Experimental Designs for Developing Adaptive Treatment Strategies

With Application to the Management of Bipolar Disorder

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Outline

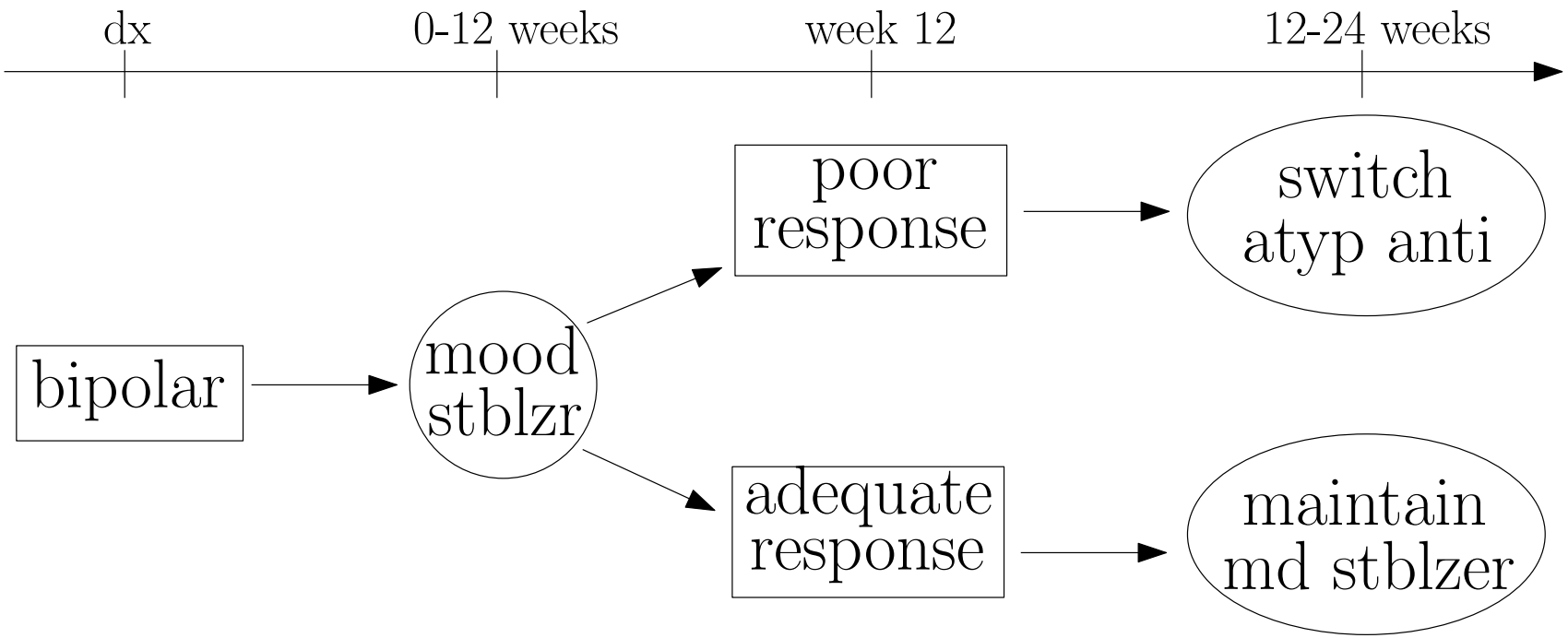
Definition of an Adaptive Treatment Strategy

An adaptive treatment strategy (ATS) is **a sequence of individually tailored decision rules** that specify whether, how, and when to alter the intensity, type, dosage, or delivery of treatment at critical decision points in the medical care process.

ATSs operationalize sequential decision making with **the aim of improving clinical practice**.

Concrete Example of an Adaptive Treatment Strategy

Bipolar Disorder



- Goal is to minimize the patient's symptom profile/trajectory.

Concrete Example of an Adaptive Treatment Strategy

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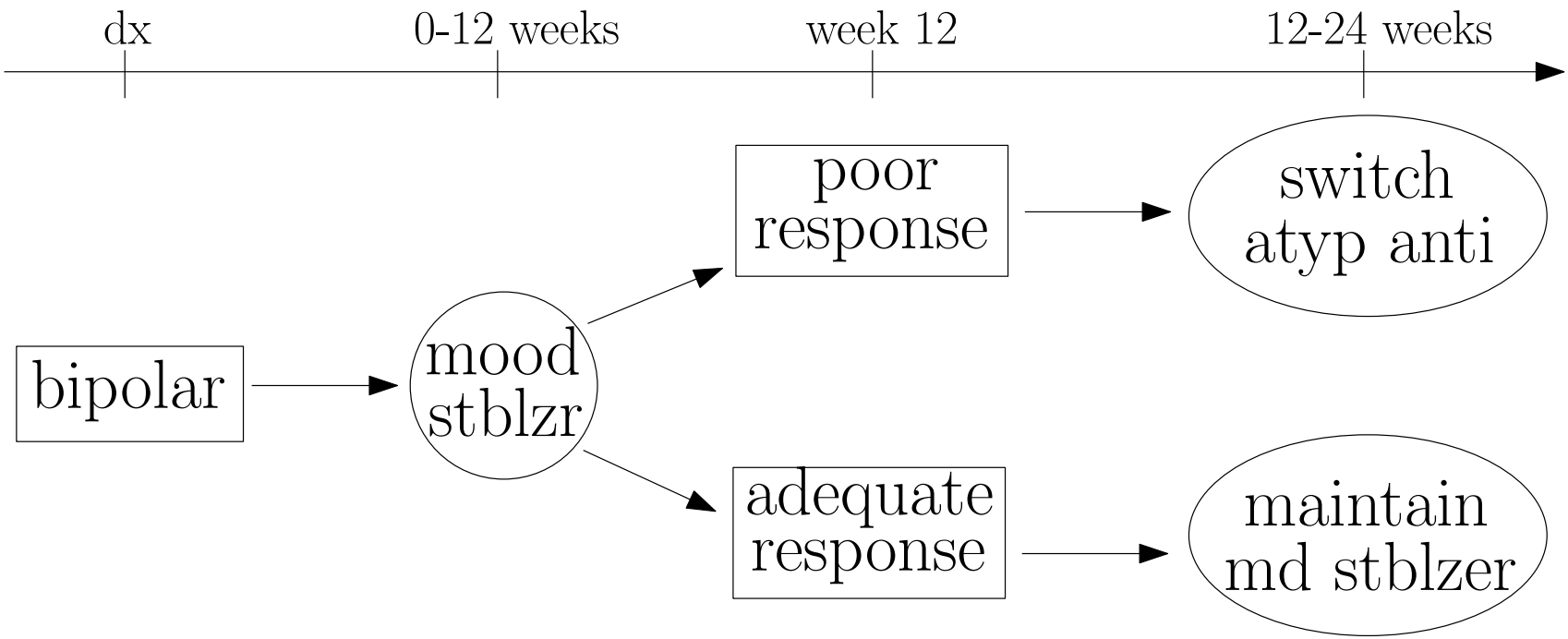

- A **treatment sequence from patient's point of view**

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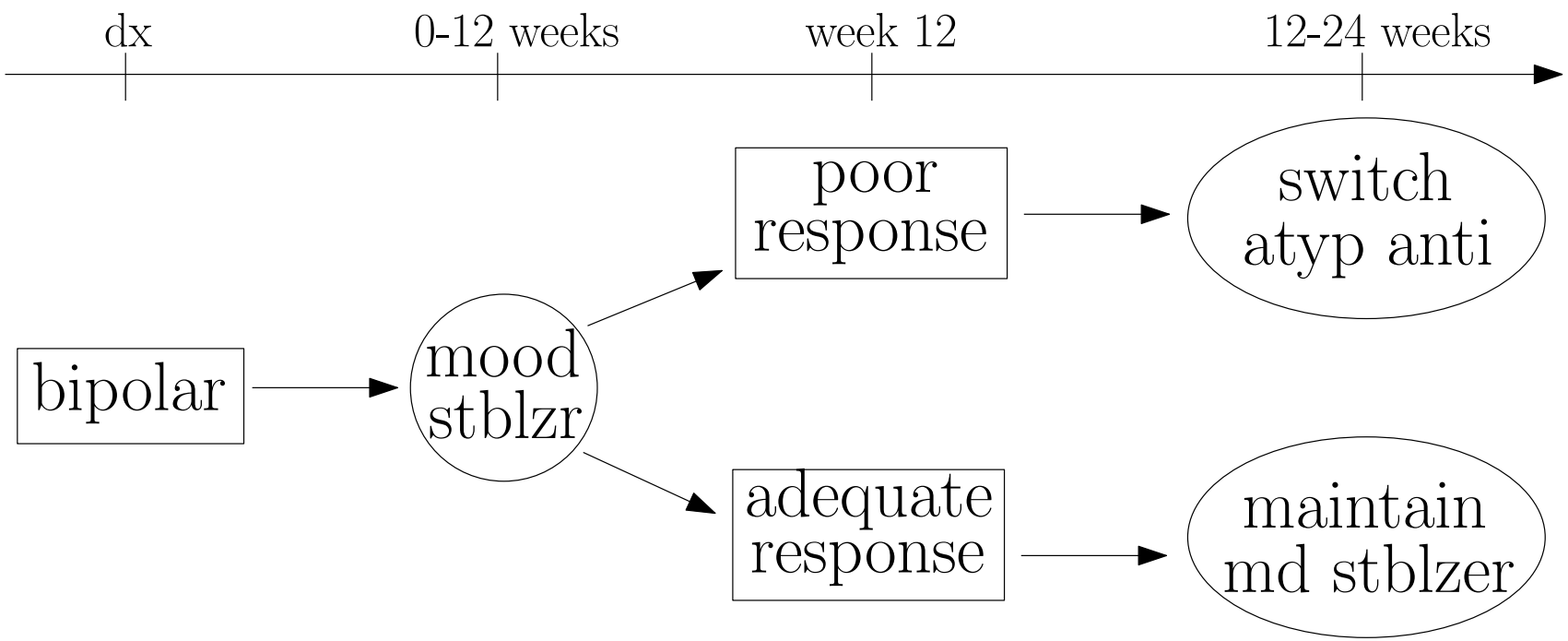
Bipolar Disorder



- A set of **decision guidelines from clinician's viewpoint**

Why Adaptive Treatment Strategies?

Necessary because...

- The chronic nature of mental health disorders
  - Bipolar disorder understood to be among the most chronic of mental health disorders
  - Waxing and waning course (multiple relapse, recurrence)
  - Genetic and non-genetic factors influence course
  - Co-morbidities may arise
- High patient heterogeneity in response to treatment
  - Within person (over time) differential response to treatment
  - Between person differential response to treatment

Why Adaptive Treatment Strategies?

Can be used to inform how to best...

- Adapt treatment to a patient's chronic/changing course
- Deliver appropriate treatment when needed most
- React to non-adherence or side-effect profiles
  - Bipolar example: Metabolic side-effects of olanzapine, risperidone
- Reduce treatment burden on the patient
- Deliver early treatments with positive downstream effects
- Have ability to sift through available treatment options in principled fashion

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- **More personalized care, over time**
- **Improving actual clinical practice**

Developing an ATS Requires Careful Consideration

- For who are we developing the adaptive strategy?
  Population, or Context, question.

- What is the goal of the adaptive treatment strategy?
  Objectives question.

- What is the optimal sequencing of treatments?
  Sequencing question.

- When do we switch, augment, or maintain treatment?
  Timing question.

- Based on what information do we make decisions?
  Tailoring question.

What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- Multi-stage trials; same participants used throughout
- Each stage corresponds to a critical decision point
- At each stage, participants are randomized to a set of treatment options
- Treatment options at randomization may be restricted depending on intermediate outcome/treatment history

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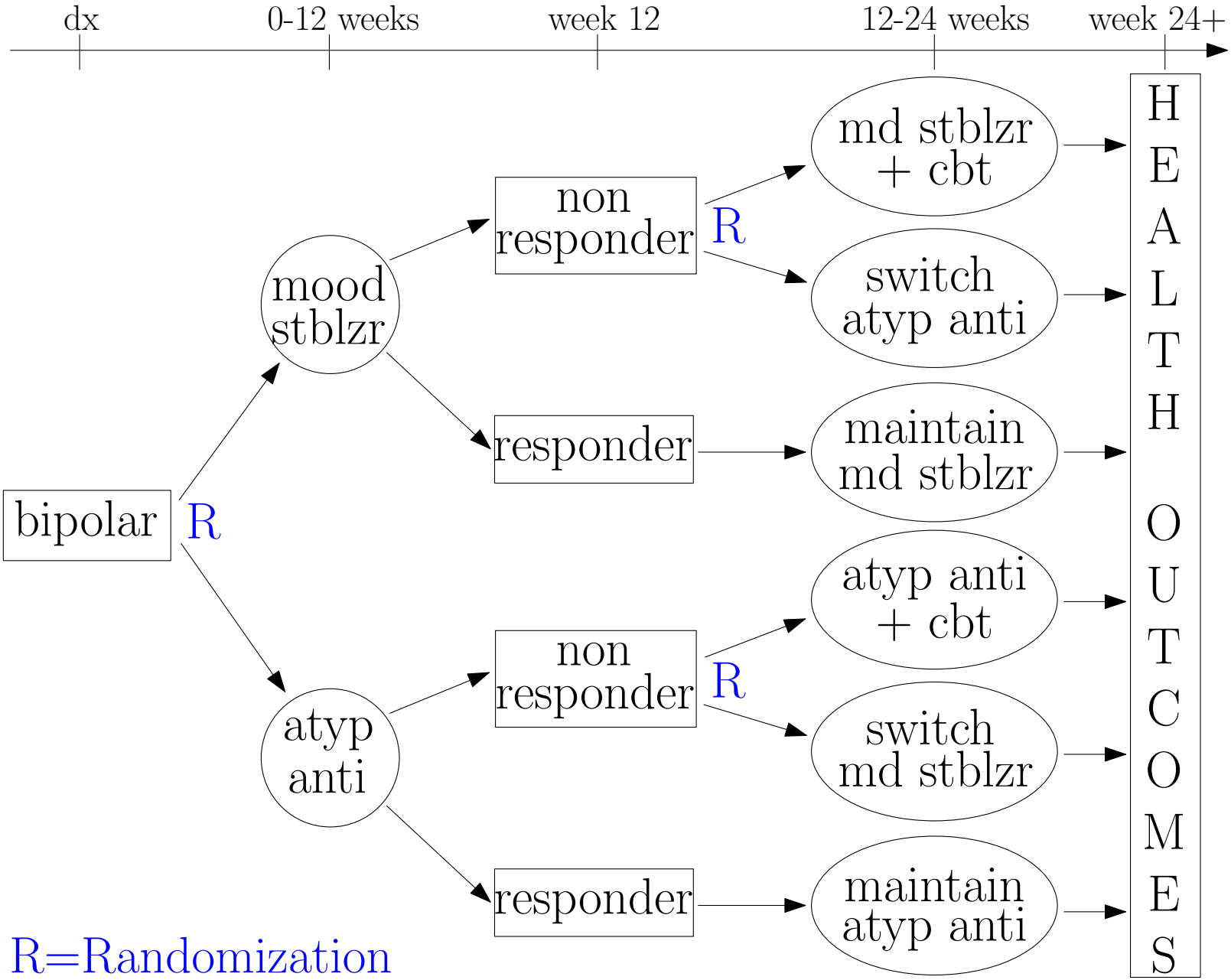
- **The goal of a SMART is to inform the development of adaptive treatment strategies.**
- **Build the evidence base for adaptive treatment strategies.**

Concrete Example of a SMART



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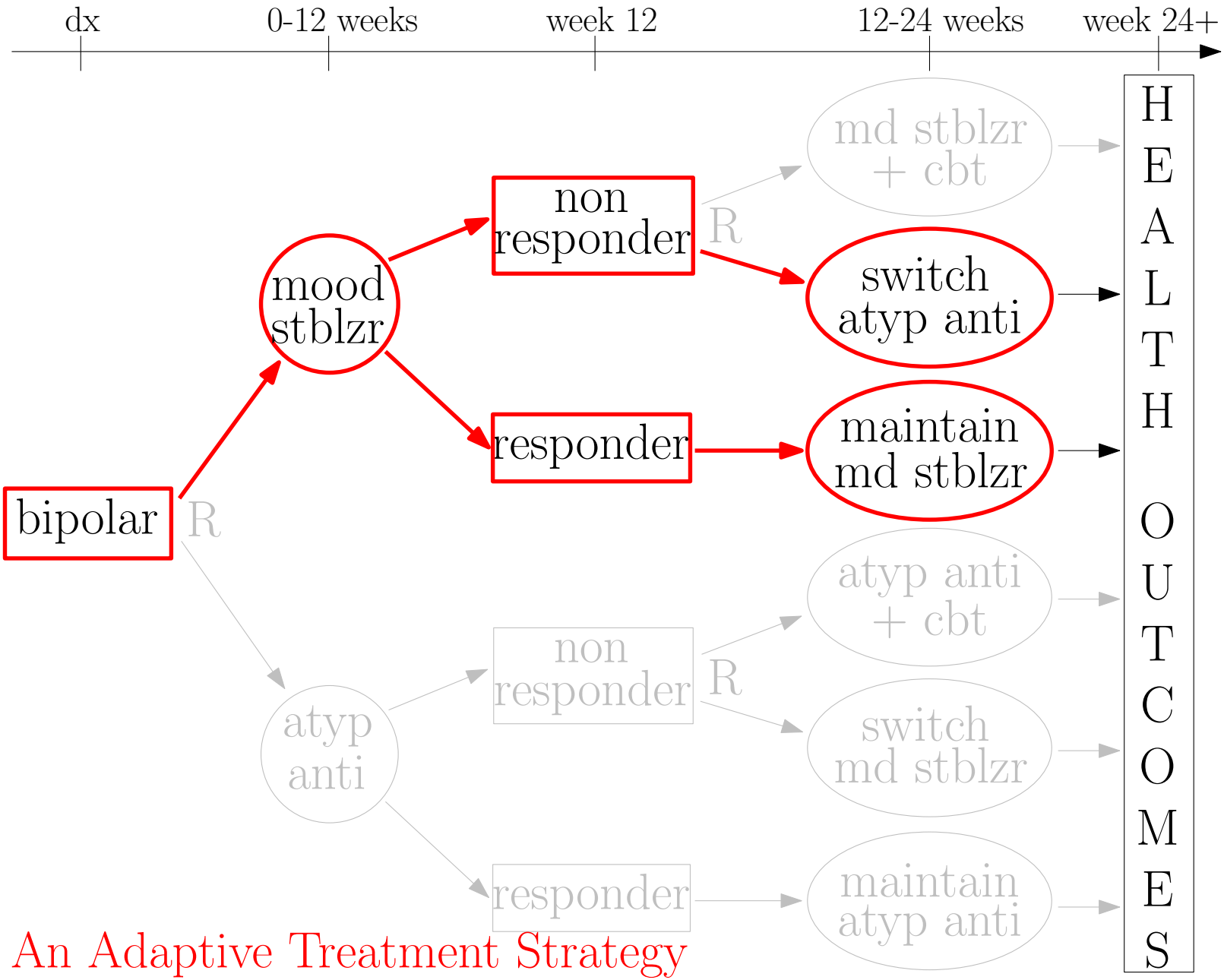
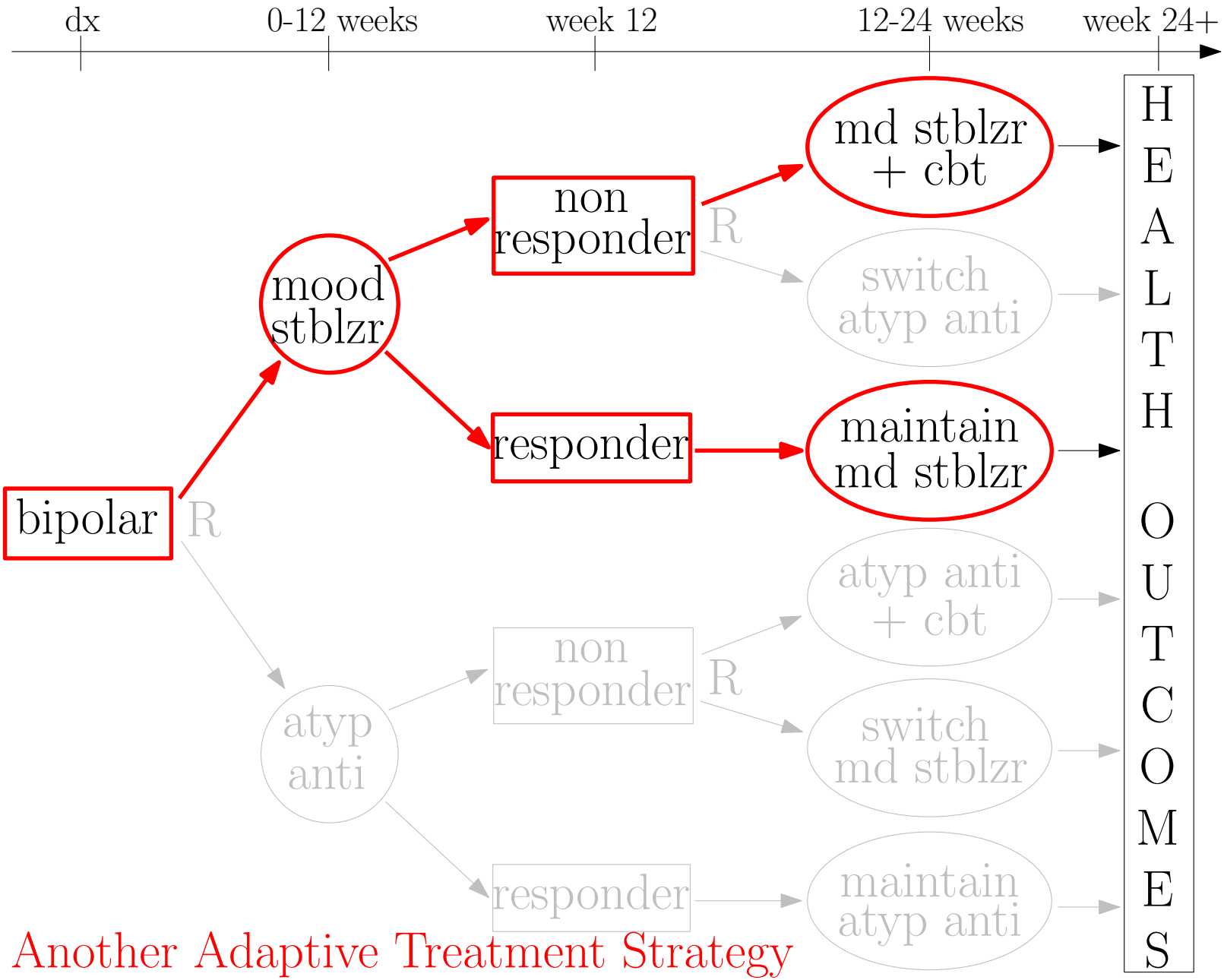


An Adaptive Treatment Strategy

Concrete Example of a SMART



Another Adaptive Treatment Strategy

SMART Designs in the Field/Literature

- CATIE (2001) Treatment of Psychosis in Patients with Alzheimer's
- CATIE (2001) Treatment of Psychosis in Patients with Schizophrenia
- STAR*D (2003) Treatment of Depression
- Pelham (on-going) Treatment of ADHD
- Oslin (on-going) Treatment of Alcohol Dependence
- Jones (on-going) Treatment of Pregnant Women with Substance Abuse Problem

Multiple Trials As An Alternative to a SMART

Using multiple trials to inform development of an adaptive treatment strategy

1. Choose best first-line treatment (example: mood stabilizer vs. atypical anti-psychotic) on the basis of a classic two-arm RCT

   ...5 years later...

2. Choose best second-line treatment for non-responders (example: switch medication vs. augment medication with cbt) on the basis of another, separate, two-arm RCT

Why Not Use Multiple Trials to Construct an ATS

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Positive Synergy Between Sequenced Treatments

Example: Mood stabilizers (first-line treatment) may not appear best initially, but may have enhanced long term effectiveness when followed by a particular augmentation, switch, or maintenance strategy (second-line treatment).

Example: Mood stabilizers may set the participant up for better success with any one of the second-line treatments.

Why Not Use Multiple Trials to Construct an ATS

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Negative Synergy Between Sequenced Treatments

Example: Atypical antipsychotics first-line treatment) may produce a higher proportion of responders at first, but may also result in side effects that reduce the variety of subsequent treatments available to non-responders.

Example: The burden (e.g., side-effects) associated with atypical antipsychotics may be so high that non-responders will not adhere to second-line treatments.

Why Not Use Multiple Trials to Construct an ATS

Concern 2: Diagnostic Effects

Example: Mood stabilizers (first-line treatment) may not produce a higher proportion of responders at first, but may elicit symptoms that allow you to better match second-line treatment to the patient.

Example: The improved matching (personalizing) on the second-line treatment may result in a better response overall as compared to any sequence of treatments starting with mood stabilizers.

Why Not Use Multiple Trials to Construct an ATS

Concern 3: Cohort Effects

- Patients enrolled in the initial and secondary trials may be different
- Patients who remain in the trial(s) may be different
- Characteristics of adherent patients may differ from study to study
- Patients that know they are undergoing adaptive treatment strategies may have different adherence patterns

Bottom line: The population of patients we are making inferences about may simply be different from study-to-study.

Why Not Use Multiple Trials to Construct an ATS

Concerns about the alternative to SMART

1. Concern 1: Delayed Therapeutic Effect
2. Concern 2: Diagnostic Effects
3. Concern 3: Cohort Effects

All three concerns emanate from the basic idea that constructing an adaptive treatment strategy based on a myopic, local decisions, and from a study-to-study point of view is not optimal.

Other Alternatives

- Observational (Non-experimental) Comparisons of ATSs
  - Using data from longitudinal randomized trials
  - May yield results that inform a SMART proposal
  - Understand current treatment sequencing practices
  - Typical problems associated with observational studies
    - Observed Time-varying confounding
    - Unobserved, unknown, unmeasured confounding
- Expert Opinion

SMART Design Principles

- Think about ATSs first; think about SMART Design second
- KISS Principle: Keep It Simple, Straightforward
- Power for Simple Important Primary Hypotheses
- Take Appropriate Steps to Develop an Optimal ATS

Keep It Simple

Overarching Principle

At each critical decision point...

- Restrict class of treatment options by ethical, feasibility, or strong scientific considerations
- Use low dimensional summary to restrict subsequent treatments
  - Example: Use $S =$ binary responder status
- Collect rich set of intermediate outcomes that might be useful in deciding later for whom treatment works best
  - Information useful for more complex ATSs

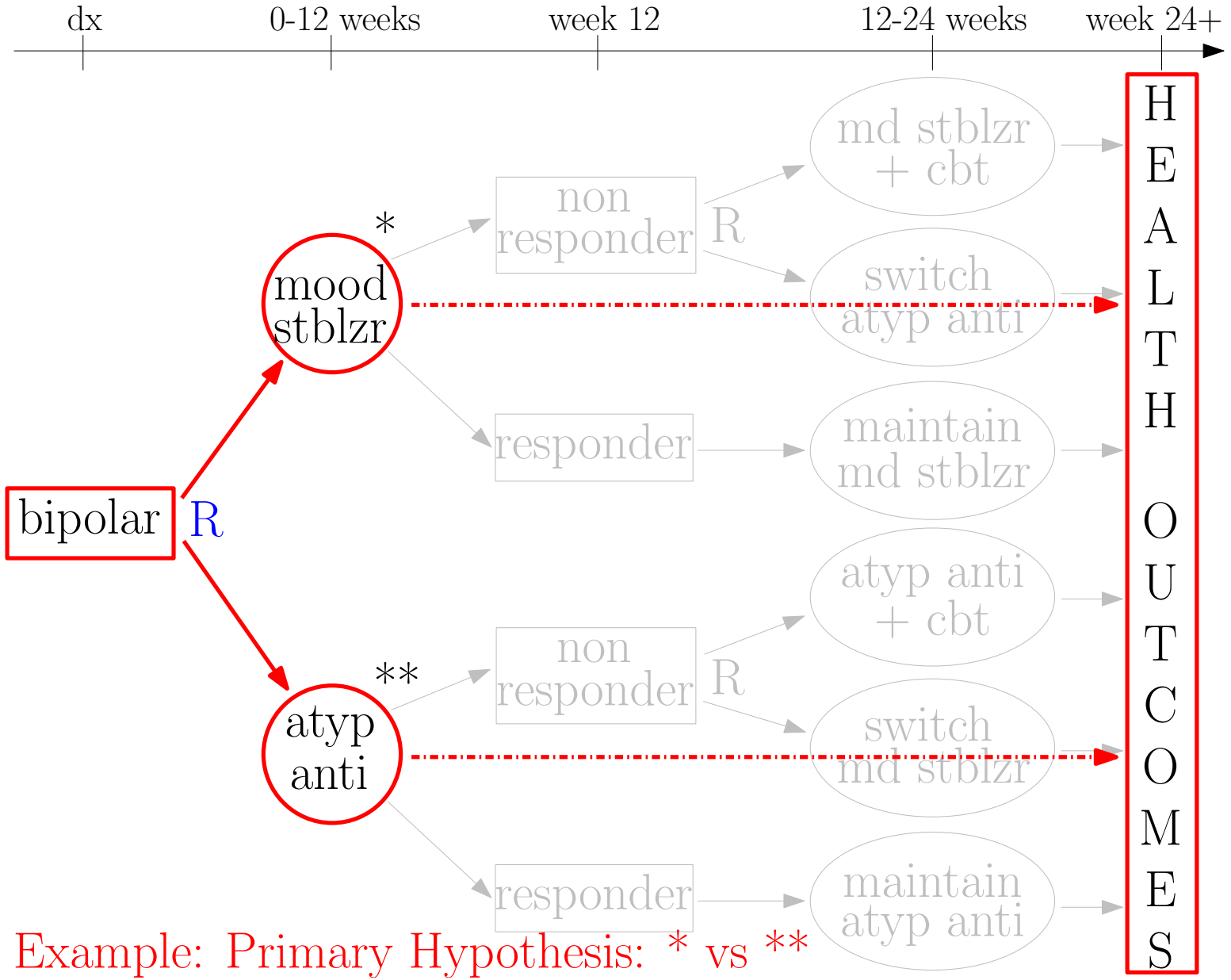
Primary and Secondary Hypotheses

Power for Simple, Important Primary Hypothesis

- Choose a **primary hypothesis** that aids development of an adaptive treatment strategy
  - The trial is powered for this hypothesis
- Choose **secondary hypotheses** that further develops the adaptive treatment strategy and takes advantage of the sequential randomization to eliminate confounding
  - Trial not necessarily powered to test these
  - Often the more interesting developmental hypotheses

SMART Design: Primary Hypothesis, Example

Is the Mood Stabilizer better than the Atypical Antipsychotic as First-line Treatment?



Example: Primary Hypothesis: * vs **

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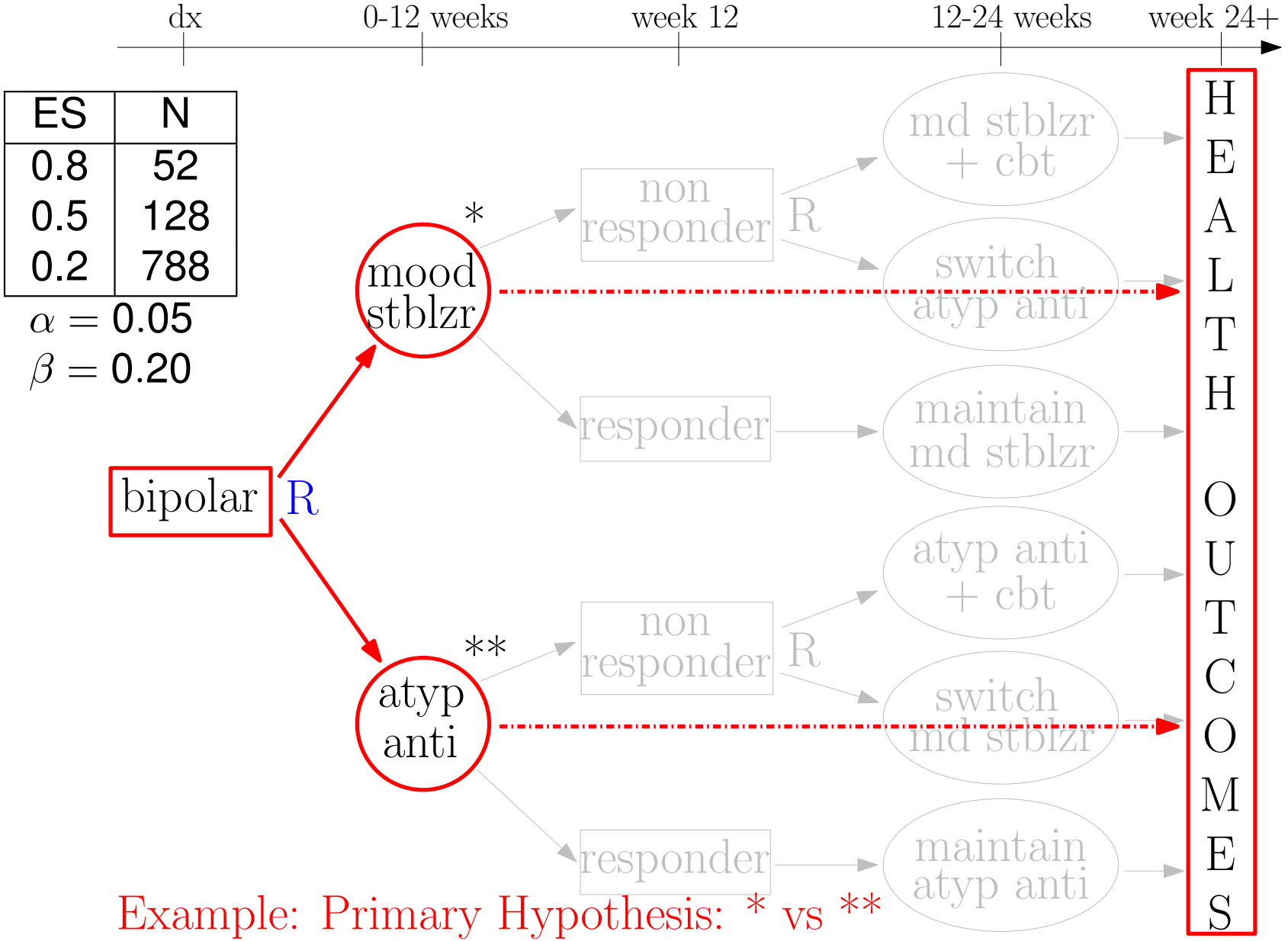

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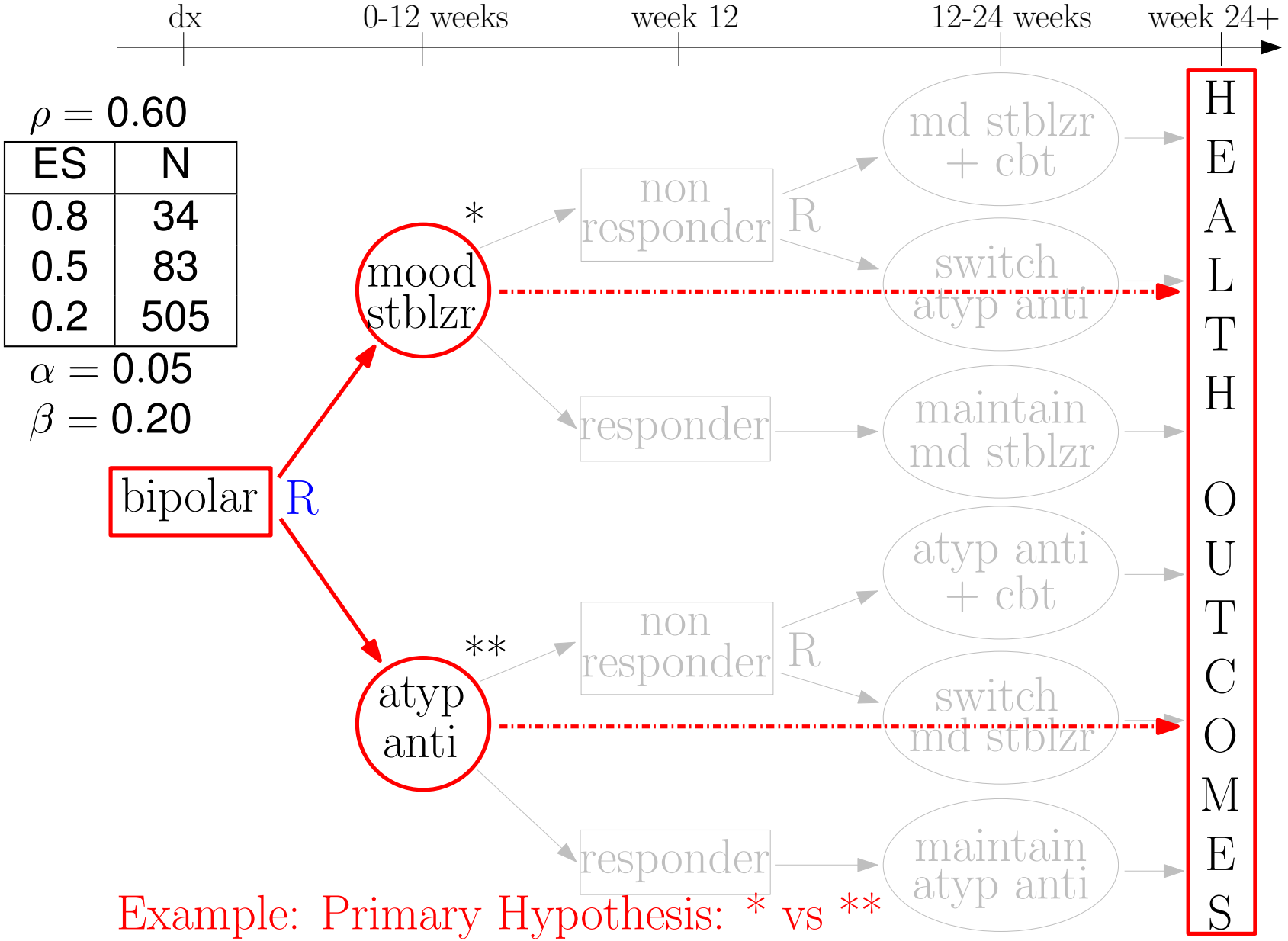
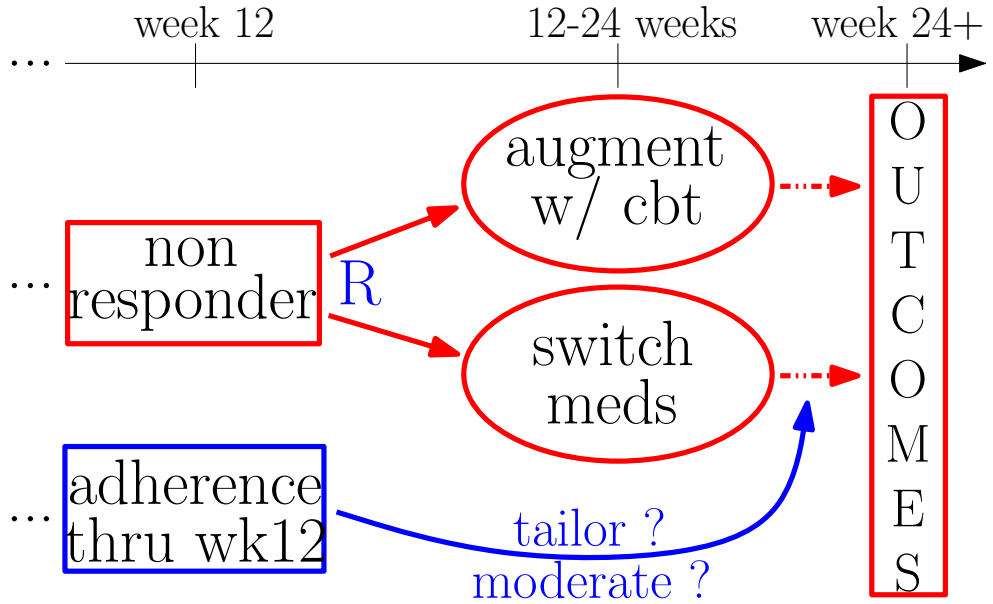


SMART Design Principles

Secondary Hypothesis, Example

Choose **secondary hypotheses** that further develop the adaptive treatment strategy and take advantage of the sequential randomization to eliminate confounding.

Example:



SMART Design Principles

Always Choose a Longitudinal Response Measure

Why **choose a longitudinal outcome**, or a with-in person summary of outcomes over time?

- These are chronic disorders
- Outcome should incorporate time to initial response as a component
- Quick initial relief of symptoms should be valued
- Increase power; reduce required sample size

Misconceptions and Misunderstandings

- SMARTs do not necessarily require larger sample sizes
- Distinction between the adaptive treatment strategy and the SMART trial design
  - Adaptive Treatment Design (ATS), versus
  - Adaptive Clinical Trial Design (SMART)
- CAREFUL: The term **adaptive design** has other meanings in the clinical trials literature
  - In a SMART, the same patients participate in multiple stages of randomization

Other Issues

- SMARTs are developmental trials
  - After SMART, run a confirmatory trial: the optimized ATS versus some standard control (treatment as usual)
  - This is not a criticism of SMARTs
- Distinction between adaptive versus non-adaptive treatment sequences
  - Non-adaptive treatment sequences are treatment strategies that are not shaped/affected by intermediate outcomes
- Statistical methods exist for comparing (e.g., testing the mean difference between) two or more ATSs

Thank you!

Please contact me for copies of the slides or to discuss planning/designing your next SMART:

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www.umich.edu/~dalmiral

A special supplement is available on this topic:

- **Customizing Treatment to the Patient: Adaptive Treatment Strategies.** *Drug and Alcohol Dependence.*
- May 2007; 88 (Supplement 2), ppS1-S72.