

# Conflict of Interest(s) Disclosure

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# Comparative Adherence Trajectories Between Oral Disease Modifying Agents in Multiple Sclerosis

## *Comparative Adherence Trajectories of Oral DMAs*

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Study Objective

Multiple Sclerosis



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Methodology

Study Design &  
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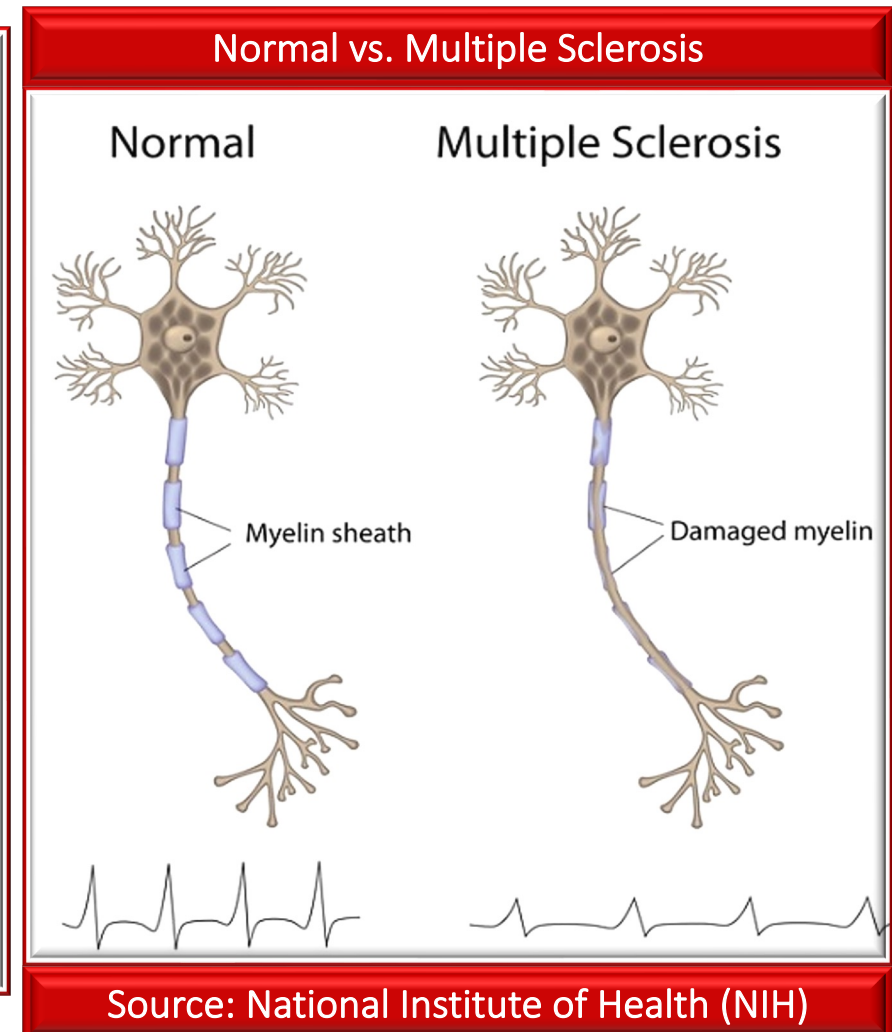
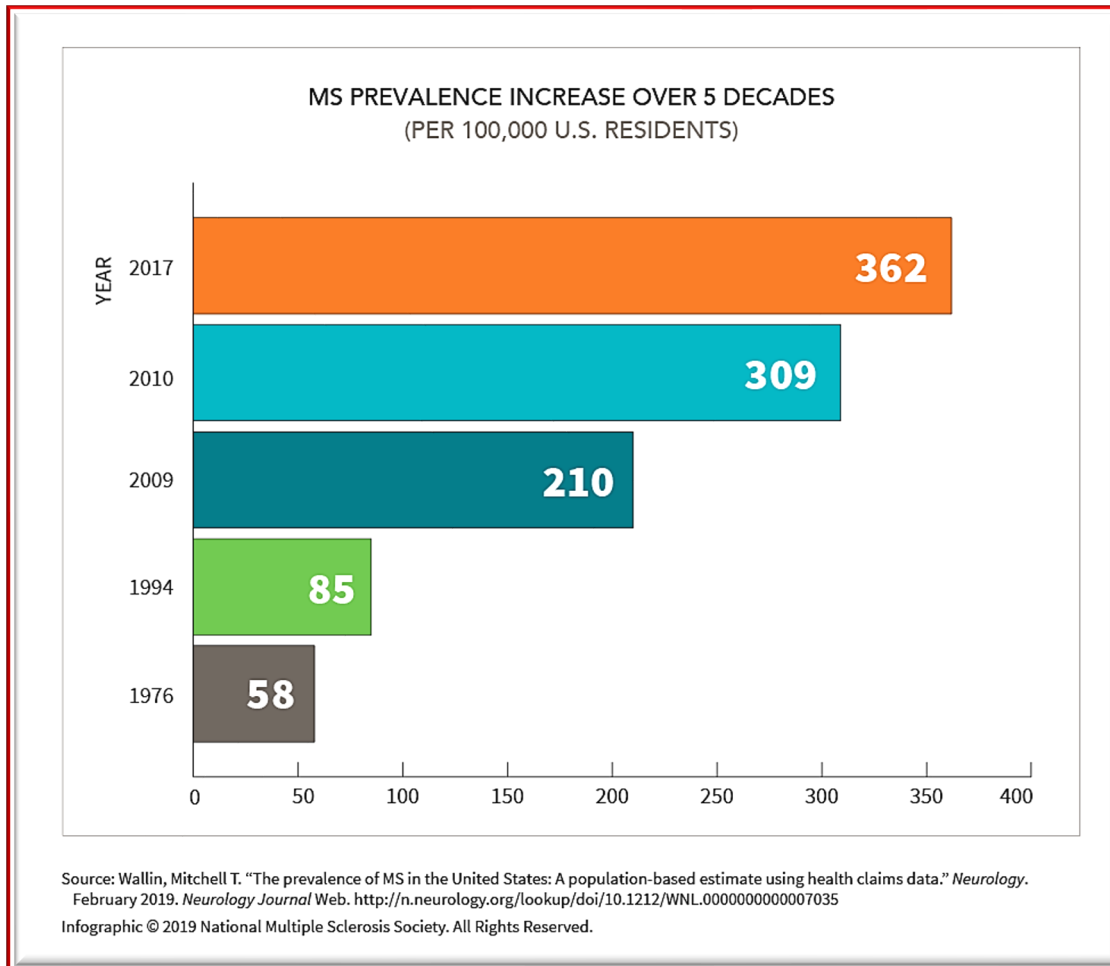
Conclusions

Take Home Message



# BACKGROUND

# Multiple Sclerosis



# Treatment of MS

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The **three-pronged approach of MS treatment** is directed towards **controlling the disease activity** and **associated symptoms** (No cure)

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**1. Disease Modifying Agents (DMA)** - To reduce relapses (28-68%) and to delay the disability progression

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**2. Corticosteroids** - To treat inflammation during acute relapse attack

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**3. Symptomatic Treatment** - To treat pain, fatigue, spasticity, bladder problems & improving walking ability, etc.

# Treatment of MS

Route of Administration	Drug Name	FDA Approved Year	Summary of Evidence
<b>Injection (SC/IM)</b> Weekly/Thrice weekly	Interferon Beta	1993	<b>Orals are comparable or superior to conventional injectables [pre-2010] in reducing relapses</b>  <b>&amp;</b>  <b>Increased flexibility/convenience in administration facilitating better adherence</b>
	Interferon Beta -1 $\beta$	1993	
	Interferon Beta -1 $\alpha$	1996	
	Pegylated Interferon $\beta$	2014	
	Glatiramer Acetate	1996	
	Ofatumumab	2020	
<b>Orals</b>	<b>Fingolimod (OD)</b>	<b>2010</b>	
	<b>Teriflunomide (OD)</b>	<b>2012</b>	
	<b>Dimethyl Fumarate (BD)</b>	<b>2013</b>	
	Siponimod	2019	
	Cladribine	2019	
	Diroximel Fumarate	2019	
	Monomethyl Fumarate	2020	
	Ponesimod	2021	
<b>Infusions</b>	Ozanimod	2020	Ulcerative Colitis
	Mitoxantrone	2000	Acute Myeloid Leukemia (AML)
	Natalizumab	2004	Crohn's disease (IBD)
	Alemtuzumab	2012	Chronic Lymphoid Leukemia (CLL)
	Ocrelizumab	<b>2017</b>	MS Specific drug (PPMS also)

# Adherence to DMA treatment is vital

*for positive health outcomes in MS patients*

## Negative Health Outcomes

- ↑ Relapses
- ↑ Disability progression
- ↑ Symptomatic burden
- ↑ Healthcare resources & costs
- ↓ Quality of life (QoL)

Poor  
Adherence



- **Route of Administration:** Oral DMAs are associated with better adherence and adherence trajectories than Injectable DMAs
- **Dosing, Efficacy & Safety:** Due to differences in frequency of dosing, efficacy and toxicity profiles, adherence between oral DMAs differs

Associated  
Factors



Fingolimod (Once Daily)
Teriflunomide (Once Daily)
Dimethyl Fumarate (Twice Daily)

# Comparative Adherence of Oral DMAs

## What is known already?

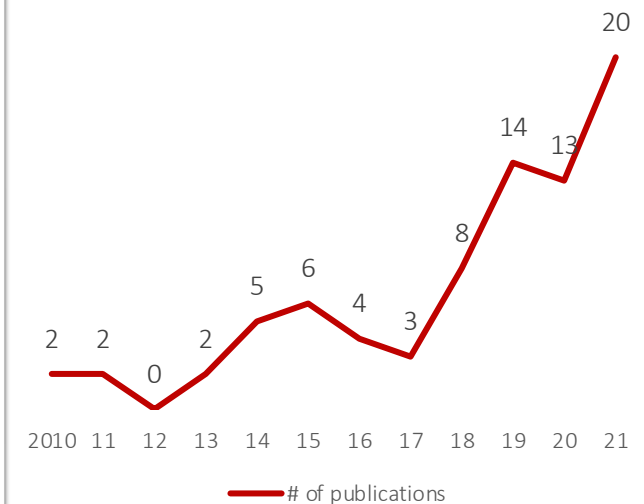
### Evidence on Comparative Adherence of Oral DMAs

- Fingolimod users are generally more adherent than teriflunomide and dimethyl fumarate
- However, there is limited insight into the longitudinal adherence patterns of oral DMAs

### Alternative Solution: Group Based Trajectory Modelling

- Individuals with similar prescription-filling pattern will be grouped into different trajectory groups
- Adherence trajectories were not used to compare adherence of oral DMAs

### # of Publications on 'Adherence Trajectories'



**Nicholas et al. (2019) assessed the adherence trajectories and associated factors among oral DMA users but didn't compare trajectories between oral DMAs**

PDC: Proportion of Days Covered, MPR: Medication Possession Ratio



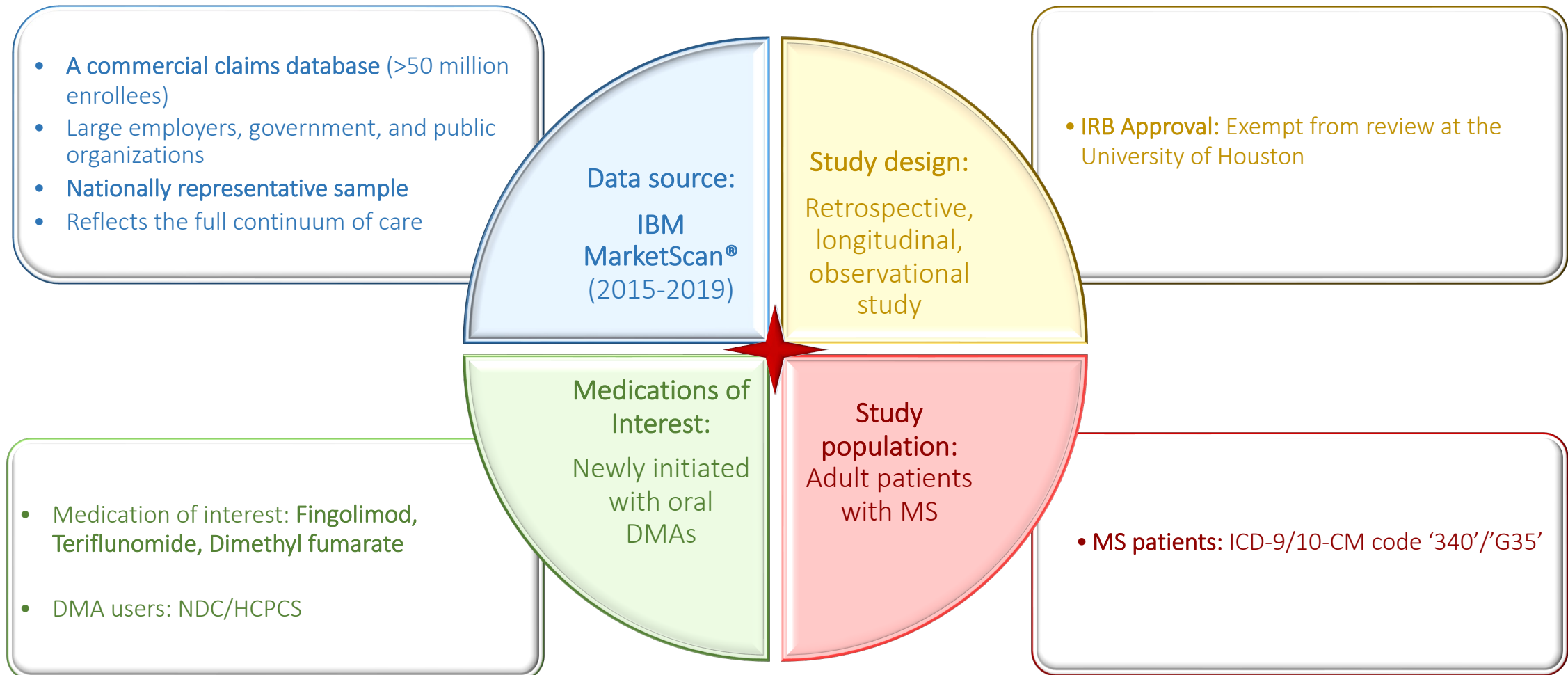
# Specific Aim/Objective

Objective:

To assess the comparative adherence trajectories between oral DMAs  
(Fingolimod vs. Teriflunomide vs. Dimethyl fumarate )

# METHODOLOGY

# Methods



# Methods

† Conceptual Framework: Andersen Behavioral Model (ABM) of Health Services Use

## Healthcare Utilization/Outcomes

[DMA adherence trajectory]

### Predisposing factors

Age Group  
Gender  
Region

### Enabling factors

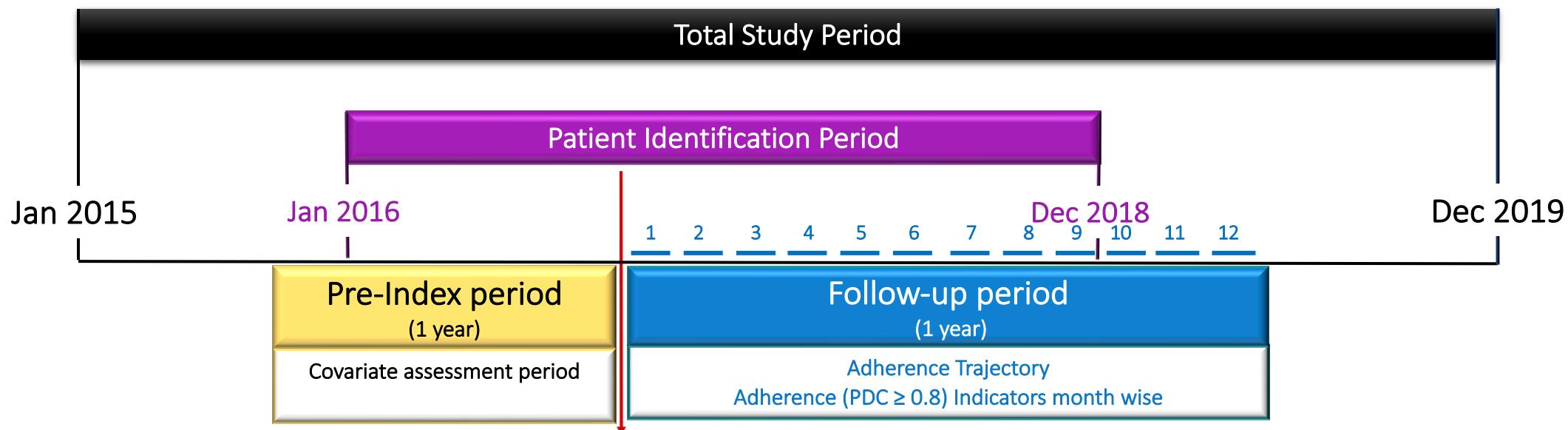
Employment Status  
Health Insurance Plan  
Physician Specialty  
Prescription Time Period  
(year of prescription)

### Need factors

Primary  
**Oral vs Injectable**  
Secondary\*  
**Prevalent Comorbidities**  
**Elixhauser Score**  
**MS Severity Score**  
**Symptomatic Medications**  
**Healthcare Utilization**

\* Based on the information during 12 months prior to index date

# Study Design Schematic



*Index Date: Date of first oral DMA prescription*

Continuous Enrollment

Inclusion Criteria:

- (i) Age  $\geq$ 18 years
- (ii) Index DMA prescription
- (iii) Continuous eligibility

Exclusion Criteria:

- (i) Combination DMA users
- (ii) Injectable/infusible DMA users

# Methods: Statistical Analysis Plan

SAS 9.4 at Level of significance( $\alpha$ )-0.05

Descriptive analyses  
Adherence (PDC  $\geq$  0.8)

Group Based Trajectory Modelling  
(GBTM): Proc Traj

12 monthly adherence indicators  
(PDC  $\geq$ 0.8) during follow-up

Selection of no. of groups:  
(i) Visual inspection  
(ii) Bayesian information criterion (BIC)

Main Analysis:

GBM based IPTW-weighted Multinomial Logistic Regression

**Adherence Trajectory Group**

[Completely Adherent as Reference]

=

Teriflunomide & Dimethyl Fumarate vs.  
Fingolimod (Reference)

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GBM based IPTWs: Covariates as per ABM

\* Covariate balance check using standard difference threshold of 0.1

Additional Analysis:

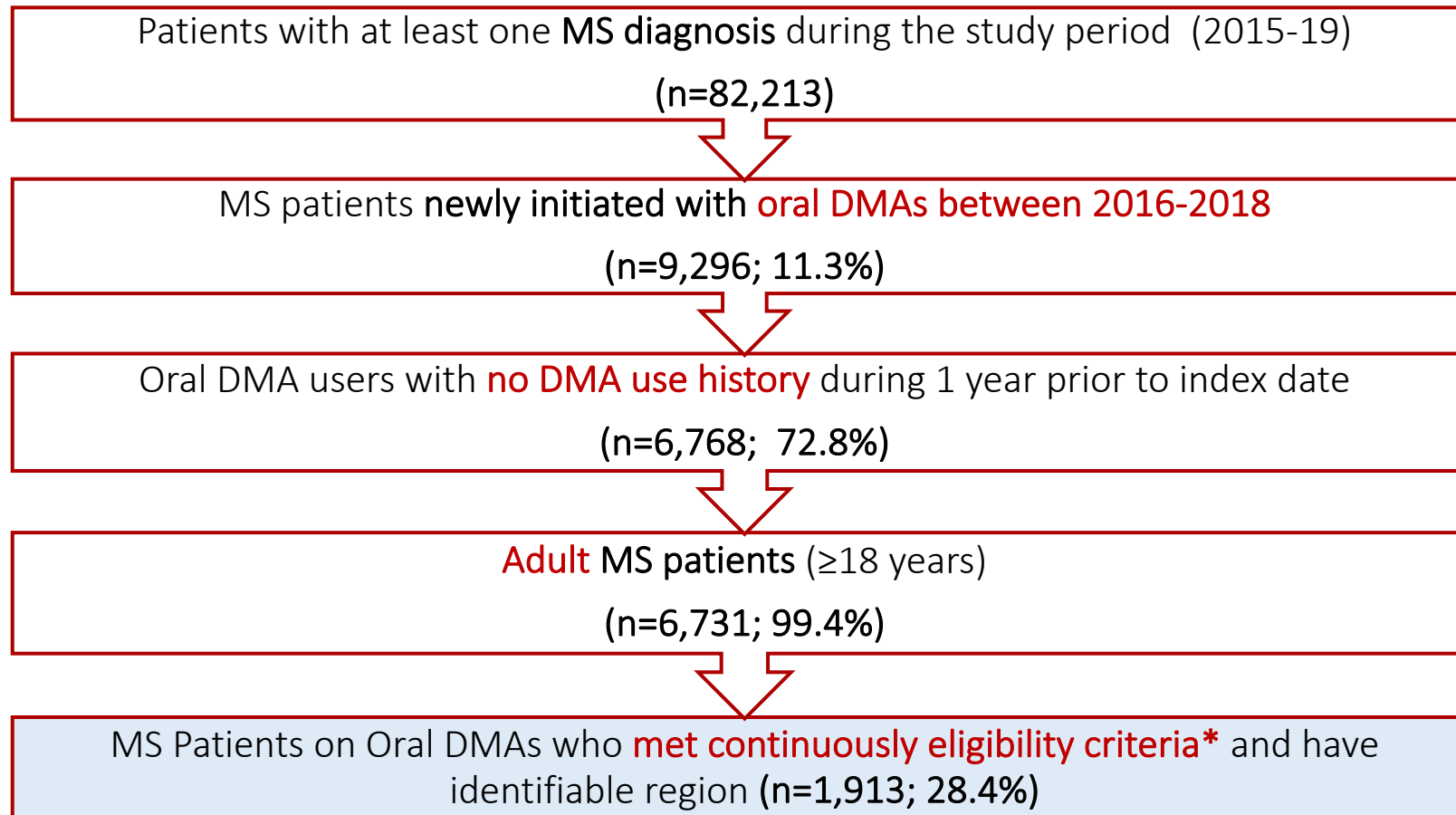
GBM based IPTW-weighted Logistic Regression

**Non-adherent (PDC  $\geq$ 0.8) vs. Adherent [Reference]**

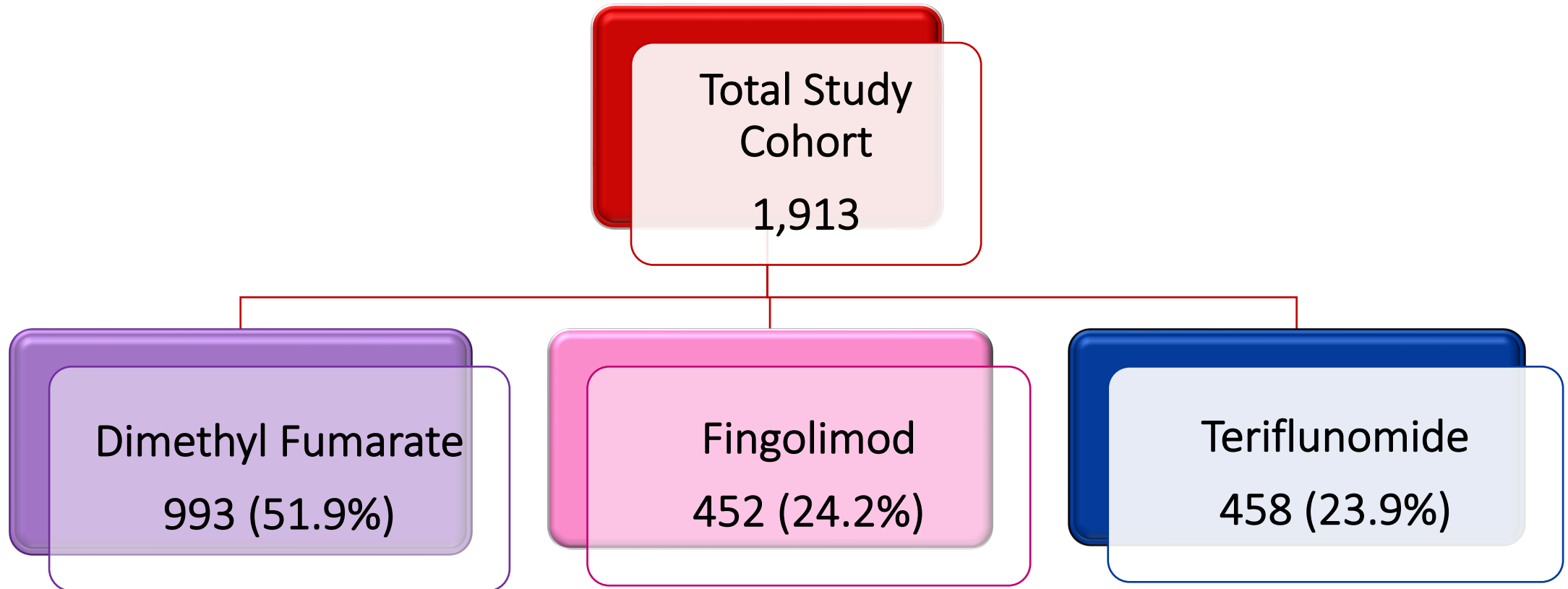
Generalized Boosted Model (GBM) based IPTW are used because they are efficient especially when dependent variable has more than 2 groups

# RESULTS & DISCUSSION

# Flowchart



# MS Patients with Oral DMAs



# Characteristics of Oral DMA users

Fingolimod, Teriflunomide & Dimethyl Fumarate users were **significantly different** in terms of

Characteristic	Dimethyl Fumarate	Fingolimod	Teriflunomide
<b><i>Predisposing Factors</i></b>			
<b>Age: Mean (SD)</b>	43 (11)	41 (11)	48 (10)
<b>Gender: Females</b>	72%	76%	79%
<b><i>Enabling Factors</i></b>			
Health plan: <b>PPO</b>	53%	56%	55%
<b><i>Need Factors (during baseline)</i></b>			
<b>Comorbidities</b>	Musculo skeletal disorders Mood disorders	Heart Diseases Eye disorders Nutritional deficiencies	Heart Diseases Eye disorders Nutritional deficiencies Mood disorders Musculo skeletal disorders
<b>MS Symptoms</b>	No differences in symptomatic burden		
<b>Medication Use (≥30%)</b>	Analgesics & Spasticity drugs	-	Analgesics & Spasticity drugs
<b>Healthcare Utilization</b>			
Relapse	35%	33%	32%
Neurologist visit	64%	70%	62%
<b>Row percentages: ✓✓✓ - Very high proportion, ✓✓ - High proportion, ✓ - Less proportion</b>			

# Adherence of Oral DMAs

Fingolimod users were significantly more adherent than Dimethyl Fumarate & Teriflunomide users  
(70.8% vs. 61.0% vs. 59.6%)

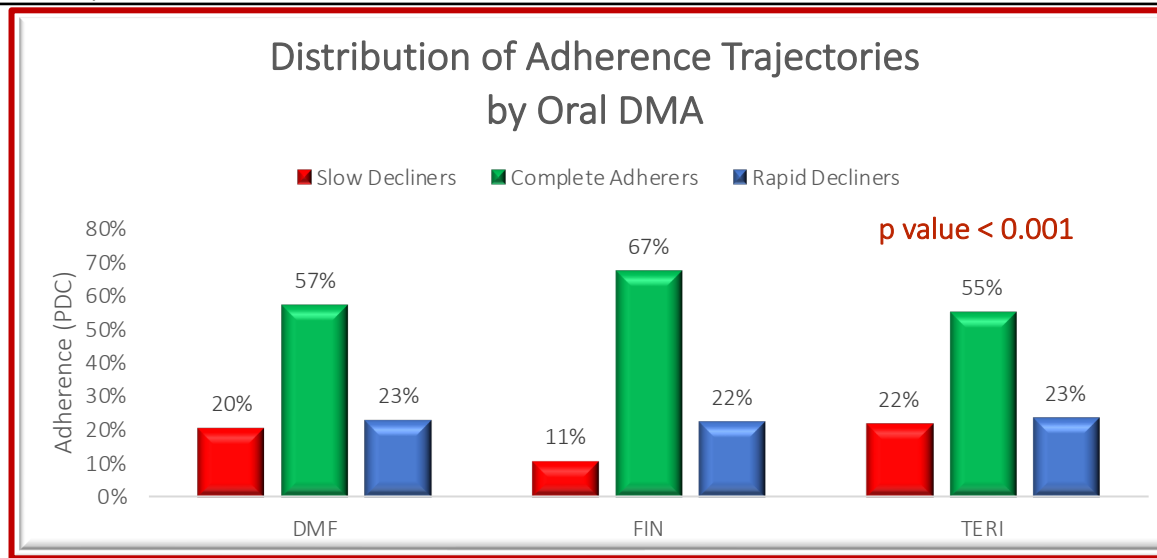
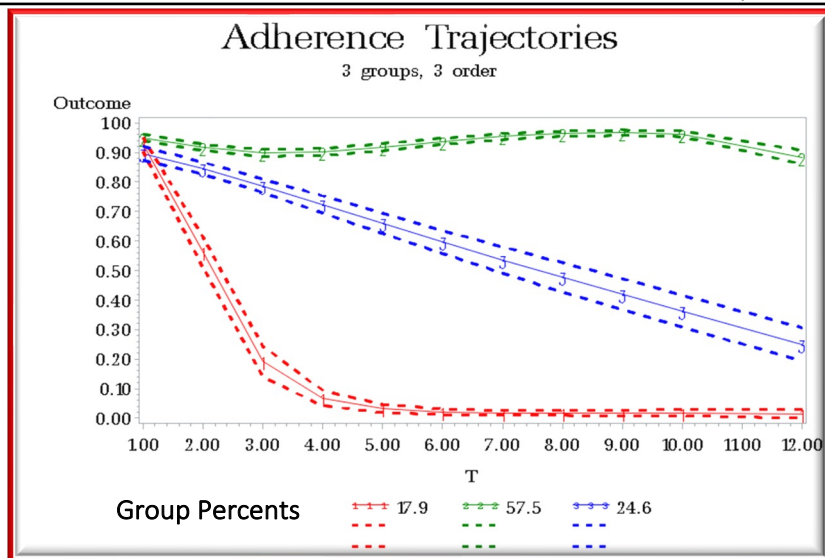
Adherence (Mean PDC ± SD)	Oral DMA			Total N=1,913 (100.00%)	p value
	Dimethyl Fumarate N=993 (51.9%)	Fingolimod N=452 (24.2%)	Teriflunomide N=458 (23.9%)		
Adherent (PDC ≥ 0.8; 0.95 ± 0.05)	606 (61.0%)	327 (70.8%)	272 (59.6%)	1206 (63.0%)	<0.01
Non adherent (PDC < 0.8; 0.41 ± 0.24)	387 (39.0%)	135 (29.2%)	185 (40.1%)	707 (37.0%)	
PDC – Proportion of days covered, SD – Standard deviation					

# Adherence Trajectories of Oral DMAs

The GBTM classified patients into three adherence trajectories

Adherence Trajectory Group (Mean PDC ± SD)	Oral DMA			Total N=1,913 (100.00%)	p value
	Dimethyl Fumarate N=993 (51.9%)	Fingolimod N=452 (24.2%)	Teriflunomide N=458 (23.9%)		
1. Rapid decliners (0.20 ± 0.12)	202 (20.3%)	49 (10.6%)	99 (21.6%)	350 (18.3%)	<0.01
2. Complete adherers (0.95 ± 0.06)	567 (57.1%)	310 (67.1%)	252 (55.0%)	1129 (59.0%)	
3. Slow discontinuers (0.66 ± 0.14)	224 (22.6%)	103 (22.3%)	107 (23.4%)	434 (22.7%)	

PDC – Proportion of days covered, SD – Standard deviation



# Comparative Adherence Trajectories of Oral DMAs

## Main Analysis

The multinomial logistic regression model with GBM based IPTW revealed that

- † DMF users had higher odds (>2 times) of being a rapid decliner relative to Fingolimod
- † TFN users had higher odds of being a rapid (>2 times) & slow decliner (>1.5 times) relative to Fingolimod

Findings of GBM based IPTW-weighted Multinomial Logistic Regression				
Treatment Group	aOR (95% CI)	p value	aOR (95% CI)	p value
	Rapid Decliners (Group 1)		Slow Decliners (Group 3)	
Fingolimod	Reference		Reference	
Dimethyl Fumarate (DMF)	2.31 (1.57-3.42)	<0.01	1.26 (0.96-1.70)	0.748
Teriflunomide (TFN)	2.50 (1.62-3.88)	<0.01	1.50 (1.06-2.13)	0.05
aOR - Adjusted Odds Ratio, CI – Confidence Interval, GBM – Generalized Boosted Methods, IPTW – Inverse Probability Treatment Weights <b>Group 2 – Completely Adherent as reference category</b>				

# Comparative Adherence of Oral DMAs

## Additional Analysis

† The logistic regression model with stabilized IPTW revealed that DMF & TFN users had higher odds (>1.5 times) of being non-adherent than FIN users

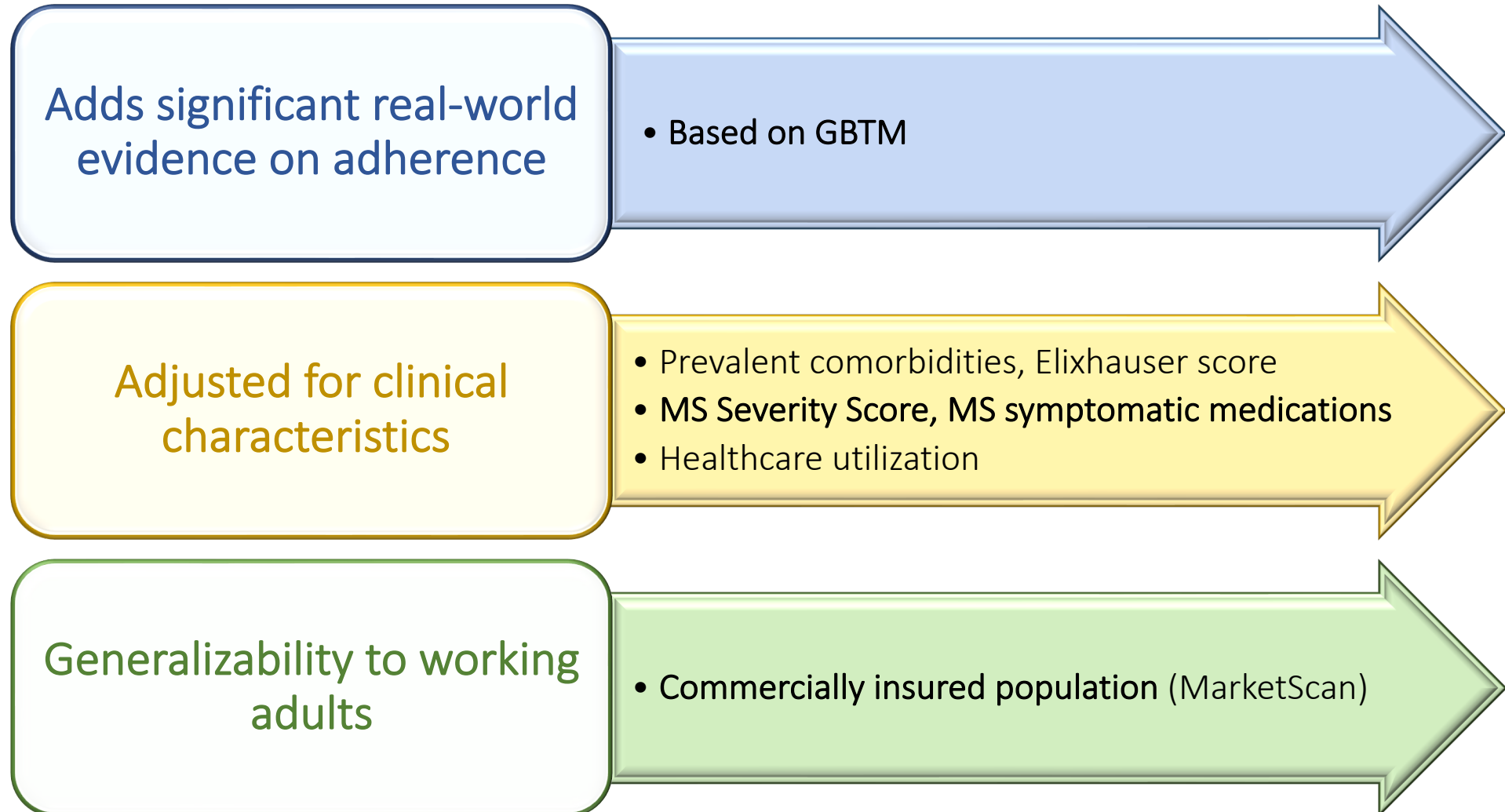
Findings of GBM based IPTW-weighted Logistic Regression		
Treatment Group	aOR (95% CI)	p value
Fingolimod (FIN)	Reference	
Dimethyl Fumarate (DMF)	1.66 (1.44-1.92)	<0.01
Teriflunomide (TFN)	1.68 (1.46-1.95)	<0.01

aOR - Adjusted Odds Ratio, CI – Confidence Interval, GBM – Generalized Boosted Methods, IPTW – Inverse Probability Treatment Weights  
Adherent as reference category

# Comparative Adherence Trajectories of Oral DMAs

- † This is the first study to compare adherence trajectories between oral DMAs
  - Application of GBTM in MS patients informs time related changes in DMA adherence
- † Based on the current study findings, fingolimod users were associated with better adherence trajectories than dimethyl fumarate & teriflunomide users
  - This finding is consistent with previous evidence based on conventional adherence measures
- † Dimethyl fumarate users have higher odds of being a rapid decliner, whereas Teriflunomide users had higher odds of being a rapid/slow decliner
  - Further research is required to compare adherence trajectories between DMF and TFN

# Strengths



# Limitations

## Unmeasured confounding

MS Disability (EDSS)

MRI lesions

Race/ethnicity

## Claims data

**Adherence** is measured on claims data which may not reflect actual utilization

## Data time period

Other **newer oral medications** were not considered

# CONCLUSIONS

## Conclusion

Fingolimod users had better adherence trajectories compared to dimethyl fumarate & teriflunomide users

The window of opportunity for interventions is different for dimethyl fumarate & teriflunomide

# THANK YOU!

I welcome your questions & comments!

Please email to [Jagadesh.e.rao@gmail.com](mailto:Jagadesh.e.rao@gmail.com) for additional questions and comments