

# Clinical Trials that Demonstrate Disease Modification: The Challenges and a Possible Solution for Schizophrenia

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# Disclaimer

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- Former employee of Novartis, Knoll (AbbVie), Pfizer, Janssen Pharmaceuticals
- Current employee of Newron Pharmaceuticals, LLC
- Stock in Johnson & Johnson and Newron

# Outline

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- Background
- Scientific Considerations
- Design Options
- Delayed-Start Study Design Challenges
- Discussion

# Disease Progression vs Disease Modification

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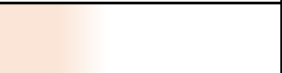
- **Disease progression**—worsening of a disease (syndrome) in terms of symptom severity, underlying pathology, and outcome.
  - Most commonly evident in chronic and often incurable diseases where the stage of the disease is an important determinant of therapy and prognosis
- **Disease modification**—Alteration of the underlying disease (syndrome) pathophysiology resulting in a long-term beneficial outcome

## Challenge to establishing disease modification:






- Convincingly demonstrate that study treatment modifies disease progression
  - Is the ultimate outcome truly stopped or delayed by the treatment?
    - Does the treatment show initial improvement in symptomology that is not maintained, such that ultimate outcomes are similar?
  - Is earlier intervention better than later intervention?

# Disease Modification in Chronic Progressive Disease






## Natural Progression of Disease

Symptomatic Patient Time 1	
Component state	
	
Component function	
	
Symptom	








Symptomatic Patient Time 2	
Component state	
	
Component function	
	
Symptom	





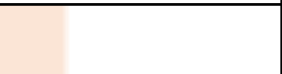


Symptomatic Patient Time 3	
Component state	
	
Component function	
	
Symptom	






## Disease Modification with Treatment?

Symptomatic Patient Time 1	
Component state	
	
Component function	
	
Symptom	



Symptomatic Patient Time 2	
Component state	
	
Component function	
	
Symptom	



Symptomatic Patient Time 3	
Component state	
	
Component function	
	
Symptom	

## Adapted from 2014 ISCTM Presentation

- Primary Endpoints must be clinically meaningful
  - Capture how patients feel, function/survive, underlying biology
- Disease modification will ultimately be identified by preponderance of the evidence and consistency of evidence in multiple domains
- Disease modification is not possible at this time for most CNS diseases

# Demonstrating Disease Modification

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- **Extensive understanding of disease (syndromal) course**
  - Knowledge of changes in biological markers over time
  - Knowledge of how biological markers correlate with symptoms, function and outcomes
  - Knowledge of variation in disease course with respect to subpopulations
    - Demographics (age, race, sex)
    - Age of onset/Duration of illness
    - Symptom severity or expression
    - Prior treatment
    - Co-morbid conditions
- **Design elements supported**
  - Indication to be pursued
  - Treatment population
  - Inclusion/exclusion criteria

# Design Considerations

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- **Identify Objective:** Disease progression? Disease modification (requires evidence of progression)?
- **Identify comparator:** Placebo or SOC or alternative
- **Blinding:** Double blind vs blinded endpoint identification committee
- **Duration:** Weeks vs Months vs Years
- **When in disease course to study:** Period of vulnerability may be limited
- **Endpoints:** Symptoms/function/biology
- **Decision rules for establishing disease progression and disease modification:**
  - How to establish a non-inferiority margin?
- **Resources:** What are available?
  - Restricts many aspects of study design



# Design Considerations

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- Withdrawal Design (P Leber, 1994,1996)
- Delayed-Start Design (PLeber, 1996)

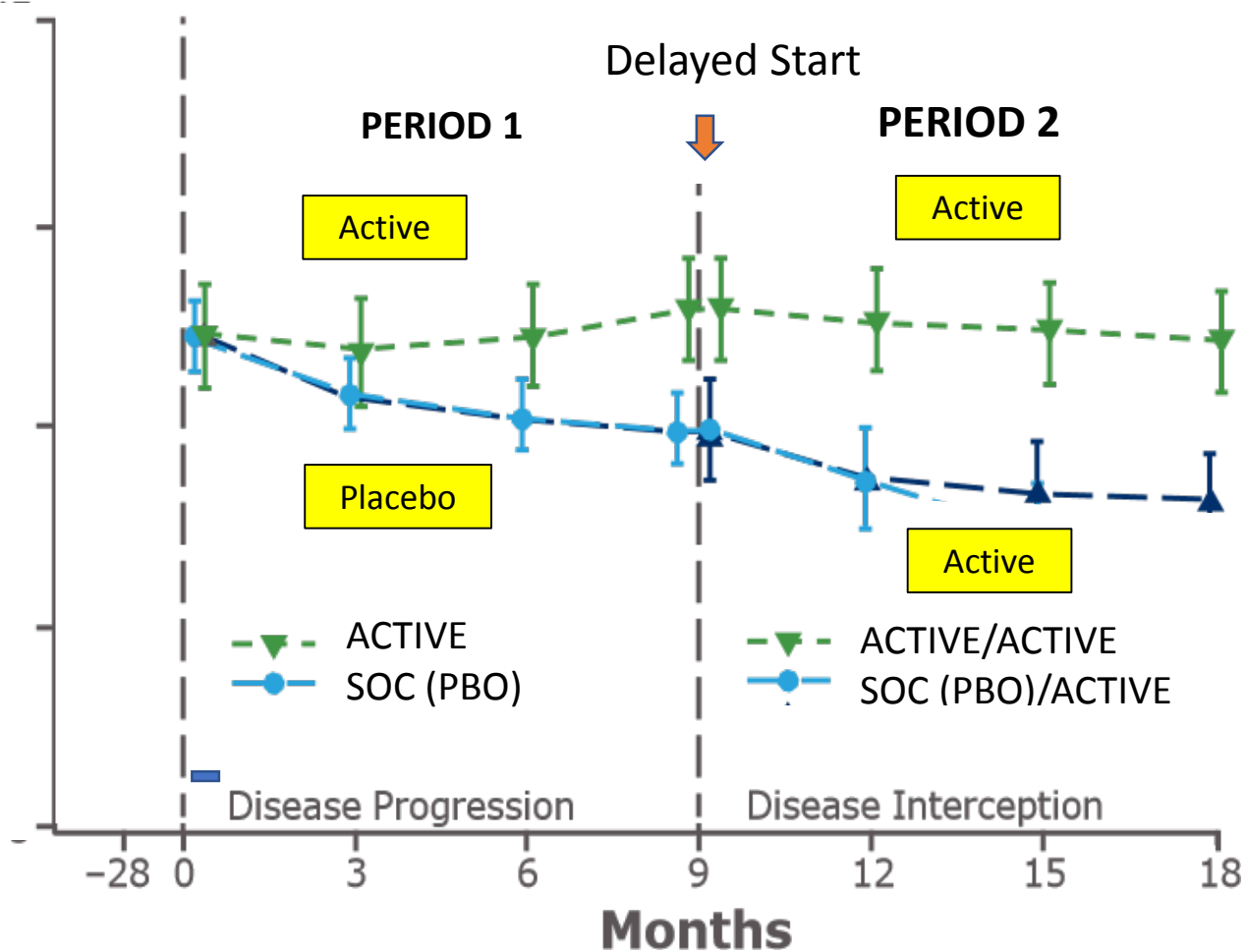
## Population selection criteria?

- Know natural history of disease
  - What is the rate of disease progression?
  - Is rate of progression linear? If not, what is shape of progression trajectory?
  - Are there identifiable subpopulations that have different progression trajectories?
- Must know the natural history of progression for
  - symptoms
  - functioning
  - biological markers

## What is comparator treatment?

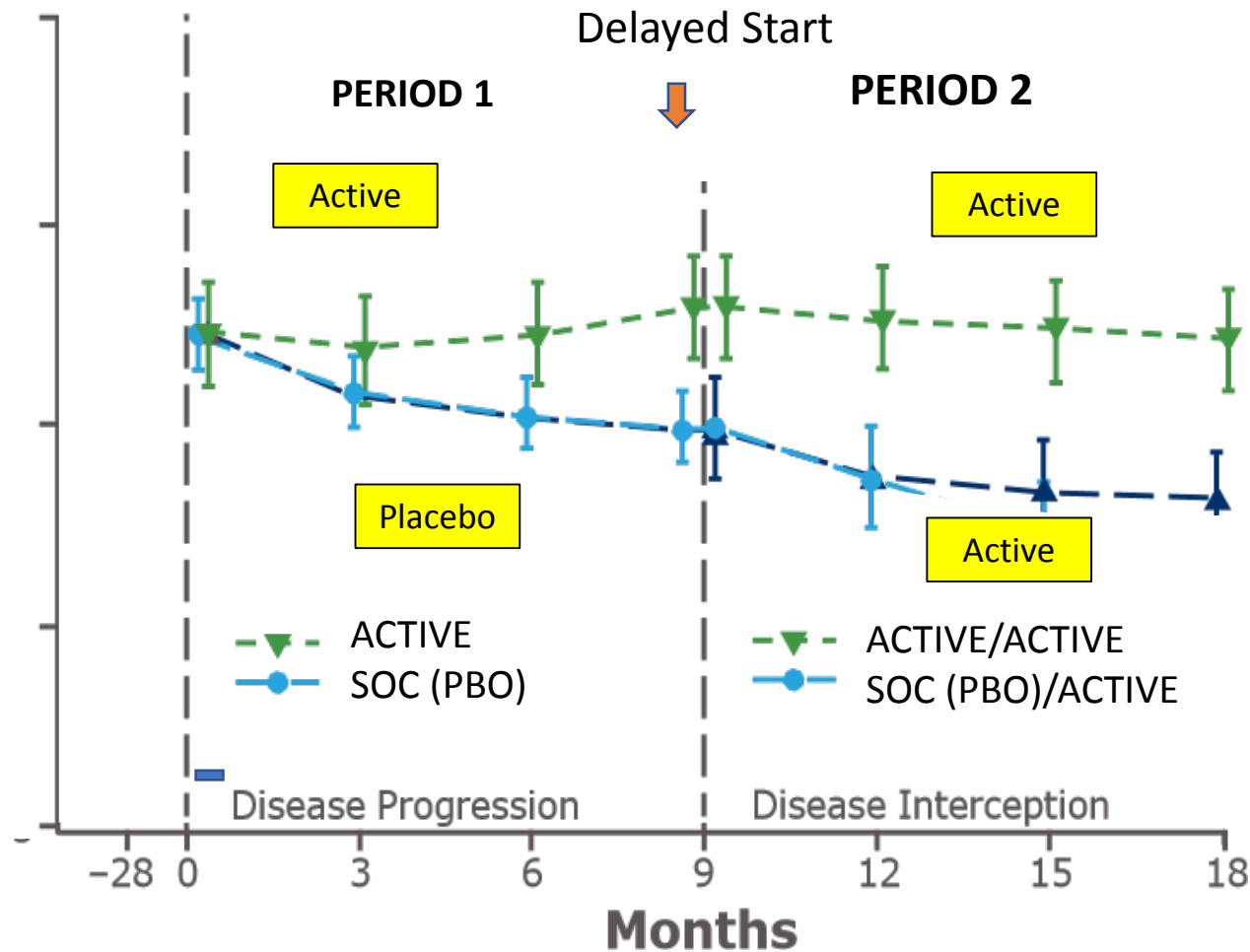
- SOC vs PBO
  - Smaller effect size likely with SOC
  - Placebo use may be unethical
  - Study logistics may limit ability to use all SOC (e.g. clozapine)

# Delayed-Start Design (Leber, 1996)



**Design depicted shows active treatment maintaining normal function and SOC tracking a deteriorating course**

# Delayed-Start Design (Leber, 1996)

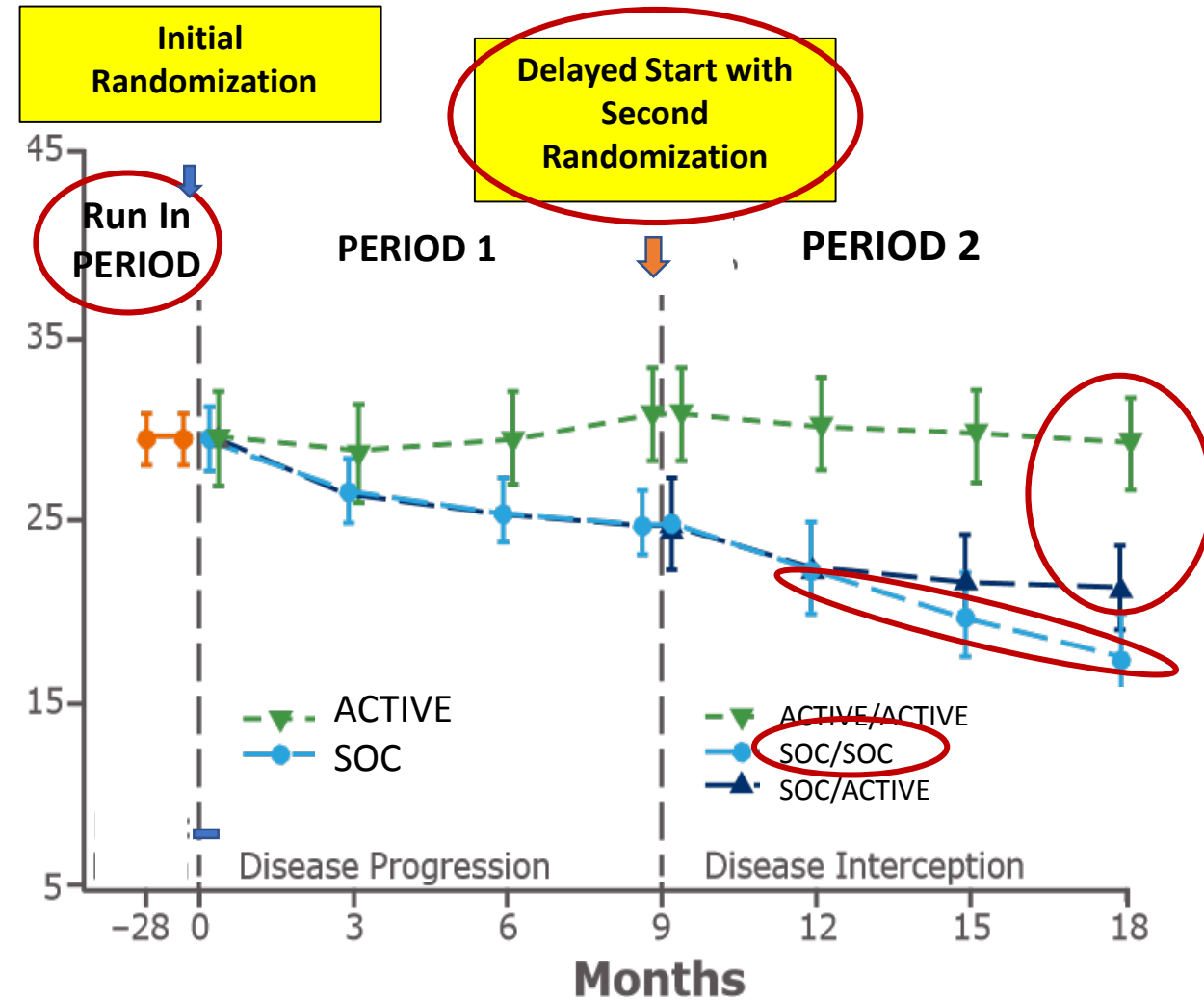


## Limitations of Delayed-Start Design

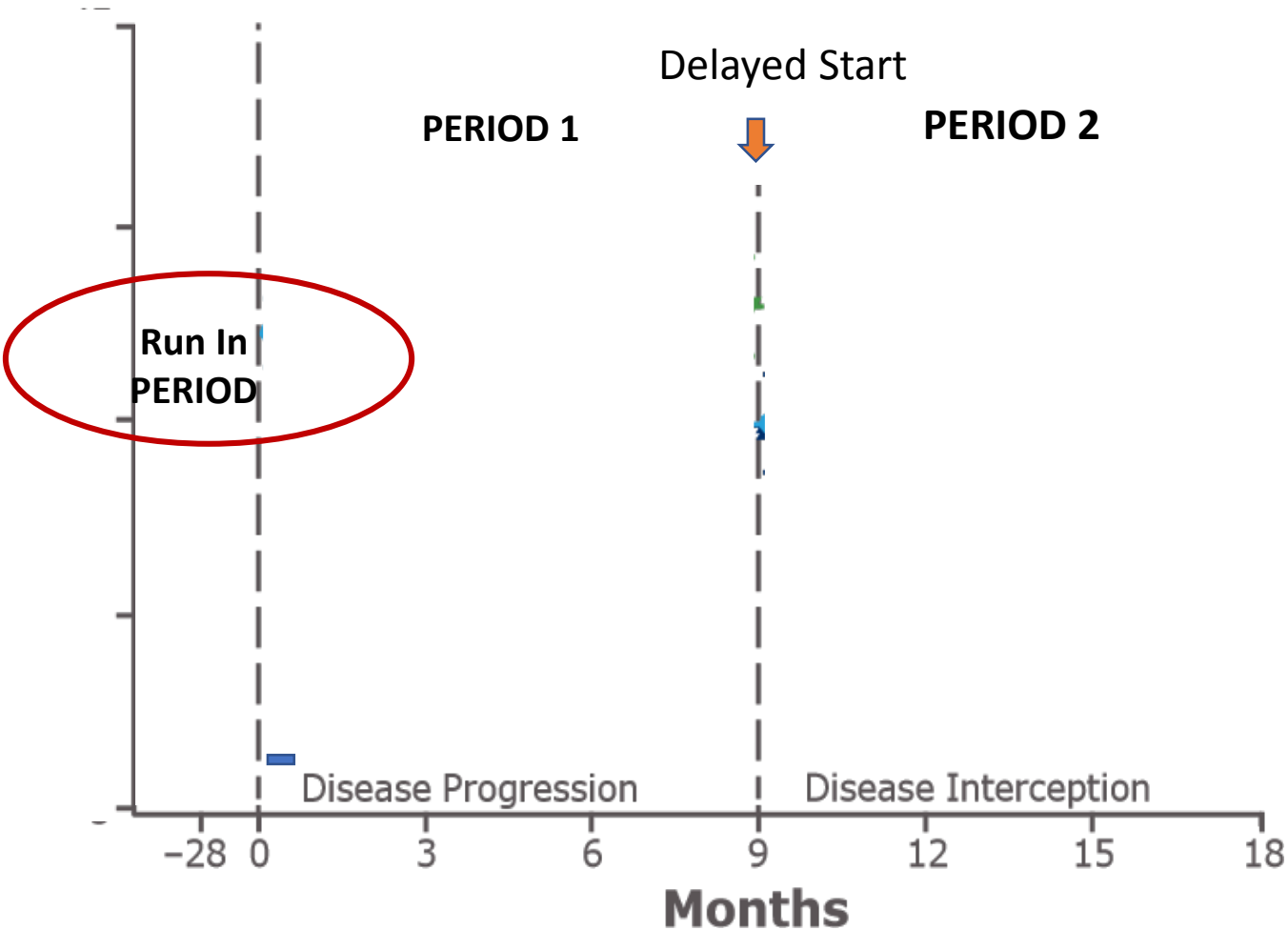
- What if active treatment is not tolerated by the patient?
- What happens if SOC (PBO) is continued?
  - Treatment could worsen disease course
- How do you manage drop outs in Period 1 and loss of randomization?
- How many patients are needed to show difference with endpoints for symptoms, function and biology?
- What is the meaning of the difference at the end of Period 2?
  - Is it different from normal disease progress?
- How do you measure for a clinically meaningful treatment effect?
  - If you use a non-inferiority margin to demonstrate a difference, how do you establish that margin?

# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design

- 3-period/3-arm proposed delayed-start design
  - Period 1:
  - Period 2:
  - Period 3:

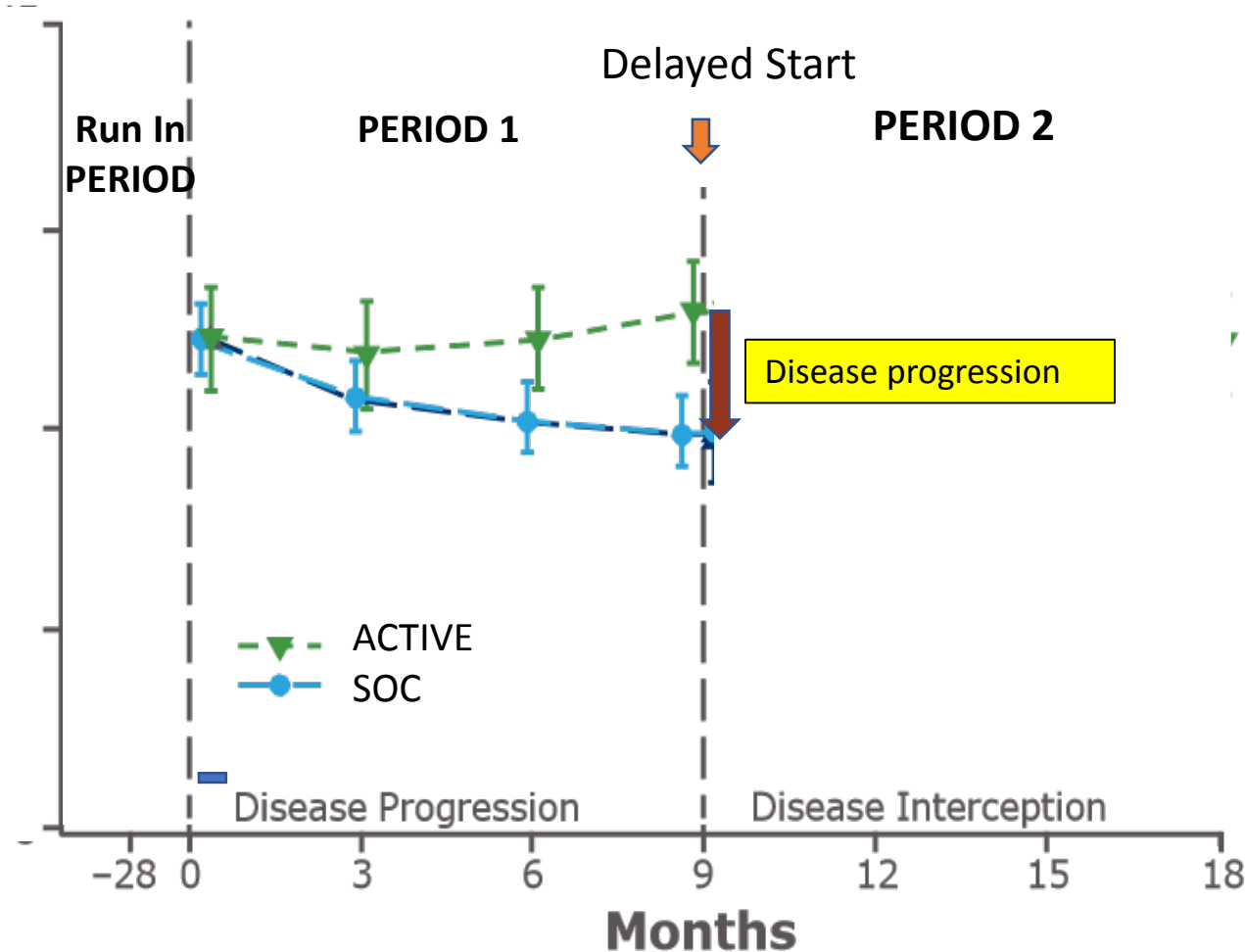


# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design



**Run In Period** to establish treatment tolerability

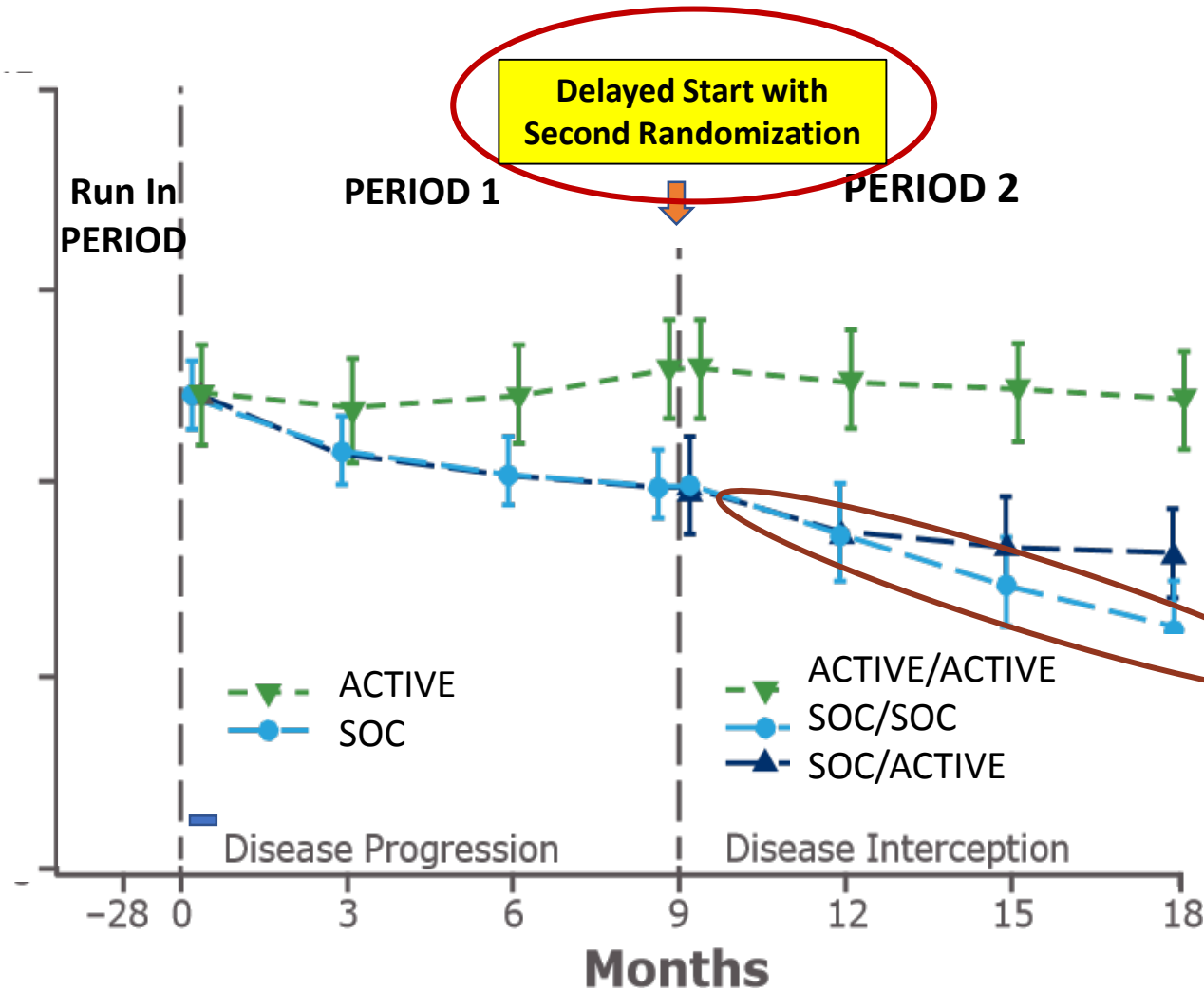
# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design



- **Period 1:** Establishes disease progression between Active treatment and SOC
  - Design depicted shows active treatment maintaining normal function and SOC tracking a deteriorating course

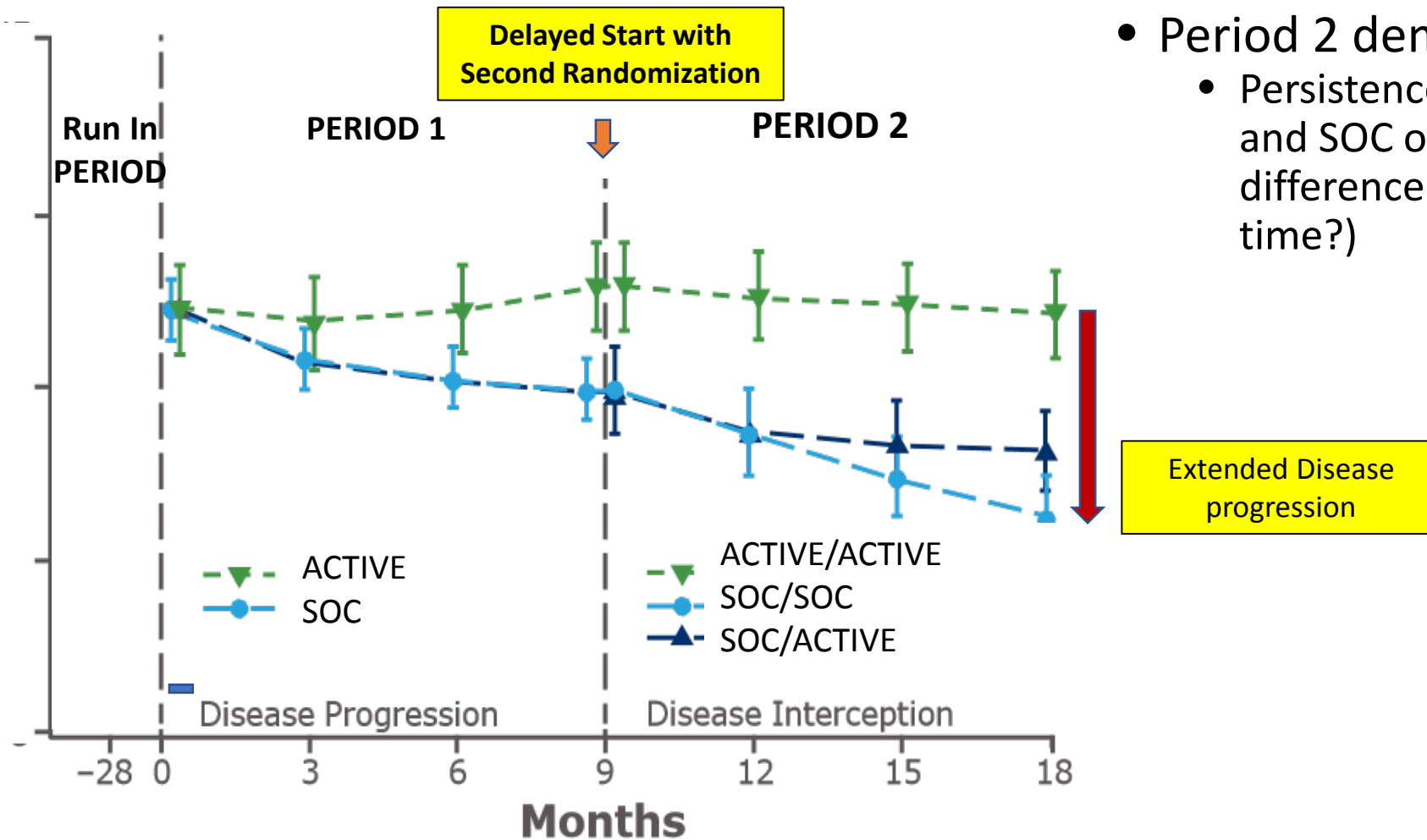


# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design



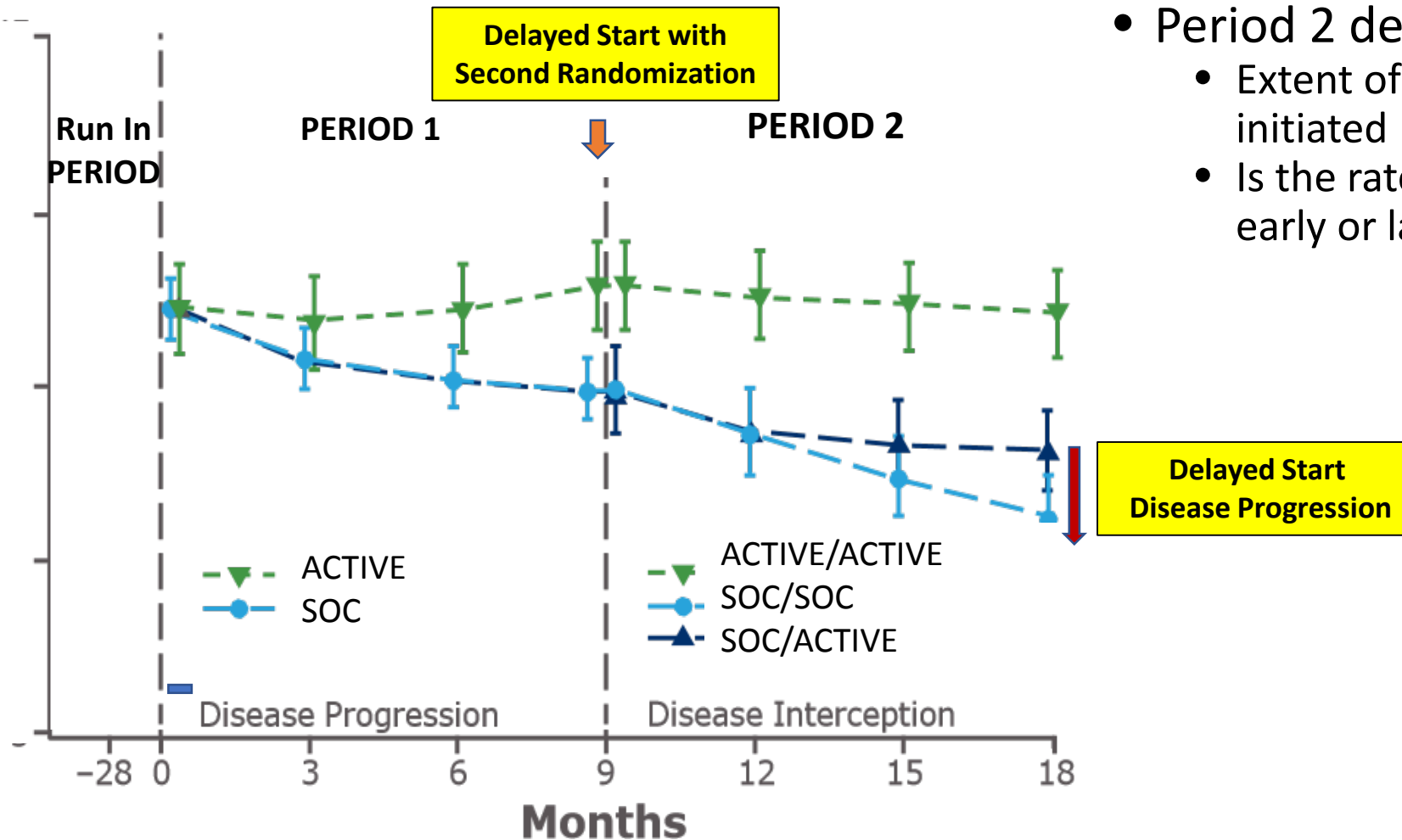
- Period 2 with delayed start and double randomization
  - Active treatment is maintained in Period 2
  - SOC group is divided in continued SOC and delayed initiation of Active
- Double randomization: used to manage problems of dropouts in Period 1
- Continuation of SOC provides stronger reference regarding natural history of disease progression against which response to SOC can better measured

# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design



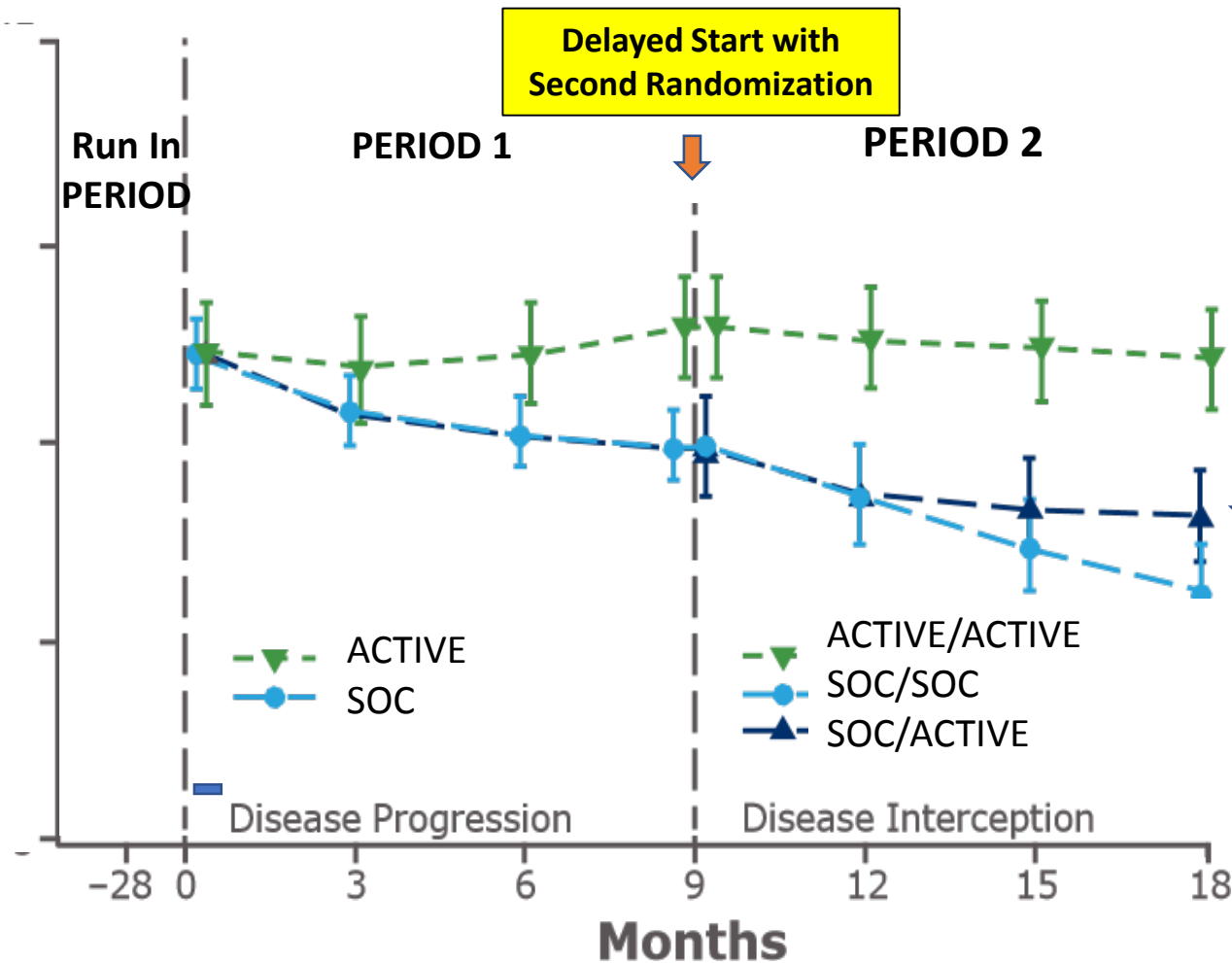
- Period 2 demonstrates
  - Persistence of difference between Active and SOC over time (Is disease progression difference maintained or extended over time?)

# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design



- Period 2 demonstrates
  - Extent of disease progression if treatment is initiated later.
  - Is the rate of progression similar if started early or late?

# 3-Period, 3-Arm, Double-Randomized Delayed-Start Design

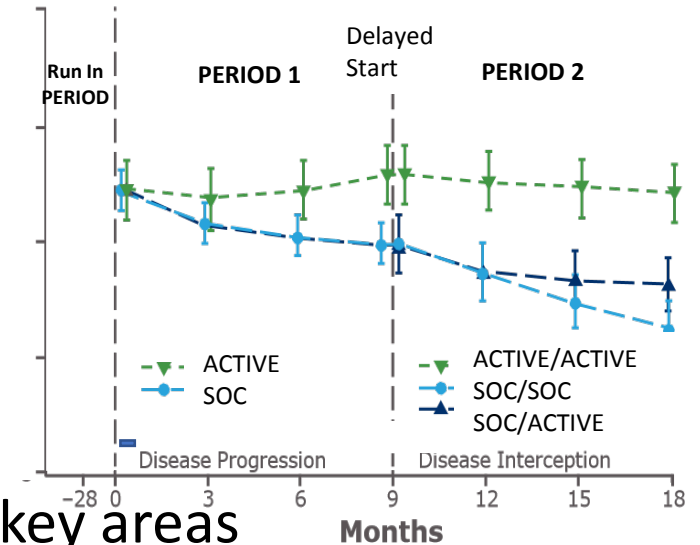


- Period 2 demonstrates
  - Evidence for sustained effect between AA and S/A after delayed-start in Period 2 (evidence for disease modification with earlier introduction of treatment)
  - Alternative to use of non-inferiority margin used to establish difference

**Early Start Treatment Effect**

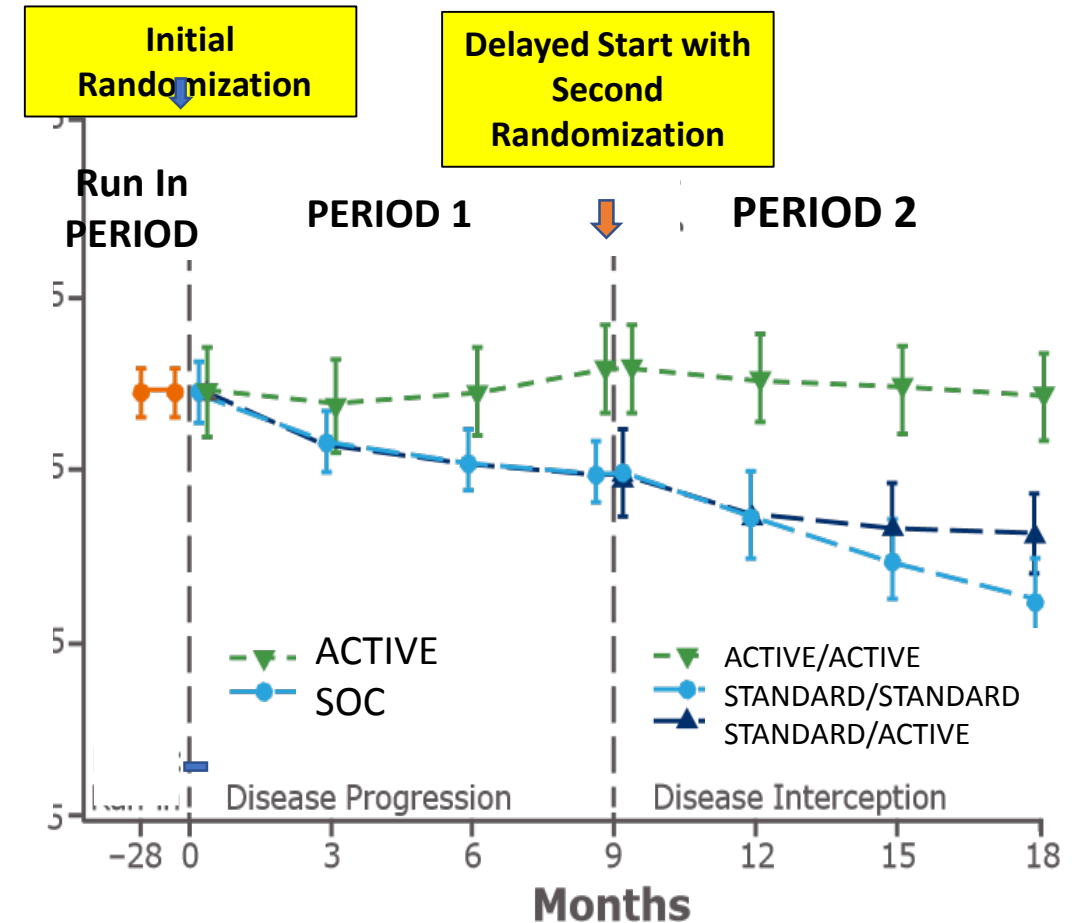
## How long to study?

- Run in Period:
  - Long enough to establish tolerability
- Period 1
  - Long enough to see disease progression in each of the key areas
    - Symptoms, Function, Biology
- Period 2
  - Probably equivalent to that of Period 1
    - Is progression in Period 2 = progression in Period 1?
    - Is progression observed in Period 1 maintained in Period 2?
    - Does improvement with delayed start catch up with that observed with early start?
    - Does disease progression observed in Period 1 continue at same trajectory in Period 2?



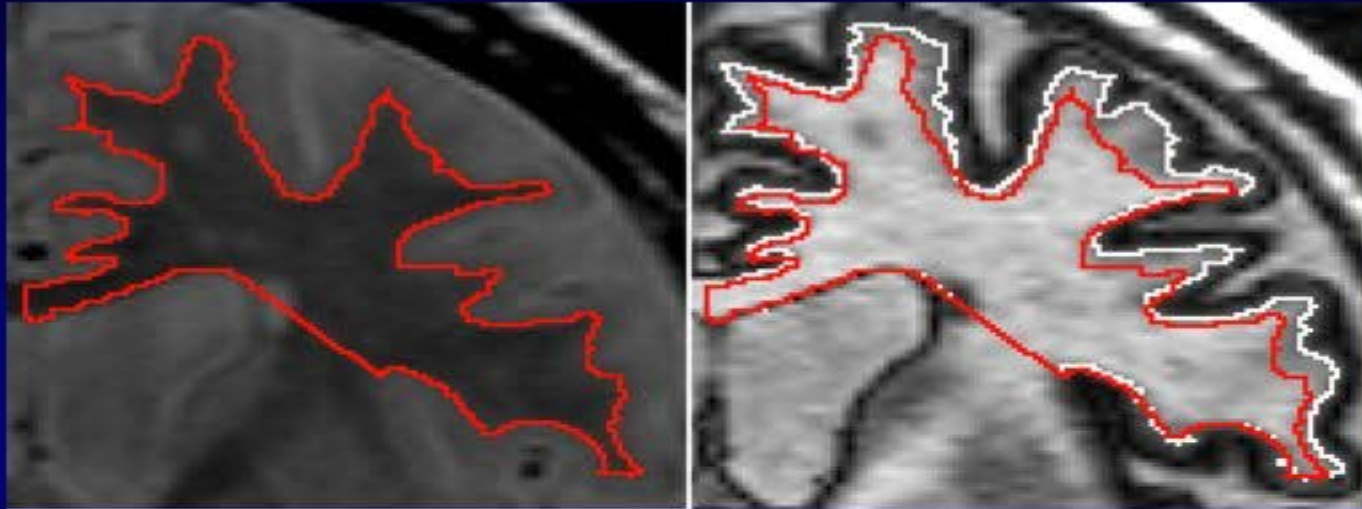
# Toward Disease Modification in Schizophrenia

- Population: Recent onset schizophrenia
- Endpoints:
  - Symptoms: PANSS
  - Functioning: GAF/CGI
  - Biology: Intracortical myelin
- Treatments: LAIs vs oral
- Duration 9 months + 9 months



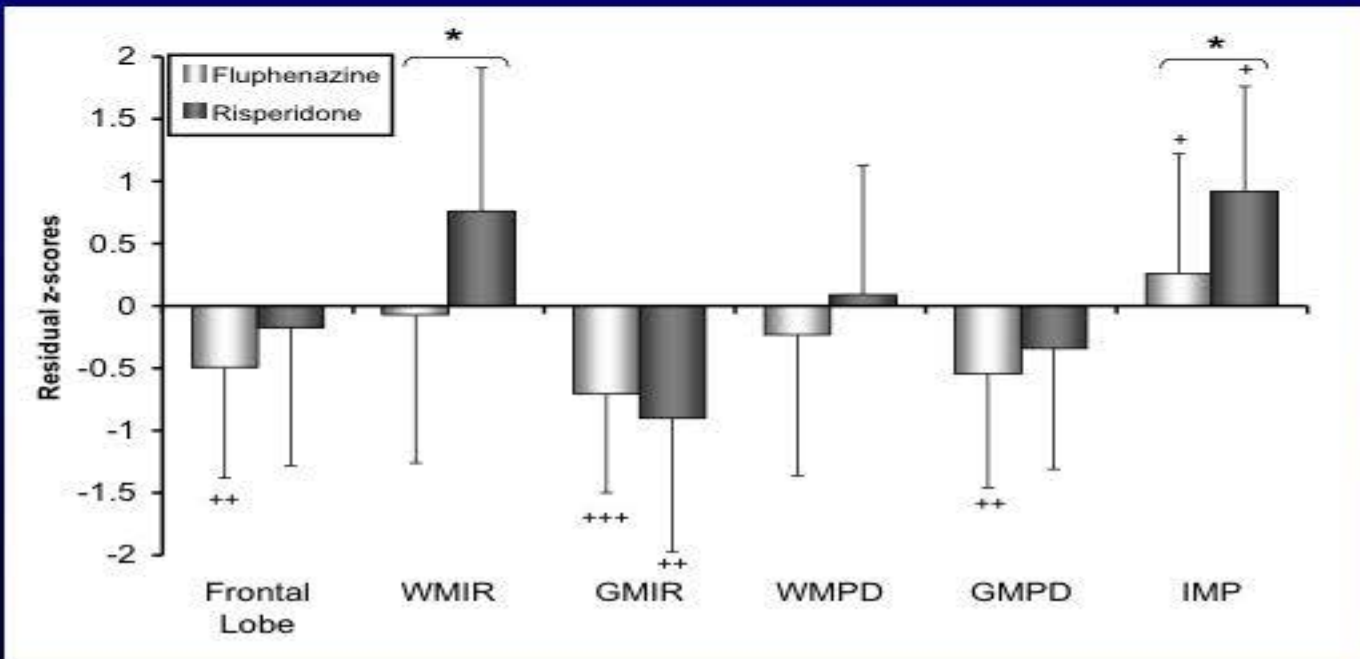


# Medication Effects on Myelinated White Matter and Intracortical Myelin Volume in Frontal Lobe



**Left image:** PD image that is *not* sensitive to the cholesterol in myelin. The red line depicts the border between the gray and white matter. This same gray/white separation line is depicted on the image on the right as the red line inside the white line.

**Right image:** IR image of the same slice of brain as in the PD image on the left (both images obtained at the same time). The IR image optimally detects the high cholesterol in myelin and is used to obtain the myelinated white matter volume that includes heavily myelinated parts of the deeper portions of gray matter. The white line separates myelinated white matter and unmyelinated gray matter. The difference between the red and white lines is a measure of *intracortical* myelination.



Risperidone is the newer "Atypical" medication. WM = Frontal lobe white matter; GM = Frontal lobe gray matter.

**Between Group Tests** (risperidone vs. fluphenazine):  
•  $p < 0.05$  for difference in bulk (WMIR) and *intracortical* (IMP) White matter (see above).

**Within Group Tests** (schizophrenic vs. healthy controls, standardized to mean = 0 and SD = 1): \* $p < 0.05$ , \*\* $p < 0.05$ , \*\*\* $p < 0.001$

# Conclusions

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- The delayed-start design proposed by P. Leber is a useful start for establishing disease modification but has many limitations.
- A modified 3-period, 3-arm delayed-start design may be a useful approach to addressing the limitations of a 2-period delayed start design.
- A 3-period, 3-arm delayed-start design study is currently being modeled for use in a trial with recent on set of schizophrenia.
  - This may provide deeper insight into demonstrating disease modification in complex CNS diseases.