

# Welcome, Purpose of the Meeting

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**Joe V. Selby, MD, MPH**  
Executive Director, PCORI  
April 2, 2015



PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

# About Us

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- An independent research institute authorized by Congress in 2010 and governed by a 21-member Board representing the entire healthcare community
- Funds comparative clinical effectiveness research (CER) that engages patients and other stakeholders throughout the research process
- Seeks answers to real-world questions about what works best for patients based on their circumstances and concerns



# Our Broad and Complex Mandate

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“The purpose of the Institute is to **assist patients, clinicians, purchasers, and policy-makers in making informed health decisions** by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed **through research and evidence synthesis...**

**... and the dissemination of research findings** with respect to the relative health outcomes, clinical effectiveness, and appropriateness of the medical treatments, services...”

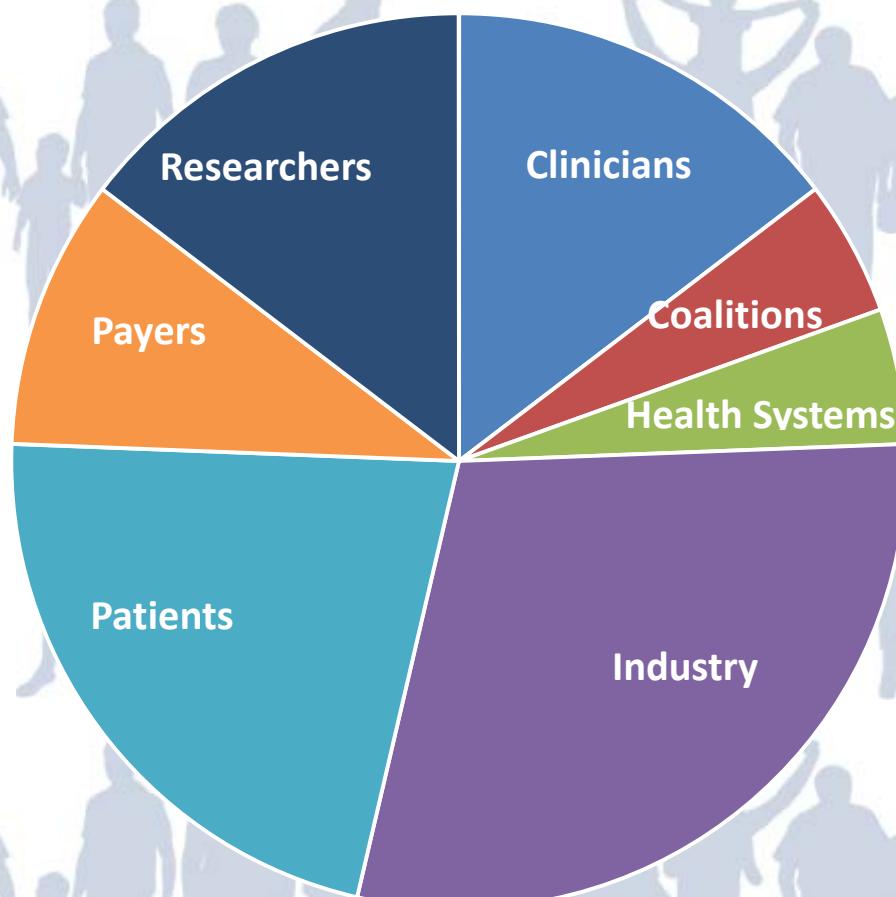
--from PCORI's authorizing legislation



# Who Are Our Stakeholders?



# Who Is Attending This Workshop?



**N=41 attendees**



# Purpose of This Workshop

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**The purpose of this workshop is to identify, refine, and prioritize comparative effectiveness research questions about the treatment of multiple sclerosis.**

Are there patient-centered comparative effectiveness research questions that PCORI should pursue?



# Reminders

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- This workshop is available via webinar/teleconference and will be archived on the PCORI website.
- This workshop is advisory.



# **Comparative Clinical Effectiveness Research and Multiple Sclerosis**

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**David Hickam, MD, MPH**

Director, Clinical Effectiveness Research Program, PCORI

April 2, 2015



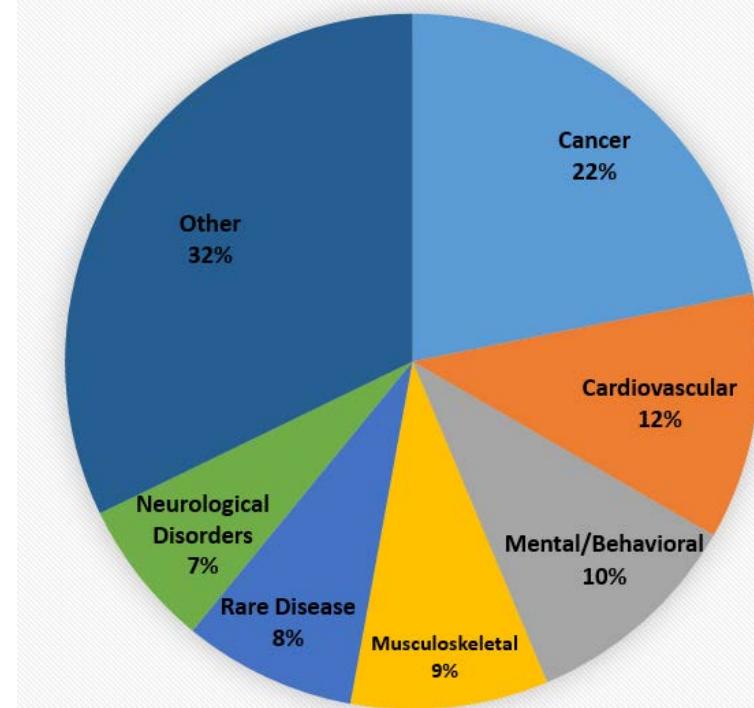
# Assessment of Prevention, Diagnosis, and Treatment Options

Seeks to fund research that:

- Compares the effectiveness of two or more options that are known to be effective but have not been adequately compared in previous studies
- Among compared population groups, investigates factors that account for variation in treatment outcomes that may influence those outcomes

## Portfolio Snapshot

- **87 Projects**
- **\$212.7 Million Awarded**



# Perspectives on Comparative Clinical Effectiveness Research

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- Comparative Effectiveness Research should be a public good that:
  - Gives healthcare decision makers—patients, clinicians, purchasers, and policy makers—access to the latest open and unbiased evidence-based information about treatment options
  - Informs choices and is closely aligned with the sequence of decisions patients and clinicians face



# First Steps in Developing New Comparative Effectiveness Research

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- Understand the choices made by patients and clinicians
  - Which clinical options are realistically available to patients?
- Define the important patient subgroups
  - Recognize disparities and their sources
- Define the outcomes that are important to patients
  - Benefits
  - Harms



# The Model of Patient-Centered Outcomes Research

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- Helps people and their caregivers communicate and make better-informed healthcare decisions
- Actively engages patients and key stakeholders throughout the research process
- Compares the effectiveness of important clinical management options
- Evaluates the outcomes that are the most important to patients
- Addresses implementation of findings in clinical care environments



# Healthcare Systems Research and Multiple Sclerosis

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**Steve Clauser, PhD**

Director, Improving HealthCare Systems Program, PCORI

April 2, 2015



# Improving Healthcare Systems

Seeks to fund comparative effectiveness research on effects of system changes on:

- Patients' access to high-quality support for self-care
- Coordination and continuity of care across healthcare settings
- Health outcomes important to patients and caregivers, e.g., overall health, functional ability, quality of life, stress, and survival
- Efficiency of healthcare delivery, as measured by the amount of ineffective, duplicative, or wasteful care provided to patients

57 PROJECTS | \$147.1 MILLION AWARDED



*By primary health topic as of Feb. 24, 2015*



# Multiple Sclerosis and Healthcare Systems

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## Research questions that address:

- Innovative use of technology (e.g., telehealth and patient self-care)
- Novel deployment of health personnel (e.g., interdisciplinary care teams and care transitions)
- Redesign of organizational healthcare models (e.g., collaborative care for comprehensive psychosocial care/symptom management)



# PCORI Research and Engagement Activities in Multiple Sclerosis

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**Diane Bild, MD, MPH**

Senior Program Officer, Clinical Effectiveness Research  
Program, PCORI

April 2, 2015



# Pragmatic Clinical Studies

**Seek to produce information that can be directly adopted by providers:**

- Compare two or more options for prevention, diagnosis, treatment, or management of a disease or symptom
- Address critical clinical choices faced by patients, caregivers, clinicians, systems
- Often conducted in routine clinical settings
- Though often large, usually less complex protocols than traditional trials
- Topics of special interest from stakeholders, Institute of Medicine, Agency for Healthcare Research and Quality

## Opportunity Snapshot

- Number of Anticipated Awards Per Funding Cycle: Six to Nine
- Funds Available Per Cycle: Up to \$90 Million
- Maximum Project Duration: 5 Years
- Maximum Direct Costs Per Project: \$10 Million



# Large Pragmatic Studies Priority Topic

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- One of up to 24 priority topics
- “Treatment options for patient with MS
  - Compare management options for modifying disease progression. These might include FDA-approved disease-modifying agents; behavioral interventions including exercise and physical therapy, and complementary medicine alternatives.”



# Large Pragmatic Studies topic on MS

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- Three rounds of requests for letters of intent for PCORI Large Pragmatic Studies (June-October 2014)
- 11 LOIs received on multiple sclerosis
- Six were observational studies to compare drug treatments
- Also received LOIs on RCTs:
  - Comparing drug treatments
  - Comparing usual care to self-management, lifestyle, use of patient navigators, or rehabilitation
- None were invited to submit a full application.
  - Small sample sizes, lack of sufficiently-detailed data in observational studies, comparators that were not compelling, outcomes that were not patient-centered



# PCORI Engagement on Multiple Sclerosis

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- October 30, 2014: Stakeholder group with patients, NINDS, AAN, MS Society, VA Centers of Excellence
- January 29, 2015: Stakeholder group with pharma and biotech
- January 30: Stakeholder group with payers



# Conclusions from three Stakeholder Meetings

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- Challenges for CER:
  - Lack of consensus on metrics for measuring markers of MS activity that align with symptoms
  - Large number of available treatment options
  - Large variability in symptom presentation and course
  - Large variability in treatment preferences among physicians and patients
  - Long natural history of disease
  - Reluctance of patients and clinicians to enroll in RCTs



# Conclusions from Stakeholder Meetings

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- Concerns of patients:
  - Lack of evidence-based decision support
  - Unclear trade-offs in benefit and harms of treatments
  - Inconsistent coverage policies



# A word about two alternative study designs for CER from previous stakeholder discussions

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- A large and “audacious” study with detailed exposure and outcome measures and sufficient follow up for meaningful outcomes; strong caution due to complexity, duration, and cost.
- Smaller, targeted studies that focus on homogeneous subsets of patients, comparing a limited number of treatment options and specific outcomes.



# Instructions for Breakout Sessions

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**Diane Bild, MD, MPH**

Senior Program Officer, Clinical Effectiveness Research  
Program, PCORI

April 2, 2015



# Purpose of This Workshop

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**The purpose of this workshop is to identify, refine, and prioritize comparative effectiveness research questions about the treatment of multiple sclerosis.**

Are there patient-centered comparative effectiveness research questions that PCORI should pursue?



# Reference Materials

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- Narrative review from Duke
  - Comparative effectiveness of disease-modifying therapies (DMTs) on symptoms in MS
  - Comparative effectiveness of symptomatic treatments in MS
  - Concluded with a set of questions and issues
- Instructions for writing a CER question
- Sets of questions for each breakout group
- A set of the original questions with background, as submitted
- Roster of participants
- Copies of these slides



# Submitted Questions, Four Buckets

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- Approximately 60 questions, plus questions from Duke
  1. Comparison of DMTs, including differential effects in subgroups
  2. Care strategies
  3. Non-pharmacologic and non-DMT therapy for specific symptoms and overall health
  4. Timing of therapy and study design
- Cross-cutting issues



# Instructions for Breakout Groups

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- Your Goal:
  - To develop up to four CER questions in priority order
- You will have about three hours.
  - Discuss the questions and issues provided.
  - Create a set of clear, valuable, and viable questions.
  - Include relevant considerations.
- The leader will present to the full group in the plenary session, using the template slide provided.



# Questions Submitted by Attendees

Bucket	Leader, PCORI Facilitator, Room
1. Comparison of DMTs, including differential effects in subgroups	Aaron Miller, Anne Trontell GRAND TETON
2. Care strategies	Alex Rae-Grant, Steve Clouser GLACIER
3. Non-pharmacologic and non-DMT therapy for specific symptoms and overall health	Heidi Maloni, David Hickam YOSEMITE
4. Timing of therapy and study design	Ursula Utz, Joe Selby CONGRESSIONAL A



# Guidance on Writing a CER Question

## How to Write a Practical & Useful Research Question



In order to ensure that a research question is practical and useful, we need to make sure that it clearly identifies the people involved, the options of care that need to be compared, and the potential outcomes from those options.



# Population Examples

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- Patients with primary or secondary progressive MS
- MS patients with depression, fatigue, bladder incontinence, and/or cognitive impairment
- MS patients with low socioeconomic status or limited healthcare access



# Intervention Examples

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- Specific DMTs
- Antidepressants as adjunctive therapy
- Non-medication treatments, such as yoga, Tai-Chi, meditation, physical therapy, rehabilitation
- Earlier versus later treatment



# Outcomes Examples

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- Low-contrast visual acuity, digit-symbol processing for cognitive assessment, upper limb and hand function, timed 25-foot walk test
- Falls, loss of work, divorce
- Cognitive impairment, bladder dysfunction, fatigue, pain, spasticity



# Examples of CER questions from hepatitis C PFA

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- How do new regimens of oral antiviral medications for the treatment of hepatitis C infection compare in long-term virologic response and adverse effects?
- What are the comparative benefits and harms of treating patients with hepatitis C infection at the time of diagnosis versus waiting to treat only those patients who show early signs of progression of liver disease or other manifestations of hepatitis C infection?



# Roles of Members in Each Breakout Group

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- Group: Review all questions among group members; refine each question; prioritize
- Leader: Lead discussion, report back to larger group
- PCORI facilitator: Enable discussion, focus on CER
- Slide maker: Make slides for final session
- Note taker: Take notes for a meeting summary, oversee teleconference



# After the Workshop

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You will receive two surveys by email:

- Evaluation survey . . . followed immediately by
- Prioritization exercise

1. Please rank the following questions from highest to lowest. The highest priority topic should be placed at the top of the list. \*

Drag items from the left-hand list into the right-hand list to order them.

Question 1: Trials targeting symptoms of MS	
Question 2: Care strategies and adherence to therapy	
Question 3: Timing and Intensity of DMTs	
Question 4: Adherence to therapy	

- The final results will be shared by email.



# Next

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- Enjoy a short break.
- Convene in breakout groups & enjoy the discussions!
- Lunch is at 12:30 in Congressional B.
- Finalize work of the breakout groups after lunch.
- Attend Plenary Session with reports of breakout groups and discussions.



# Breakout Groups

Bucket	Leader, PCORI Facilitator, Room
1. Comparison of DMTs, including differential effects in subgroups	Aaron Miller, Anne Trontell GRAND TETON
2. Care strategies	Alex Rae-Grant, Steve Clouser GLACIER
3. Non-pharmacologic and non-DMT therapy for specific symptoms and overall health	Heidi Maloni, David Hickam YOSEMITE
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# **Treatment Options for Multiple Sclerosis**

## **Multi-stakeholder Workshop: Plenary Session**

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**Bryan Luce, PhD, Chief Science Officer, PCORI**

**David Hickam, MD, MPH Director, Clinical Effectiveness Research, PCORI**



# **Group 1: Comparison of DMTs, including differential effects of subgroups**

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**Leader: Aaron Miller, MD**

Medical Director, Corinne Goldsmith Dickinson Center for  
Multiple Sclerosis



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# Question 1:

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What are the comparative harms and benefits of different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis on disease activity, progression, symptoms, and quality of life?

Considerations:

- Patient preference/tolerance
- Large number of drugs available/challenge to design ethical RCT
- Lack of clarity on who will respond to which drugs
- Challenge of getting patients to agree to randomization
- What is the right patient population? Newly diagnosed patients?
- Identifying outcomes that are both meaningful to patients and clinically meaningful
- Challenge of designing a robust, methodologically sound observational study
- Study must include sufficient time horizon (e.g. 10+ years) -> including disease progression, QOL, etc. -> data (e.g. PROs/QOL metrics) could be collected along the way



# Question 1:

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What are the comparative harms and benefits of different disease-modifying therapies in newly diagnosed relapsing, remitting multiple sclerosis on disease activity, progression, symptoms, and quality of life?

## Considerations:

- Variability in insurance coverage for various treatments
- Cognition function, depression, fatigue, bladder dysfunction, spasticity, pain, and patient satisfaction are key outcome measures
- Subgroups: How to include patients with comorbidities in trials: depression/anxiety/heart disease/smoking (population usually excluded from RCTs) – potentially through an observational study
  - SES: Medicaid populations, disparity in access to care
  - Racial/minority groups: African Americans
  - Postpartum/peri-partum management of MS



## Question 2:

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Among MS patients receiving a DMT who experience disease activity, what are the benefits and harms of continuing the same therapy versus changing to a new medication?

Considerations:

- Need to define disease activity – combination of non-minimal clinical and MRI disease activity
- Few patients remain on injectable drugs for substantial period of time – may need to focus on oral drugs
- No evidence of disease activity is key outcome for MS patients but the EDSS component is problematic
- EDSS response is highly variable -> alternative outcome measure might be better
- Variability of insurance coverage – fail first requirements, etc.
- Patient preferences and risk acceptance also drive decision to change treatments /preference of treatment
- Might be able to randomize to new treatment v. remain on current treatment when unacceptable disease activity threshold is achieved
- Variability of clinician practice of when to switch treatments



## Question 3:

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Is treatment escalation as effective as starting treatment with higher efficacy treatments in early active, previously untreated patients

Considerations:

- Definition of higher efficacy
- Length of study
- Early treatment
- Blinding of assessment
- Side effects



## Question 4:

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What is the comparative effectiveness of smoking cessation efforts upon disease activity, progression, symptoms, and quality of life in MS?

### Considerations:

- Smokers generally do worse
- Effect on secondary symptoms e.g.. pulmonary compromise



## Question 5: (This question was raised but not discussed at length)

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What is the comparative effectiveness of stopping versus continuing therapy after a period of prolonged disease stability

Considerations:

- Discussed under cross-cutting group?



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# Brief Discussion (5 min)



## **Group 2: Care Strategies**

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**Leader: Alex Rae-Grant, MD**

Staff Neurologist, Mellen Center for Multiple Sclerosis



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# Question 1:

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In people with progressive MS, what is the comparative effectiveness of different care delivery approaches (i.e., MS specialty center vs. community neurology; direct care vs. telemedicine; “specialized medical home” vs. community neurology delivery of care) in improving outcomes such as functional status, quality of life, symptom measurements, ER use, hospitalization?

Considerations:

Function and quality of life will need to be measured with standardized instruments.

Outcomes will need to be measured over an extended period.



## Question 2:

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In people with relapsing MS within 2 years of diagnosis, what is the comparative effectiveness of changing DMT using a NEDA strategy (no relapse, no new MRI or enhancing lesion, no change in disability [EDSS]) vs. not changing DMT in terms of functional status, quality of life, symptom measurements, ER use, and hospitalization?

### Considerations

Secondary outcomes include , difficulty of switching medications, disabling relapses, adverse effects of medications, specific symptoms.

People with highly active disease should be able to provide useful outcomes within 5 years.



## Question 3:

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In people with relapsing MS, what is the comparative effectiveness of physician-directed vs allied health-directed vs navigator-directed, vs technological-enabled self management tools for improving initial decision making, patient care experiences, decision regret, quality of life and adherence to therapy?

### Considerations

Interventions should include shared decision-making tools.



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Considerations for all questions:

Regional variations in care and race/ethnicity



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# Brief Discussion (5 min)



# **Group 3: Non-pharmacologic and non-DMT therapy for specific symptoms and general health**

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**Leader: Heidi Maloni, PhD**

National Clinical Nursing Director, MS Center of Excellence



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## Question 1:

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Does an integrative model of care along with DMT in a newly diagnosed individuals affect disability progression and symptoms (physical, emotional and cognitive) compared to DMT alone?



## Question 2:

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What are the comparative benefits and harms of non-pharmacological and pharmacological approaches in relation to key symptoms (e.g. emotional health, fatigue, cognition, pain) in people with MS?



## Question 3:

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What are the comparative benefits and harms of specific dietary regimens in people with MS?



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# Brief Discussion (5 min)

- Symptoms: Chronic pain, fatigue, mood/depression, cognition, physical functioning
- Cross-cutting issues: standardization of interventions; access to the intervention
- Subgroups: gender, socioeconomic status and race, geography
- Caregivers



# **Group 4: Timing of therapy and study design**

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**Leader: Ursula Utz, PhD**

Program Director, NINDS



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# Introduction

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- Guiding principles were
  - Evidence gaps
  - Importance to patients
  - Would it change clinical practice?
- The big topic
  - How soon to start therapy? – treatment delay
  - How long to remain on therapy? -- discontinuation



# Question 1:

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What are the benefits and harms of early vs. delayed treatment with DMTs, in terms of symptoms, function, QOL, and disease activity in treatment-naive patients meeting McDonald criteria within 12 months?

## Considerations:

- Consider differential effects in subgroups
- Ethical and recruitment challenges for an RCT; more likely observational
- Not all DMTs are equally available
- Would confine study to adults
- Define delay



## Question 2:

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In patients who recently transitioned from relapsing to progressive MS or recently diagnosed with SPMS, what are the benefits and harms of continuing compared to discontinuing DMTs on outcomes including but not limited to symptoms, QOL, function, disease activity, disability, and/or mortality?

### Considerations:

- SPMS is a retrospective diagnosis
- Question may become less relevant for natalizumab with ongoing trial (ASCEND)



# Study design

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What are the advantages and disadvantages of clinical trials that focus on a specific subset of populations, interventions, and outcomes vs a larger, more comprehensive observational study?

## Considerations:

- Concern with ethics and feasibility of RCTs in study of DMTs using placebos
- Possibility of natural experiments comparing populations with differential levels of care for MS (e.g., US vs. EU)



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# Brief Discussion (5 min)



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# General Discussion



# Closing Remarks

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**Bryan Luce, PhD, MS, MBA**

Chief Science Officer, PCORI



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