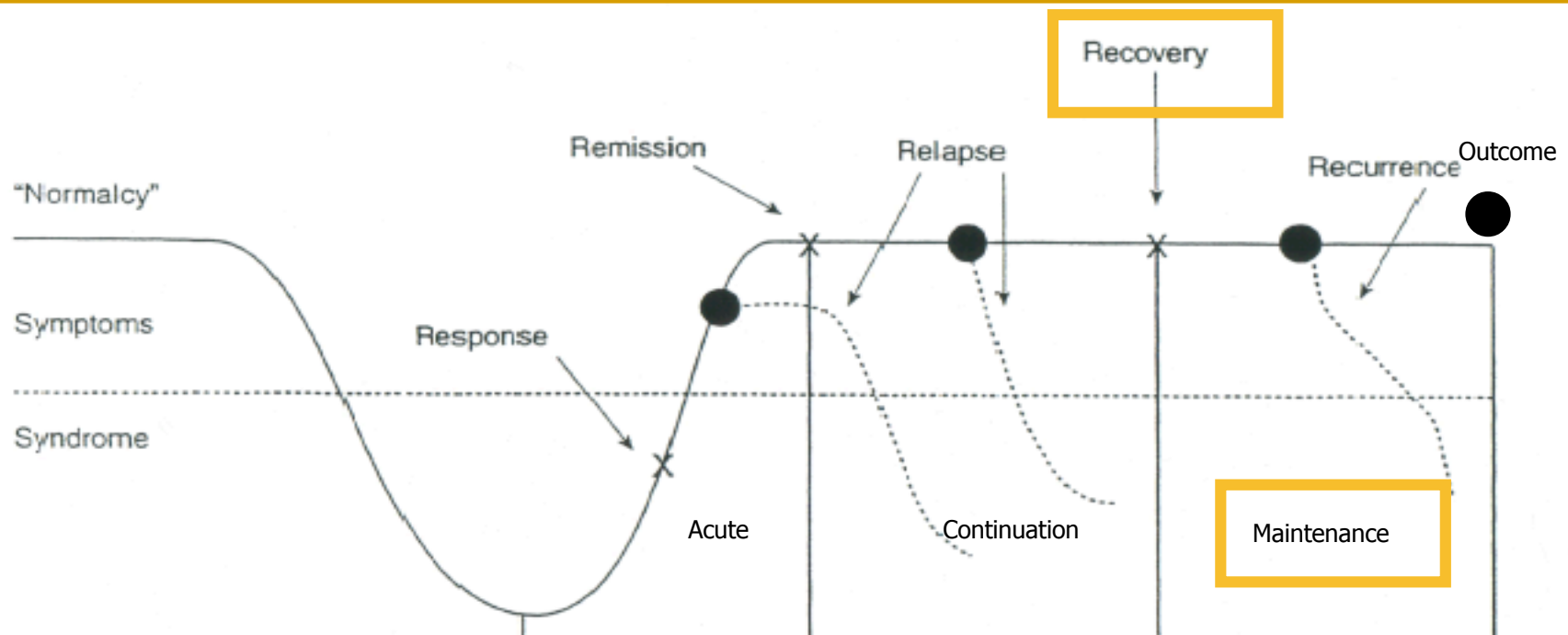
Question: During continued treatment with medication will time to relapse or incidence of relapse be reduced?



Possible Indication: "Compound X has been demonstrated to reduce the time to relapse (or incidence of relapse) in patients who had previously responded to treatment as compared to a control during 52 weeks of continuation treatment."

Clinical questions for long-term efficacy

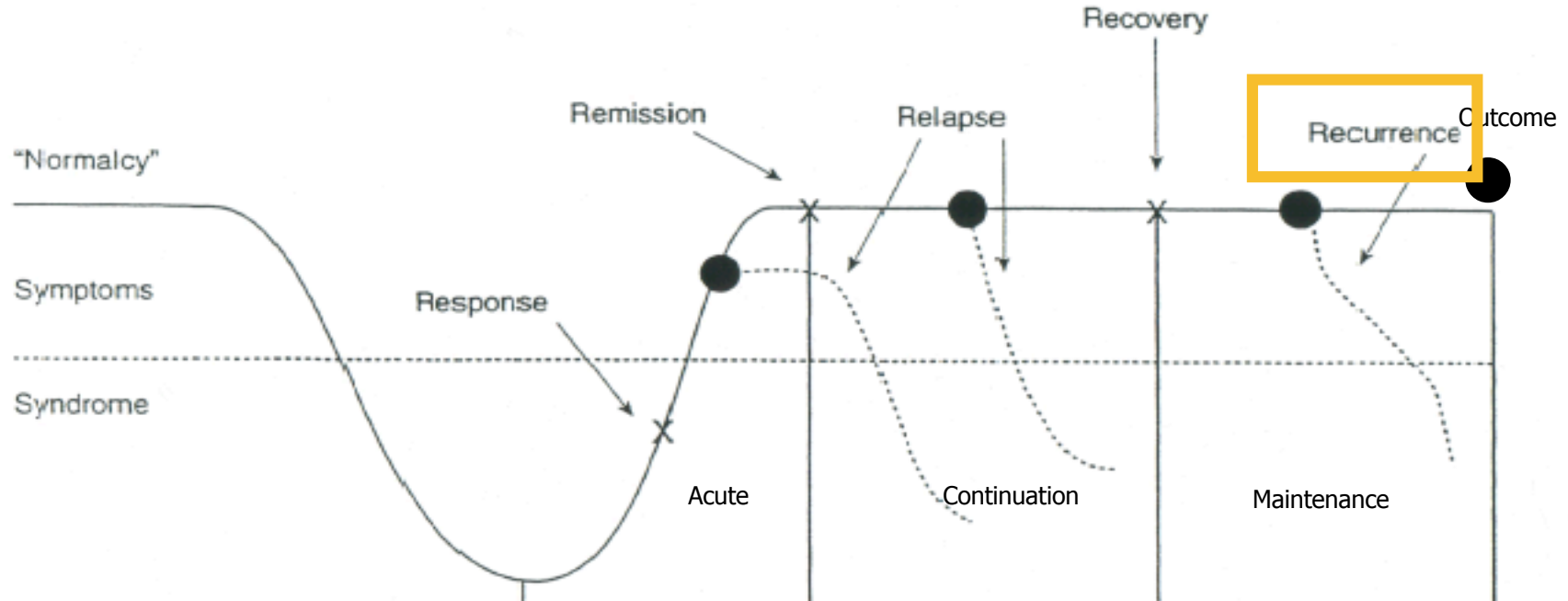
Question: If a patient has responded to medication, will continued long-term treatment result in persistence of the response?



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."

Clinical questions for long-term efficacy

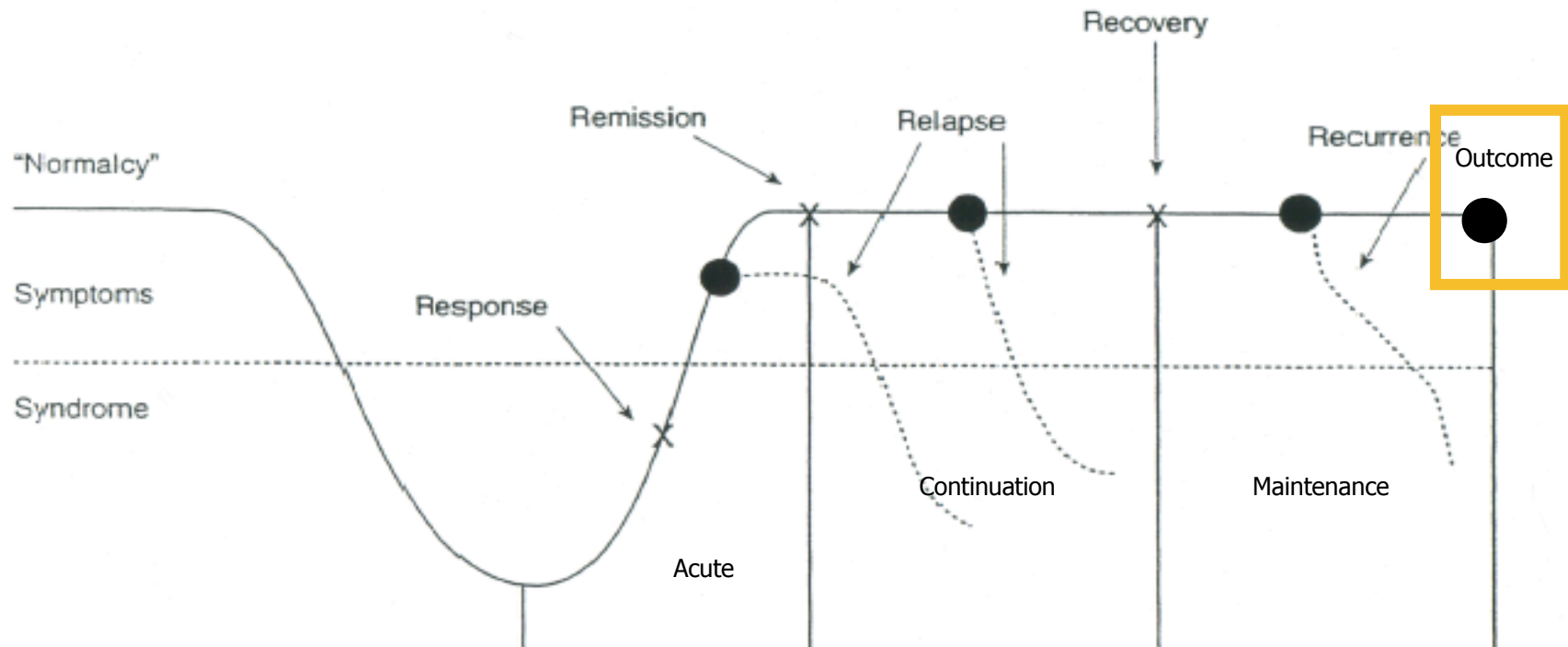
Question: If a patient has responded to medication and produced remission for an extended period, will continued treatment result prevent recurrence of prior symptomatology?



Possible Indication: "Compound X has been demonstrated to be effective in preventing recurrence of illness following long-term treatment compared to a control."

Clinical questions for long-term efficacy

Question: "Will long-term outcome be affected by continued treatment?"



Possible Indication: "Compound X has been demonstrated to improve clinical outcome (e.g., number of severity, duration of episodes; as measured by an acceptable scale) compared to a control in during 52 weeks of long-term treatment."

Additional Questions Related to Long-Term Efficacy

- **What is the optimal design to address the question at hand?**
 - **Do you need to demonstrate response to study medication? If so, how do you do it?**
 - **If you stabilize treatment, how do we define stability?**
 - **How do we define and demonstrate persistence of effect?**
 - **What is the control agent? (placebo/active)**
 - **What is the duration of treatment to be evaluated?**
 - **What is the analytic technique? (superiority/non-inferiority)**
 - **Is the design ethical?**
 - **Is the design feasible?**

Specific Problems with Some Approaches

- **Will treatment discontinuation after a 6 month period of stable treatment of patients with schizophrenia, result in reduced frequency of relapse relative to a control?**
 - **Why 6 months of stable treatment?**
 - **How to define stable treatment?**
 - **How to define relapse?**
 - **Is a design that permits patients to relapse ethical?**
 - **Is randomization of stably treated patients to placebo ethical and feasible?**
 - **Is this a priority clinical question?**
 - **The question presumes a possibility for the treatment to be curative. However, the general clinical assumption is that treatments are not curative and that treatment discontinuation will result in relapse**

Conclusions

- **Long-term efficacy represent several clinical issues**
- **Must clearly define the clinical questions related to long-term efficacy**
- **Since resources are not unlimited, must prioritize questions to be addressed**
- **Not all clinical questions can be addressed**
 - **Clinical interest**
 - **Ethical constraints**
 - **Logistic constraints**
 - **Business priorities**
- **Liaison with academia/regulatory/industry optimal to develop questions and answers efficiently**
- **Next Steps: develop a consensus in the field**