ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Long-term evaluation of psychotropic drugs in major psychiatric disorders: outcome measures, study-designs and statistical approaches

Industry Perspective

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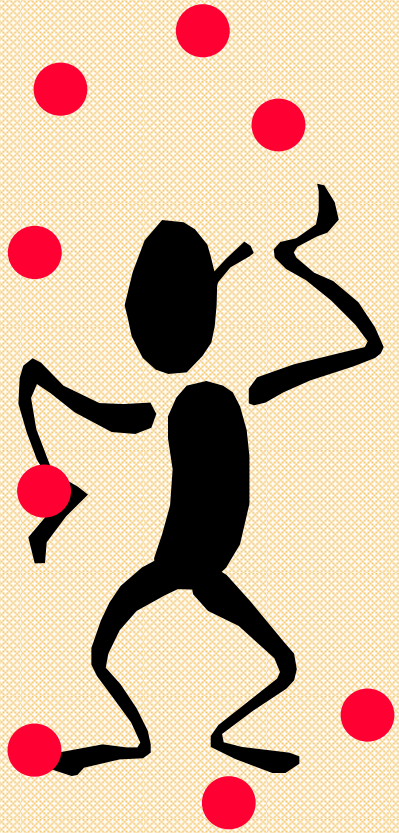
Questions Industry Must Address in Long-Term Trials

The study questions that industry addresses and the consequent selection of trial designs are driven by its key customers

Customers Whom Industry Must Serve

- Patients
- Clinicians
- Patient families and caregivers
- Global regulatory bodies (US/EU/Asia)
- Payers



Industry-sponsored trials must simultaneously meet the needs of many customers.

Customers for Industry-Sponsored Trials

- **PATIENTS**
  - "If I take this medicine for a long time will I be better off than if I do not take it?" or "Do I need to continue to take this medication?"
- **CLINICIANS**
  - "Will the drug/dose that effectively treated symptoms in my patient continue to have an adequate effect long term and will it be safe?"

Endpoints: Individual response questions; not directly addressed in most clinical trials; best addressed by "responders' analyses"

- **REGULATORS**
  - "Does the drug which demonstrated an acute effect in a defined population of patients continue to provide a favorable risk: benefit ratio when continued for long periods?"
- **PAYERS/SOCIETY**
  - "What is the value of this treatment?" or "Will the long-term use of this medication help reduce the overall cost needed to manage the disease and keep patients in an optimally functional state?"

Endpoints: Population questions; subject of most clinical trials

Strategic Considerations in Design Selection

- **Differentiation**
  - How does the study medication distinguish itself from currently available long-term treatments?
- **Satisfaction of different regulatory agencies**
  - How can competing regulatory requirements from around the world regarding long-term treatment be harmonized to make an efficient development program?
- **Similarity of environment**
  - Is the diagnostic and clinical treatment environment sufficiently similar to permit multi-country development?
  - Is there sufficient similar understanding of the disease and its diagnosis to permit multi-country development?

Industry Trial Design Considerations

- **Selection of comparator (placebo/active)**
  - Which comparator meets regulatory requirements?
  - Which provides best information regarding un-met needs for long-term efficacy, safety and tolerability of the study drug?
- **Selection of endpoints**
  - Determined by specific design selected and history of work in the field of interest
  - Change from baseline/trajectory of change from baseline/ AUC
  - Complex endpoints?

Industry Trial Design Considerations

- **Selection of scales**
  - Often defined (and limited) by history of field
  - Many existing scales limited in ability to adequately characterize full profile of drug
  - Need to know psychometric properties
    - Validity, reliability, item analysis, trainability
- **Outcomes Issues**
  - How cost-effective is the study drug for the indication relative to a comparator?
    - Address improvements in functioning and quality of life
    - Does the duration of trial and the environment reasonably permit detection of improvement ?
    - Do outcomes measures work across sites?
    - Are outcome measures sufficiently specific to reflect treatment?

Industry Trial Design Considerations

- **Potential outcome measures**
  - Time to first event
  - Time to multiple events
  - Complex (composite) endpoints
  - Differential weighting of endpoints over study duration
  - AUC/Trajectory
    - Days without interventions
    - Patient rated “days well”
    - Scale scores within boundaries
    - Combination of scales scores and other measures

Industry Trial Logistic Considerations

- **Selection of countries in which to study patients**
  - **Are patient disease characteristics, diagnostic approaches and medical practice similar enough to be included in a single trial?**
- **Selection of investigators**
  - **University-based vs clinical practice vs State/VA hospital vs tertiary care vs SMO**
    - **How treat impending relapse?**
    - **How identify patients**
    - **What staff is available?**
    - **What outcome measures can be meaningfully assessed?**
- **Selection of raters**
  - **Problems of reliability of informant; availability of informant; consistency of informant**

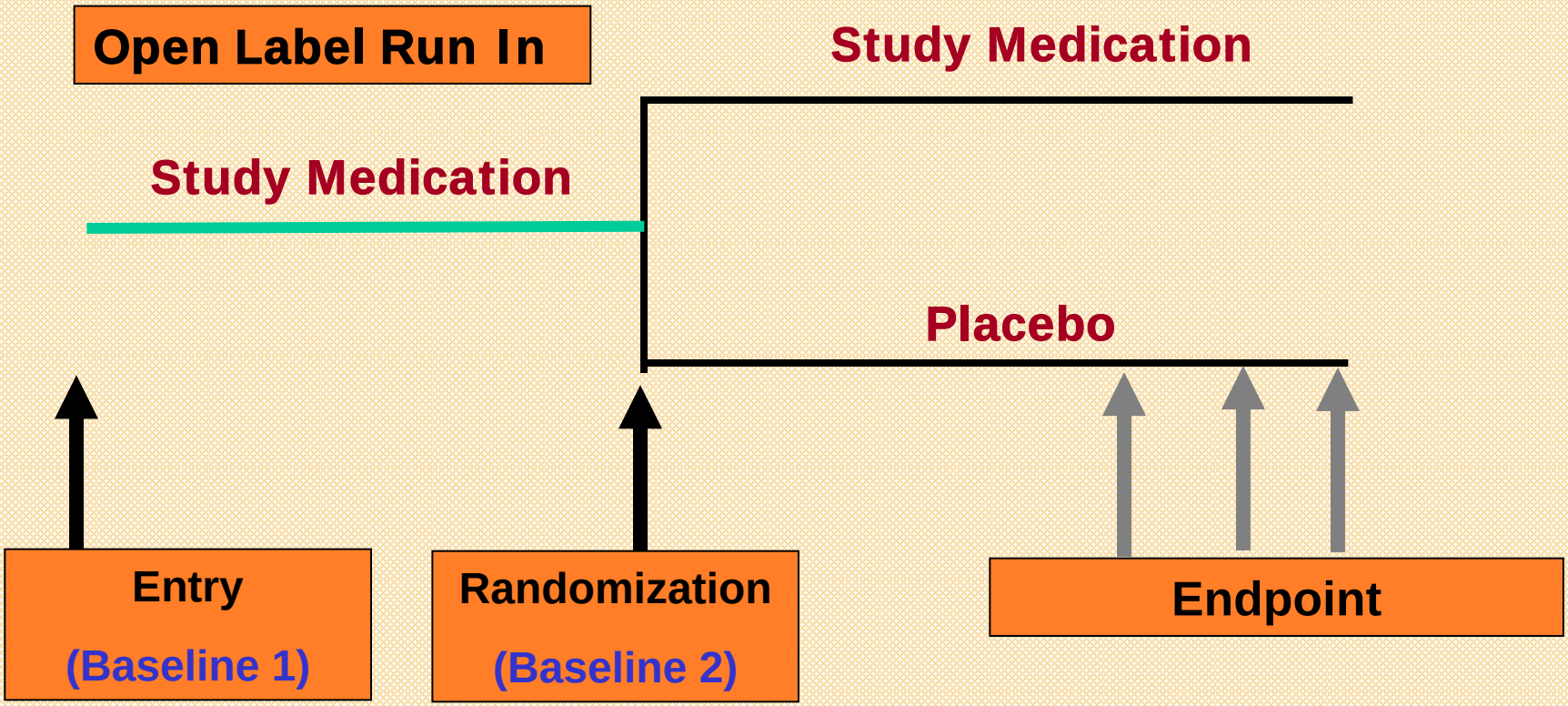
Industry Trial Logistic Considerations

- **Selection of patients**
  - Do we pay them for participation?
  - How much do we pay them?
  - For what do we pay them?
  - How does this affect generalizability of data?
- **Retention**
  - How do we keep patients in the trial so as to maintain a reasonable sample size and timelines?
- **Cost**
  - How can we maximize the value of the trial within financial constraints?
  - There are limits to our budgets

Possible Trial Designs

- Randomized Withdrawal
- Double-Blind Long-Term Efficacy
- Double-Blind Long-Term Maintenance
- Adjunctive Designs

Randomized Withdrawal



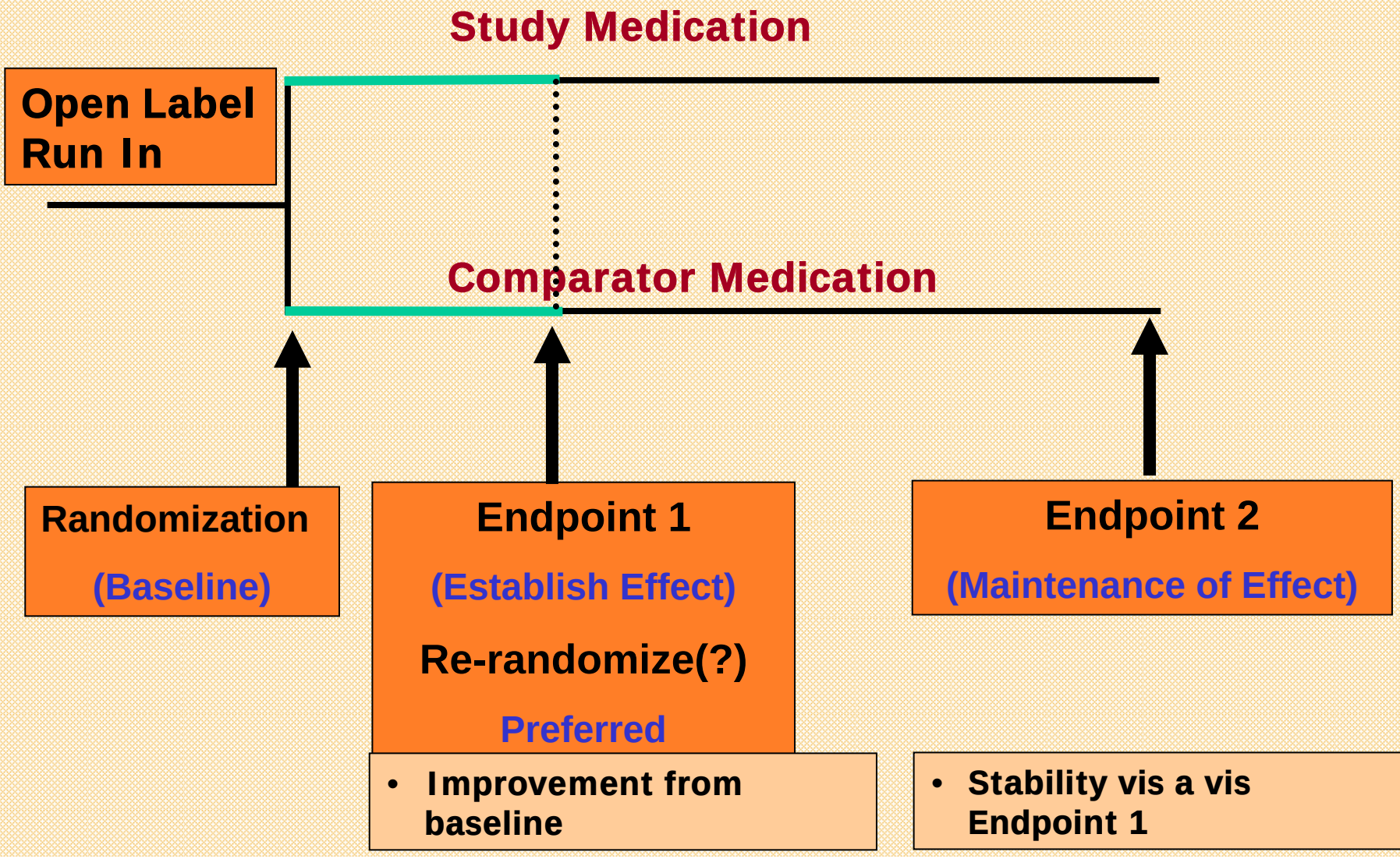
Randomized Withdrawal

- **Design summary**
  - **Patient population: Currently stable patients**
    - **May or may not be acute at screening**
    - **Must manage problems with rate of treatment discontinuation**
  - **Initial open label Rx: Prospective stabilization**
  - **Randomized Rx: Subjects meeting stabilization criteria randomized to Rx arms**
  - **Endpoint = Time to event / Change from Baseline /AUC/Trajectory/**

Randomized Withdrawal

- **Advantages**
  - Avoids placebo exposure in acute phase of illness
  - Facilitates recruitment from stable patient populations
  - Precedented approach, particularly in US
- **Disadvantages**
  - Problems with enrichment if stabilize on study medication
  - Requires a subset of the patients to be treated with placebo
  - Identifying suitable study placement sites

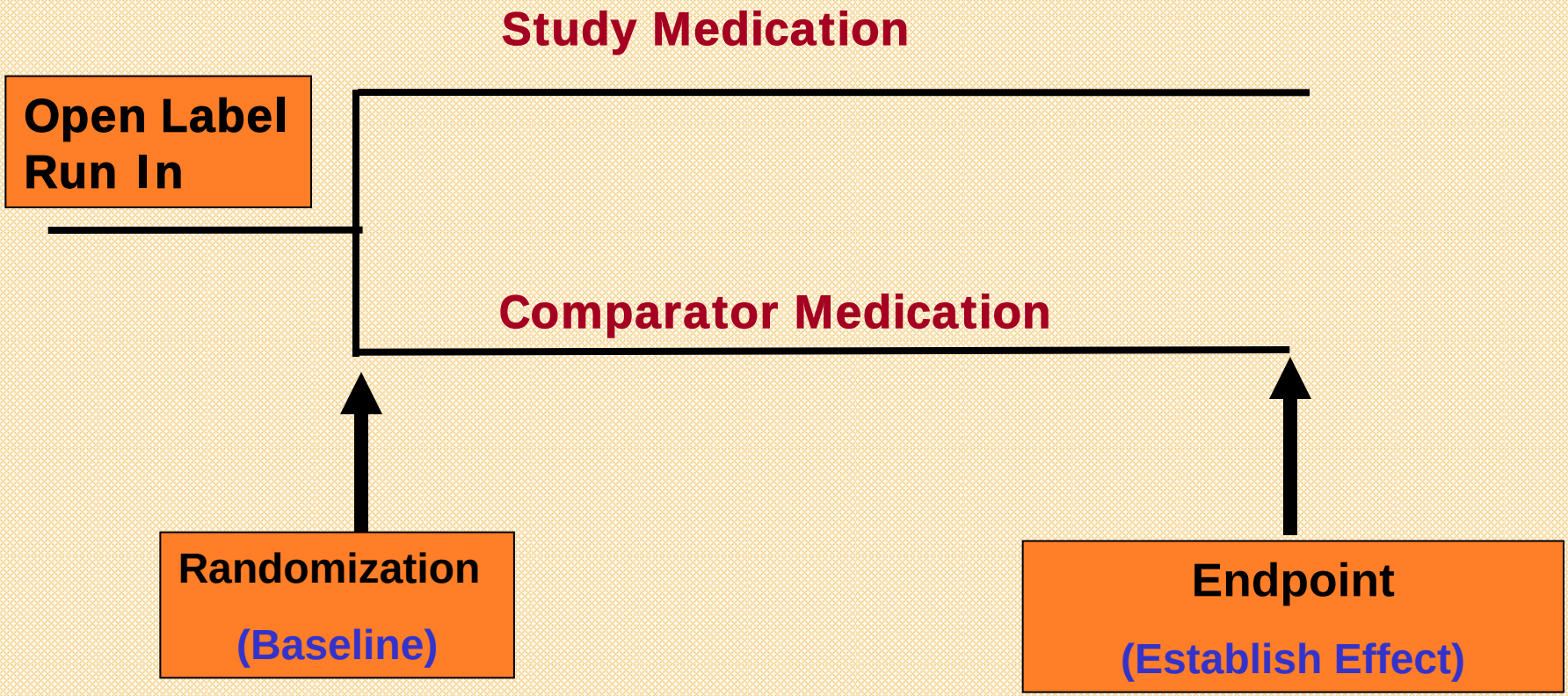
Maintenance of Effect Design



Maintenance of Effect Design

- **Design summary**
  - Patient population: Acute exacerbation of condition
  - Randomized to treatment arms after screen
  - Identify initial effect (remitters) at Endpoint 1 (e. g., 3 weeks) … then evaluate for long-term maintenance of this effect
  - Endpoint = Stability of [Endpoint 2- Endpoint 1] study medication v. comparator
    - rating scale change from baseline/AUC/trajectory
- **Advantages**
  - Demonstration of initial effect in DB randomized trial
  - If re-randomized, this design provides may provide descriptive information into switching from one drug to another
- **Disadvantages**
  - Large sample size, i.e. high placebo drop out during acute episode
  - Design novelty with no regulatory precedence
  - No placebo; bias to efficacy for non-inferiority; superiority difficult to demonstrate

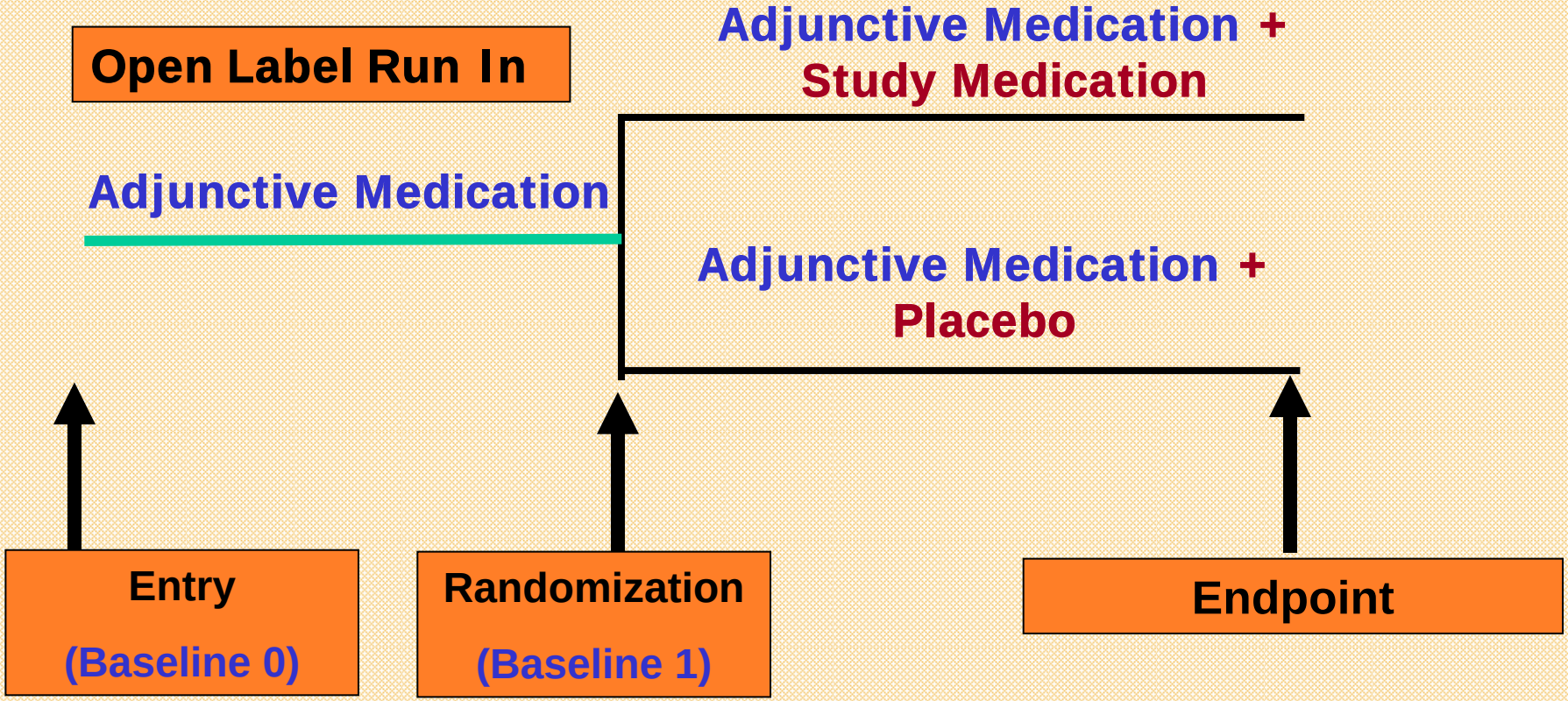
Long-Term Efficacy Design



Long-Term Efficacy Design

- **Design summary**
  - Patient population: Acute exacerbation of condition under study
  - Randomised to treatment arms after screen
  - Endpoint = Rating scale change from baseline v. comparator / AUC / trajectory
- **Advantages**
  - Most closely mimics clinical practice
- **Disadvantages**
  - Large sample size; high placebo drop out during acute phase
  - Novel design for CNS trials with little regulatory precedence
  - Standard endpoints may not address key regulatory efficacy question
  - No placebo; bias to efficacy for non-inferiority; superiority difficult to demonstrate

Adjunctive Designs



Adjunctive Design

- **Design summary**
  - Patient population: Acute and/or currently stable patients
  - Initial open label Rx: Prospective stabilization established but incompletely effective medication
  - Randomized Rx: Subjects meeting criteria are randomized to placebo or study medication (added on to prior treatment)
  - Endpoint = Rating scale change from baseline v. comparator/AUC/trajectory
- **Advantages**
  - Permits use of placebo exposure
  - Facilitates recruitment
  - Precedented approach

Adjunctive Design

- **Disadvantages/Issues**
  - Interpretation of safety data
    - Drug/drug interactions
  - Choice of adjunctive medication
  - Identifying suitable patients
  - Restricted label/fails to demonstrate effect as monotherapy

Statistical Issues

- **Choice of analysis**
  - **Driven by choice of endpoint**
    - **Risk of events / number of events / time to event /trajectories**
  - **Missing data is a key issue**
  - **Considerations**
    - **LOCF / OC / Mixture Model / AUC / Trajectory / Others**

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Summary

- **Success in trials is dependant on a risk-benefit analysis comparing safety, tolerability and efficacy**
- **Several long-term designs can be considered**
  - **Selection depends on needs to be addressed**
  - **Have variable regulatory and statistical buy-in**
- **We will never have all the scientifically rigorous information that we might possibly want.**
- **When do we have enough information to make meaningful predictions?**

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THANK YOU

A General Study Schematic for Long-Term Treatment

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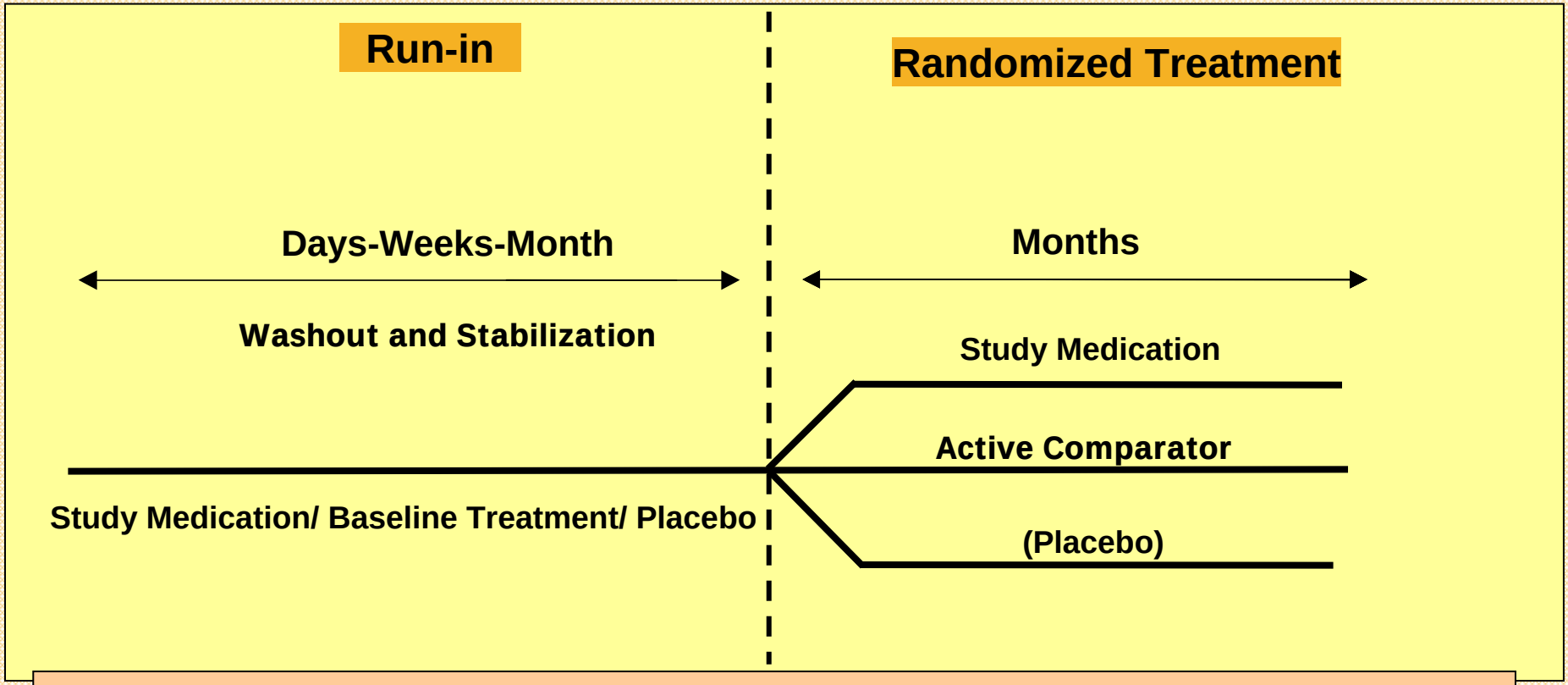

- In most relapse/adjunctive studies have a pbo comparator
- Maintenance of effect studies have an active comparator

Slide 26

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binnemanb, 6/20/2006