Disease-Modifying Therapies for Multiple Sclerosis

Surveillance

Washington P&T Committee Meeting

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Overview

- Topic History and Background
- PICOS and Key Questions
- Methods
- Findings
  - Clinical Landscape
  - Research Landscape
- Summary Since Last Review

Abbreviations

CIS	clinically isolated syndrome
DERP	Drug Effectiveness Review Project
DMT	disease-modifying therapy
FDA	US Food and Drug Administration
MRI	magnetic resonance imaging
MS	multiple sclerosis
PPMS	primary progressive multiple sclerosis
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis
SPMS	secondary progressive multiple sclerosis

Topic History, Background, PICOS, and Key Questions

Topic History

Report
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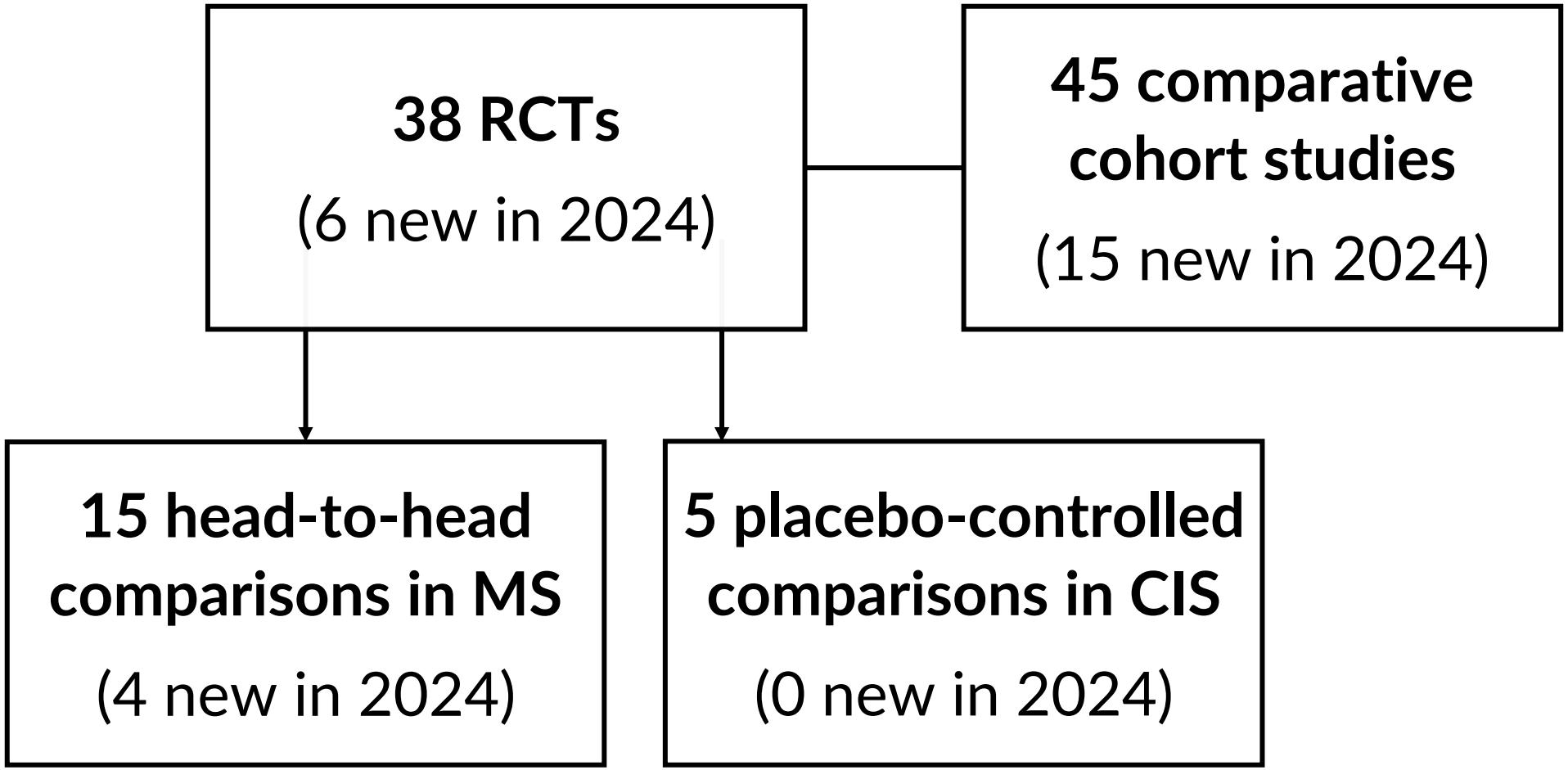
DERP Research Product Type	Date Presented	Search Dates
Systematic Review Update 5	March 2024	October 1, 2019, to July 31, 2023[a]
Systematic Review Update 4	May 2020	January 1, 2016, to February 3, 2020[a]
Systematic Review Update 3	May 2016	Database inception through January 2016
Systematic Review Update 2	September 2013	Database inception through January 2013
Systematic Review Update 1	August 2010	Database inception through December 2009
Systematic Review	July 2007	Database inception through September 2006

Note. [a] *If therapies were not included in the prior systematic review, the database was searched through inception.*

2024 DERP Systematic Review Findings



Background *(1 of 2)*

- MS is a disease in which the body's immune system attacks the myelin, leading to neurologic dysfunction
  - Myelin insulates neurons, allowing efficient transmission of nerve impulses
- Symptoms include numbness, muscle weakness or spasms, vision problems, dizziness, and trouble walking or speaking
- While the exact cause is not known, risk factors for MS include age, Epstein-Barr virus exposure, smoking, and genetics

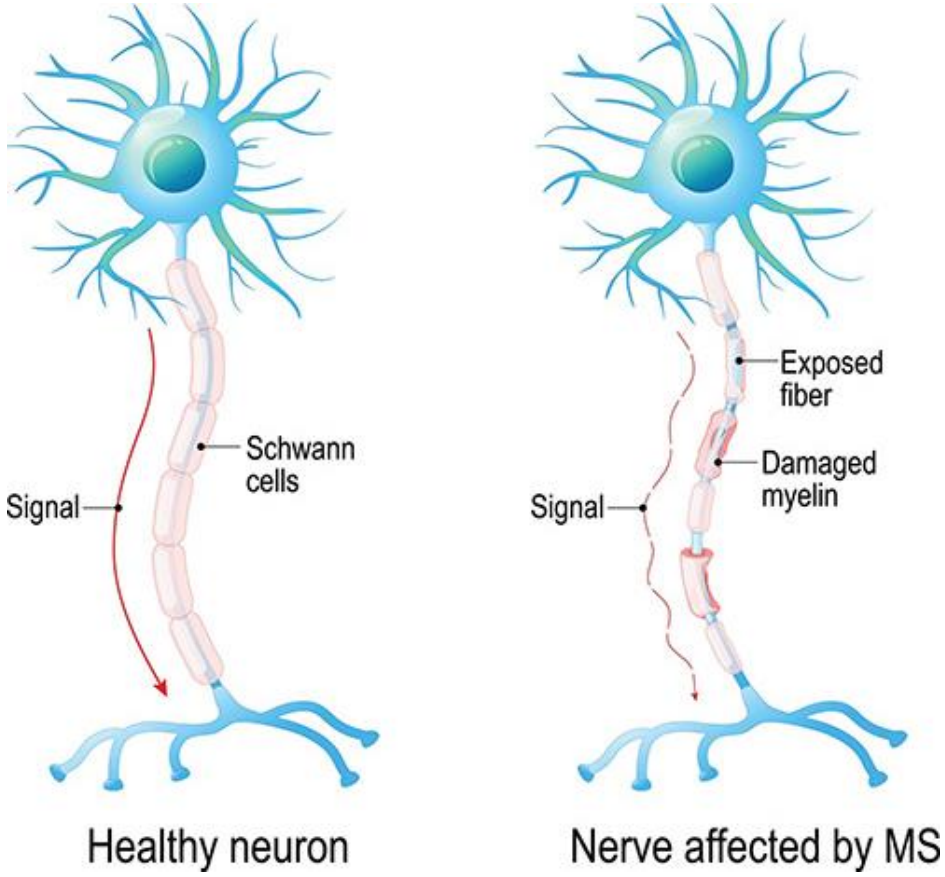


Image Source. OHSU Brain Institute. Understanding Multiple Sclerosis.

Background *(2 of 2)*

- MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system
- 2021 US prevalence was 126 per 100,000 population, based on data from the Global Burden of Disease study
  - The same study indicated variation in prevalence by geographic region in the US, with northern states experiencing higher prevalence rates compared with southern states

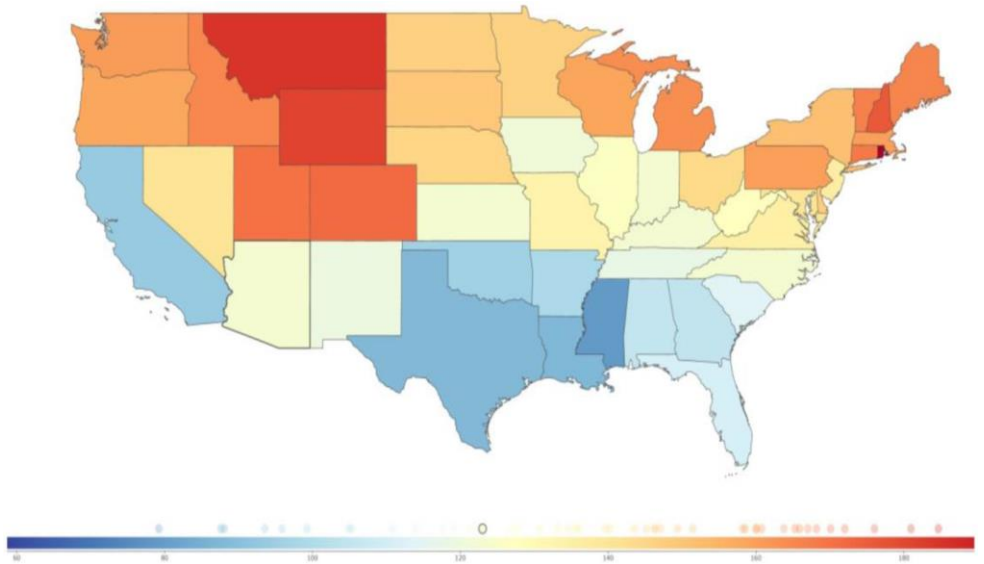


Image Source. Khan and Hashim, 2025.

Types of MS

Clinical Type	Definition
Clinically isolated syndrome (CIS)	First episode of neurologic symptoms suggestive of MS
Relapsing-remitting MS (RRMS)	Clearly defined attacks of new or increasing neurologic symptoms, followed by periods of partial or complete recovery (remission).
Secondary progressive MS (SPMS)	Progressive worsening of neurological function, or disability accumulation, from RRMS; with or without occasional relapses, minor remissions, and plateaus in severity.
Primary progressive MS (PPMS)	Neurologic function worsens, or disability accumulates, from disease onset with occasional plateaus in severity, temporary minor improvements, or acute relapses.

*Note. RRMS, SPMS, and PPMS can be further characterized as either **active** (with relapses, evidence of new MRI activity over a specified period of time, or both) or **not active**.*

Disease-Modifying Therapies for MS and CIS

- At the time of this surveillance, FDA has approved over 20 DMTs for MS and CIS
  - The aim of DMTs is to reduce the number of relapses, delay progression of disability, and limit new MS disease activity (as seen on MRI)

PICOS

- Populations:
  - Adult outpatients (aged 18 years and older) with MS
    - RRMS
    - SPMS
    - PPMS
  - Adult outpatients with CIS
- Comparators:
  - Another listed intervention (head-to-head comparison)
  - Placebo (for CIS only)

PICOS: Included Disease-Modifying Therapies *(1 of 3)*

Generic Name	Brand Name(s)	Indication	Administration Route	Frequency	First FDA Approval Date
Ublituximab	Briumvy	Relapsing forms of MS in adults	Injectable, intravenous infusion	Every 6 months	December 28, 2022
Ponesimod	Ponvory	Relapsing forms of MS in adults	Oral	Daily	March 18, 2021
Ofatumumab	Kesimpta	Relapsing forms of MS in adults	Injectable, subcutaneous	Monthly	August 20, 2020
Monomethyl fumarate	Bafiertam	Relapsing forms of MS in adults	Oral	Twice daily	April 28, 2020
Ozanimod	Zeposia	Relapsing forms of MS in adults	Oral	Daily	March 25, 2020
Diroximel fumarate	Vumerity	Relapsing forms of MS in adults	Oral	Twice daily	October 30, 2019

PICOS: Included Disease-Modifying Therapies *(2 of 3)*

Generic Name	Brand Name(s)	Indication	Administration Route	Frequency	First FDA Approval Date
Cladribine	Mavenclad	RRMS and active SPMS in adults	Oral	Yearly (for 2 years)	March 29, 2019
Siponimod	Mayzent	Relapsing forms of MS in adults	Oral	Daily	March 27, 2019
Ocrelizumab	Ocrevus	Relapsing forms of MS and PPMS, in adults	Injectable, intravenous infusion	Every 6 months	March 28, 2017
Alemtuzumab	Lemtrada	RRMS and active SPMS in adults	Injectable, intravenous infusion	Daily for 5 days, then daily for 3 days 12 months after the first course	November 14, 2014
Peginterferon beta-1a	Plegridy	Relapsing forms of MS in adults	Injectable, subcutaneous	Every 14 days	August 15, 2014

PICOS: Included Disease-Modifying Therapies *(3 of 3)*

Generic Name	Brand Name(s)	Indication	Administration Route	Frequency	First FDA Approval Date
Dimethyl fumarate	Tecfidera	Relapsing forms of MS in adults	Oral	Twice daily	March 27, 2013
Teriflunomide	Aubagio	Relapsing forms of MS in adults	Oral	Daily	September 12, 2012
Fingolimod	Tascenso ODT, Gilenya	Relapsing forms of MS in people aged ≥ 10 years	Oral	Daily	September 21, 2010
Interferon beta-1a	Rebif	Relapsing forms of MS in adults	Injectable, subcutaneous	Three times per week	March 7, 2002
Glatiramer acetate	Glatopa, Copaxone	Relapsing forms of MS in adults	Injectable, subcutaneous	Daily or 3 times per week	December 20, 1996
Interferon beta-1a	Avonex	Relapsing forms of MS in adults	Injectable, intramuscular	Weekly	May 17, 1996
Interferon beta-1b	Extavia, Betaseron	Relapsing forms of MS in adults	Injectable, subcutaneous	Every other day	July 23, 1993

PICOS

- Outcomes:
  - Relapse
  - Disability
  - Quality of life
  - Functional outcomes
  - Persistence
  - Conversion to MS (for CIS)
  - Adverse events
    - Overall adverse events
    - Serious adverse events
    - Withdrawals due to adverse events
    - Specific adverse events (e.g., hepatotoxicity)

PICOS

- Study designs:
  - Randomized controlled trials (RCTs)
    - 12 weeks study duration or longer
  - Placebo-controlled trials for clinically isolated syndrome only
    - 12 weeks study duration or longer
  - Retrospective and prospective cohort (nonrandomized) studies comparing an intervention type with another for outcomes on harms
    - 12 weeks study duration or longer
    - Minimum total sample size of 1,000*

** While cohort studies remain in scope for this topic, we did not search for cohort studies during surveillance given the general lack of registration of cohort studies in trial registries.*

Key Questions

1. **Effectiveness** of DMTs for MS
2. **Effectiveness** of DMTs for CIS
3. **Variations in harms** by indications (MS or CIS)
4. **Variation in effectiveness or harms** by subgroup
5. Characteristics of **ongoing studies**

Methods

Methods

- All searches covered July 31, 2023, through June 25, 2025

REGISTERED TRIALS

- ClinicalTrials.gov
- ScanMedicine

PUBLISHED EVIDENCE

Using clinical trial numbers or other identifiers (e.g., trial name):

- Ovid MEDLINE
- Google Scholar

FDA ACTIONS

- FDA website
- IPD Analytics

Findings: Clinical Landscape

New Drugs, Formulations, Indications,
Serious Harms, or Warnings

New Drugs and Formulations

- We did not identify any new FDA-approved DMTs for MS
- We did identify 1 newly approved formulation of ocrelizumab
  - Approval was based on the OCARINA II trial (NCT05232825)
  - Faster administration than IV form

Generic Name *Brand Name*	Indications	Administration Route and Frequency	FDA-Approved Dose(s)	FDA Approval Date	WAC
Ocrelizumab hyaluronidase *Ocrevus Zunovo*	**Relapsing forms of MS and PPMS, in adults**	**Injectable**, subcutaneous; **every 6 months**	920 mg ocrelizumab; 23,000 units hyaluronidase	September 13, 2024	**$82,564**

Bold text *indicates no difference from the previously approved intravenous form of ocrelizumab.*
Abbreviations. FDA: US Food and Drug Administration; mg: milligram; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; WAC: wholesale acquisition cost.

Pipeline Therapies in Phase 3 Testing

- We identified 1 DMT for MS in the pipeline with an upcoming Prescription Drug User Fee Act (PDUFA) date
  - Potential approval is based on the published HERCULES trial (NCT04411641)

Generic Name	Pipeline Drug Name	Indications	Administration Route	Mechanism of Action	PDUFA Date
Tolebrutinib	SAR442168	Non-relapsing SPMS	Oral	Bruton's tyrosine kinase inhibitor	September 28, 2025

Abbreviations. PDUFA: Prescription Drug User Fee Act; SPMS: secondary progressive multiple sclerosis.

New Indications

- We did not identify any new indications for the eligible DMTs for MS

New Serious Harms or Warnings (1 of 2)

- We identified 1 new black box warning:
  - On January 22, 2025, the FDA issued a warning of the risk of a rare, serious allergic reaction (anaphylaxis) associated with **glatiramer acetate** injection
  - Cases reported have been life-threatening and fatal

New Serious Harms or Warnings *(2 of 2)*

Therapy	New Harms or Warnings	Updates to Prior Harms or Warnings
Alemtuzumab	Immune-mediated colitis	--
Cladribine	--	Liver injury; infection
Fingolimod	--	Cutaneous malignancies; macular edema
Glatiramer acetate	**Anaphylaxis (black box warning);** administration errors[a]	--
Ofatumumab	Contraindication[b]	Infection
Ocrelizumab	--	Infection
Ozanimod	Cutaneous malignancies; PML	Macular edema; liver injury; subgroup recommendation[c]
Ponesimod	--	Cutaneous malignancies; macular edema
Siponimod	PML	Cutaneous malignancies; macular edema

Notes. [a] Issues with the use of an incompatible autoinjector. [b] History of hypersensitivity or life-threatening injection-related reaction to the therapy. [c] Clarification that this therapy is not recommended for individuals with severe hepatic impairment (Child-Pugh class C). Abbreviations. FDA: US Food and Drug Administration; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy.

Findings: Research Landscape

New Published Studies and Ongoing Studies

New Published Studies

- We identified 2 new RCTs

Author, Year Study Name NCT Number	Study Location	Participant Characteristics N Randomized	Intervention Comparator	Eligible Outcomes	RCT Duration
Newsome et al., 2025 OCARINA II NCT05232825	8 countries (including the US)	Adults with RMS or PPMS N = 236	• Ocrelizumab with hyaluronidase (SC) • Ocrelizumab (IV)	• Relapse[a] • Adverse events[b] • Serious adverse events	24 weeks
Newsome et al., 2024 OCARINA I NCT03972306	20 sites in the US	Adults with RMS or PPMS N = 70	• Ocrelizumab with hyaluronidase (SC) • Ocrelizumab (IV)	• Adverse events[b] • Serious adverse events	Unclear[c]

Notes. [a] Although study authors indicate in the methods that relapse rates are a secondary outcome of interest during the RCT period of this trial, results on relapse rates during the RCT period are not reported in this publication. [b] Including withdrawals due to adverse events and specific adverse events. [c] The study authors indicated they cutoff the dose selection period once the last randomized participant completed 12 weeks.

Abbreviations. IV: intravenous; MS: multiple sclerosis; N: number; NCT: National Clinical Trials; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; RMS: relapsing multiple sclerosis; SC: subcutaneous; US: United States.

Ongoing Studies *(1 of 2)*

- We identified **5 ongoing RCTs** for DMTs for MS and CIS
  - Estimated and actual enrollment numbers range from 123 to 900
  - Estimated primary completion dates range from November 2025 to August 2028

Ongoing Studies *(2 of 2)*

Comparators	Primary Completion Date	Study Name (Trial Number)	Population[a]	Estimated Enrollment
Active Comparator RCTs				
Ofatumumab vs. first-line DMT[b]	November 2025	STHENOS (NCT04788615)	Relapsing MS	185 (actual)
Early aggressive therapy[b] vs. traditional therapy[b]	August 2026	TREAT-MS (NCT03500328)	RRMS	900 (actual)
Ofatumumab vs. other approved DMT[b]	December 2026	SOSTOS (NCT05090371)	RRMS	150
Early highly effective therapies[b] vs. escalation therapies[b]	July 2027	DELIVER-MS (NCT03535298)	RRMS	800
Placebo-Controlled RCTs				
Ocrelizumab vs. placebo	August 2028	AMS05 (NCT05285891)	Relapsing MS (including CIS)	123

Notes. [a] Populations include adults only. [b] DMT categories as published in the registry and defined by trial investigators.
Abbreviations. CIS: clinically isolated syndrome; MS: multiple sclerosis; NCT: US National Clinical Trial number; RCT: randomized controlled trial; RRMS: relapsing-remitting multiple sclerosis.

Summary Since Last Review

Clinical Landscape *(1 of 2)*

- **No new FDA-approved DMTs**
- **1 new FDA-approved formulation** for a subcutaneous (SC) form of ocrelizumab (ocrelizumab with hyaluronidase)
- **No new indications for FDA-approved DMTs**
- **1 pipeline DMT** in a phase 3 trial
  - Tolebrutinib; PDUFA date in September 2025

Clinical Landscape *(2 of 2)*

- New warnings and serious harms in 5 DMTs
  - **Black box warning of anaphylaxis for glatiramer acetate**
  - **Cutaneous malignancies** for ozanimod
  - **Progressive multifocal leukoencephalopathy** for ozanimod and siponimod
  - **Immune mediated colitis** for alemtuzumab
  - **New contraindication** for ofatumumab
  - Warning on **administration errors** with the use of incompatible autoinjectors for glatiramer acetate
- A series of updates to previously listed warnings and harms in 7 DMTs

Research Landscape

- **2 new RCTs** comparing the newly approved SC formulation (ocrelizumab with hyaluronidase) with the previously approved intravenous (IV) form of ocrelizumab
- **5 ongoing RCTs**
  - 4 active comparator RCTs in adults with MS comparing ofatumumab to other DMTs (2 trials) or a group of DMTs compared with other DMTs (2 trials)
  - 1 placebo-controlled trial of ocrelizumab inclusive of adults with CIS

Questions?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