

Endpoint Modernization in Registered Multiple Sclerosis Trials: A ClinicalTrials.gov Analysis of Progression-Sensitive, Biomarker, Patient-Reported, and Digital Outcomes

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Research Article

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Abstract

Background:

Multiple sclerosis (MS) disability may accrue through both relapse-associated worsening and progression independent of relapse activity. However, it is unclear how often registered MS trials incorporate endpoints designed to capture smoldering disease biology, biomarkers, cognition, patient-reported outcomes, or digital monitoring.

Objective:

To examine temporal trends in conventional and progression-sensitive outcome measures, including biomarkers, cognition, patient-reported outcomes, and digital endpoints in interventional MS trials registered in ClinicalTrials.gov.

Methods

We performed a cross-sectional registry analysis of interventional MS, clinically isolated syndrome (CIS), and radiologically isolated syndrome (RIS) studies first posted on ClinicalTrials.gov from 1 January 2010 through 11 May 2026. Outcome-measure fields were coded using predefined keyword dictionaries for conventional endpoints, progression independent of relapse activity (PIRA), progression independent of relapse or MRI activity (PIRMA)/smoldering progression, atrophy, advanced MRI, fluid biomarkers, cognition, patient-reported outcomes, and digital/wearable/remote endpoints. Temporal trends were assessed using chi-square tests across posting eras and binomial logistic regression with calendar year rescaled per five-year increase.

Results

Among 2077 eligible trials, disability endpoints were the most common conventional measure, appearing in 737 trials (35.5%), followed by conventional inflammatory MRI endpoints in 368 (17.7%) and relapse endpoints in 356 (17.1%). Explicit PIRA/PIRMA/smoldering-progression endpoints were rare, appearing in 15 trials (0.7%). Broad modern/patient-centered endpoint use increased from 64.5% in 2010–2014 to 76.4% in 2020–2026 (chi-square = 22.7, df = 2, $p < .001$; OR per five years 1.36, 95% CI 1.22–1.51). In contrast, strict biological progression-sensitive endpoint use did not significantly change across eras (16.9%, 15.1%, and 17.0%; chi-square = 1.16, df = 2, $p = .559$) or calendar time (OR per five years 1.01, 95% CI 0.89–1.14; $p = 0.924$).

Conclusion

Registered MS trial outcomes increasingly incorporate patient-centered, cognitive, biomarker, and digital endpoint domains, but explicit PIRA/smoldering-progression language and strict biological progression-sensitive endpoints remain uncommon. These findings suggest a gap between contemporary concepts of MS progression and the outcome language used in trial registries.

Introduction

Multiple sclerosis (MS) clinical trials have historically relied on relapse activity, conventional inflammatory magnetic resonance imaging (MRI) lesion metrics, and Expanded Disability Status Scale (EDSS)-based disability outcomes. These endpoints remain central to trial design because they capture clinically meaningful inflammatory disease activity and neurological disability. However, contemporary understanding of MS biological mechanisms underlying disease progression has highlighted that disability accrual may occur outside overt relapses and may not be fully represented by conventional MRI lesion-count outcomes. Disability may accumulate in the absence of clinically apparent relapses, a phenomenon increasingly conceptualized as silent progression or progression independent of relapse activity (PIRA) [1–3].

This conceptual shift has major implications for outcome measurement. Endpoints aligned with chronic active lesions, smoldering-associated worsening, neuroaxonal injury, brain and spinal cord atrophy, and fluid biomarkers may capture biological processes underlying non-relapsing progression. Cognitive testing, patient-reported outcomes (PROs), and digital or wearable monitoring may also assess functional domains that are incompletely measured by relapse counts, conventional MRI lesion activity, and EDSS-based disability assessments. Together, these domains reflect a broader movement toward more mechanism-informed and patient-centered trial design [4–12].

Despite this scientific shift, the extent to which registered MS trials have incorporated newer endpoint domains remains uncertain. Trial registries provide a reproducible way to examine outcome language at scale, but registry-based descriptions may lag behind full protocols, publications, and evolving terminology [13–15]. It is unclear whether trial registrations explicitly identify relapse-independent progression, smoldering progression, or progression-sensitive biomarkers as outcomes.

We therefore analyzed interventional MS, clinically isolated syndrome (CIS), and radiologically isolated syndrome (RIS) trials registered on ClinicalTrials.gov from 2010 through May 2026.

The objective is to quantify the incorporation of traditional clinical and imaging endpoints, including relapse activity, conventional MRI measures, and disability outcomes, alongside emerging domains reflecting non-relapsing disease activity.

These emerging domains included constructs of relapse-independent progression (PIRA/PIRMA/smoldering progression), neurodegenerative measures such as atrophy, advanced MRI metrics, fluid biomarkers, cognitive outcomes, patient-reported outcomes (PROs), and digital, wearable, or remote monitoring approaches, and to evaluate temporal trends in endpoint modernization.

Methods

Data source and eligibility

We performed a cross-sectional registry analysis of ClinicalTrials.gov records exported as a CSV file. The database was searched using the condition/disease term "Multiple Sclerosis," restricted to interventional studies of any recruitment status or phase first posted from 1 January 2010 through 11 May 2026 [13]. Eligible records included interventional studies in which the condition field referenced multiple sclerosis, clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), equivalent Medical Subject Heading-style wording, or clear progressive/relapsing MS terminology. Records were excluded if they were non-MS-related, expanded-access, observational, or otherwise ineligible after screening. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies, and a completed STROBE checklist is provided as supplementary material [16].

Endpoint-domain coding

Primary, secondary, and other outcome-measure fields were concatenated into a single analyzable outcome-text field for each registry record. Each record was coded using predefined keyword dictionaries for relapse, conventional inflammatory MRI, disability, explicit PIRA/PIRMA/smoldering progression, brain or spinal cord atrophy, advanced MRI biomarkers, fluid biomarkers, cognition, patient-reported outcomes, and digital, wearable, or remote monitoring endpoints. Matched terms and corresponding outcome-text excerpts were retained for audit purposes.

Conservative coding rules were applied to reduce false-positive classification. Routine safety laboratories were not classified as fluid biomarkers, electronic case-report forms were not coded as digital endpoints, and conventional MRI measures were not coded as an advanced MRI biomarker. Conventional inflammatory MRI endpoints were defined as lesion-count–based or inflammatory activity measures. Advanced MRI biomarker endpoints included imaging domains beyond conventional inflammatory lesion counts, such as quantitative or nonconventional MRI-derived measures when explicitly described in the registry outcome language.

A strict progression-sensitive endpoint definition included explicit PIRA/PIRMA/smoldering-progression endpoints, brain or spinal cord atrophy endpoints, advanced MRI biomarker endpoints, or fluid biomarker endpoints. A broader modern or patient-centered endpoint definition additionally included cognition, PROs, and digital, wearable, or remote endpoint domains. First-posted year was grouped into 2010-2014, 2015-2019, and 2020-2026. The keyword dictionary, matched terms, and representative audit excerpts are provided as supplementary material with the manuscript.

Quality-control audit

After applying the endpoint dictionaries, all records flagged for explicit PIRA/PIRMA/smoldering-progression language were reviewed at the source-text level as this rare endpoint category represented the central finding of the analysis. Fifteen records were confirmed to contain explicit PIRA, progression-independent, relapse-independent, smoldering, or including smoldering endpoint language in the outcome-measure fields. Ambiguous wording in other domains was adjudicated conservatively during coding. Because endpoint categorization relied on an automated, deterministic keyword dictionary rather than subjective human extraction, a traditional interrater reliability statistic (e.g., Cohen's Kappa) was not calculated. This approach reduces reviewer-level subjectivity and supports rule-based reproducibility, but it remains vulnerable to misclassification if registry records utilized novel or highly nonstandard terminology omitted from the predefined dictionary. The final coded trial-level dataset was used for all statistical analyses.

Funding-source classification

Funding source was classified using ClinicalTrials.gov sponsor and funder-type information. Trials were categorized as industry-funded when the ClinicalTrials.gov funder type was listed as industry; all other funder types were categorized as non-industry funded.

Statistical analysis

Descriptive statistics were used to summarize trial characteristics and endpoint-domain frequencies. Categorical variables are reported as counts and percentages. Registered enrollment is reported as median and interquartile range. Endpoint-domain proportions were compared across first-posted year eras using chi-square tests, with Fisher's exact testing used for sparse endpoint categories where appropriate. Temporal trends were assessed using binomial logistic regression with first-posted calendar year rescaled per five-year increase. Odds ratios (ORs) were reported with 95% confidence intervals (CIs). The primary trend outcomes were broad modern/patient-centered endpoint use and strict biological progression-sensitive endpoint use; domain-specific analyses were considered exploratory. Analyses were conducted at the trial-record level using Jamovi version 2.7.33.

Results

Registry sample

The dataset contained 2306 interventional registry records, of which 229 were excluded after screening, leaving 2077 eligible MS/CIS/RIS trials for analysis (Figure 1). Included trials were first posted in 2010-2014 (n = 467), 2015-2019 (n = 642), and 2020-2026 (n = 968). Most trials were non-industry funded (1589/2077, 76.5%); 488 (23.5%) were industry funded. Median registered enrollment was 48 participants (interquartile range 24-100; available n = 2076) (Table 1).

Overall endpoint-domain frequencies

Conventional endpoint domains remained common but were not universal in registered outcome language. Relapse endpoints were present in 356 trials (17.1%), conventional inflammatory MRI endpoints in 368 (17.7%), and disability endpoints in 737 (35.5%). Explicit PIRA/PIRMA or smoldering-progression endpoints were rare, appearing in 15 trials (0.7%).

Among progression-sensitive and modern endpoint domains, atrophy endpoints appeared in 204 trials (9.8%), advanced MRI biomarkers in 89 (4.3%), and fluid biomarkers in 148 (7.1%). Cognition, patient-reported, and digital/wearable/remote endpoints appeared in 621 (29.9%), 1241 (59.7%), and 135 (6.5%) trials, respectively. Strict biological progression-sensitive endpoints appeared in 341 trials (16.4%), and broad modern/patient-centered endpoints appeared in 1505 trials (72.5%) (Figure 2).

Temporal trends

Broad modern/patient-centered endpoint use increased from 301/467 trials (64.5%) in 2010-2014 to 464/642 (72.3%) in 2015-2019 and 740/968 (76.4%) in 2020-2026 (chi-square = 22.7, df = 2, $p < .001$). In logistic regression using calendar year rescaled per five-year increase, broad modern/patient-centered endpoint use increased over time (OR 1.36, 95% CI 1.22-1.51; $p < .001$). In contrast, strict biological progression-sensitive endpoint use did not significantly change across eras: 79/467 (16.9%) in 2010-2014, 97/642 (15.1%) in 2015-2019, and 165/968 (17.0%) in 2020-2026 (chi-square = 1.16, df = 2, $p = .559$). Logistic regression similarly showed no significant temporal change (OR per five years 1.01, 95% CI 0.89-1.14; $p = 0.924$). Among exploratory endpoint domains, fluid biomarker endpoints, digital/wearable/remote endpoints, cognition endpoints, and patient-reported endpoints increased over time. Explicit PIRA/PIRMA/smoldering-progression endpoint language remained rare overall but was more frequently observed in later-era trials, increasing from 0/467 (0.0%) in 2010-2014 to 2/642 (0.3%) in 2015-2019 and 13/968 (1.3%) in 2020-2026 (chi-square = 10.1, df = 2, $p = .006$; Fisher's exact $p = .005$). Because this endpoint category included only 15 trials overall, these results were interpreted descriptively (Figure 3, Table 1).

Discussion

This ClinicalTrials.gov analysis demonstrates an asymmetrical pattern of endpoint modernization in registered interventional MS trials. Broad modern/patient-centered endpoint use increased over time, driven by greater incorporation of patient-centered, cognitive, digital, and biomarker-related domains. In contrast, explicit PIRA/PIRMA/smoldering-progression language remained rare, and strict biological progression-sensitive endpoint use did not significantly increase across eras or calendar time. These findings suggest that registered MS trial outcome language has modernized in some domains but has not consistently adopted terminology or measures directly aligned with relapse-independent progression and smoldering disease biology [2-4,8,9].

The finding that explicit PIRA/PIRMA or smoldering-progression endpoints appeared in only 0.7% of eligible trials is notable given the growing recognition that disability can accumulate independently of overt relapses. Relapse rate, conventional inflammatory MRI activity, and EDSS-based worsening remain

important, but they may not distinguish relapse-associated worsening from relapse-independent progression. Trials targeting chronic active lesions, neuroaxonal injury, remyelination, or disability progression should specify whether disability worsening is relapse-associated, relapse-independent, or not classifiable from available registry fields [3,8,9].

The distinction between broad modern/patient-centered endpoints and strict biological progression-sensitive endpoints is important. Patient-reported outcomes, cognition, digital monitoring, and fluid biomarkers can enhance trial relevance and sensitivity, but they are not interchangeable with explicit relapse-independent progression definitions. A trial may incorporate modern patient-centered measures without directly operationalizing PIRA, PIRMA, or smoldering progression. Conversely, a biologically targeted trial may use atrophy, advanced MRI, or fluid biomarker endpoints without capturing patient-perceived functional change. Future MS trials should align endpoint selection with therapeutic mechanism and target population, incorporating atrophy measures, advanced MRI markers, fluid biomarkers, cognition, digital monitoring, and PROs when scientifically appropriate [5–7,10–12].

These results also have implications for registry reporting. ClinicalTrials.gov is a public-facing registry designed for transparency, but outcome-measure fields are often brief and may use heterogeneous terminology. If relapse-independent progression is central to a trial hypothesis, explicit registry language may improve interpretability for clinicians, researchers, systematic reviewers, and patients. More standardized registry terminology for PIRA, PIRMA, smoldering progression, atrophy, advanced MRI, and fluid biomarker endpoints could make future trial landscapes easier to evaluate [14,15].

Importantly, the low frequency of explicit PIRA/PIRMA or smoldering-progression language should not be interpreted as evidence that trial protocols ignored relapse-independent progression. Some trials may have captured disability progression, atrophy, biomarkers, or advanced imaging without labeling those outcomes using newer terminology. The main implication is therefore not that modern biological concepts were absent from all trials, but that registered outcome language often does not clearly communicate whether disability worsening is relapse-associated, relapse-independent, or mechanistically linked to smoldering disease. This distinction is particularly relevant as PIRA definitions continue to be harmonized and smoldering-associated worsening is increasingly discussed as a trial-relevant construct [8,9].

Limitations

This study has limitations. ClinicalTrials.gov records may be incomplete, amended over time, or less detailed than full protocols and publications. Because this analysis examined registry outcome language rather than full protocols, publications, or participant-level data, it cannot determine whether PIRA or smoldering progression was assessed but not explicitly labeled in the registry. Keyword-based endpoint coding may misclassify ambiguous outcome language despite conservative rules and retention of audit-text excerpts. This approach may underestimate endpoint use when trials used nonstandard terminology

and may overestimate use when terms appeared in broad exploratory or safety-related outcome descriptions. In addition, an interrater reliability statistic was not calculated because coding was not performed independently by two blinded reviewers. The findings therefore reflect registered endpoint language, rather than definitive protocol-level endpoint content. Nevertheless, the analysis identifies a reproducible measurement gap in registered MS trial outcomes. Multiple endpoint-domain models were performed, and domain-specific temporal analyses should be interpreted as exploratory. Sparse endpoint categories, particularly explicit PIRA/PIRMA/smoldering-progression language, may yield unstable model estimates; therefore, this category was interpreted primarily using descriptive era-based frequencies and exact testing.

Conclusion

Registered MS trial outcomes show increasing adoption of broad modern and patient-centered endpoint domains, including patient-reported, cognitive, digital, and biomarker-related measures. However, explicit PIRA/smoldering-progression language and strict biological progression-sensitive endpoints remain uncommon and did not show a significant temporal increase. These findings suggest a persistent gap between evolving concepts of MS progression and the outcome language used in current trial registries. Greater standardization of relapse-independent progression and smoldering-disease outcome reporting may improve interpretability of future MS trials.

Declarations

Ethics approval and consent to participate: This study used publicly available ClinicalTrials.gov registry records and did not involve patient-level identifiable data; institutional review board approval and informed consent were not required.

Consent for publication: Not applicable.

Declarations of interest: None.

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CRedit authorship contribution statement:

Viswabhaskar Susarla: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review and editing, Project administration.

Lokesh Katiki: Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review and editing.

Data availability: The ClinicalTrials.gov export, coded trial-level dataset, endpoint summary table, keyword dictionary, audit files, and Jamovi output files generated for this analysis are available as supplementary material. Source registry records are publicly available from ClinicalTrials.gov.

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Tables

Table 1
Logistic regression models for endpoint-domain use over calendar time.

Endpoint outcome	OR per 5-year increase	95% CI	p value
Broad modern endpoint	1.36	1.22–1.51	< .001
Strict progression-sensitive endpoint	1.01	0.89–1.14	0.924
Fluid biomarker endpoint	1.58	1.30–1.92	< .001
Digital/wearable/remote endpoint	1.61	1.31–1.98	< .001
Cognition endpoint	1.34	1.20–1.49	< .001
Patient-reported endpoint	1.36	1.23–1.50	< .001
Atrophy endpoint	0.79	0.68–0.93	0.004
Advanced MRI endpoint	1.15	0.91–1.46	0.234
Relapse endpoint	0.68	0.60–0.77	< .001
Conventional inflammatory MRI endpoint	0.71	0.63–0.80	< .001
Disability endpoint	0.97	0.88–1.07	0.498
Note. Odds ratios were estimated using binomial logistic regression with first-posted calendar year rescaled per five-year increase. Each endpoint was modeled separately. Domain-specific models were considered exploratory.			

Figures

Figure 1

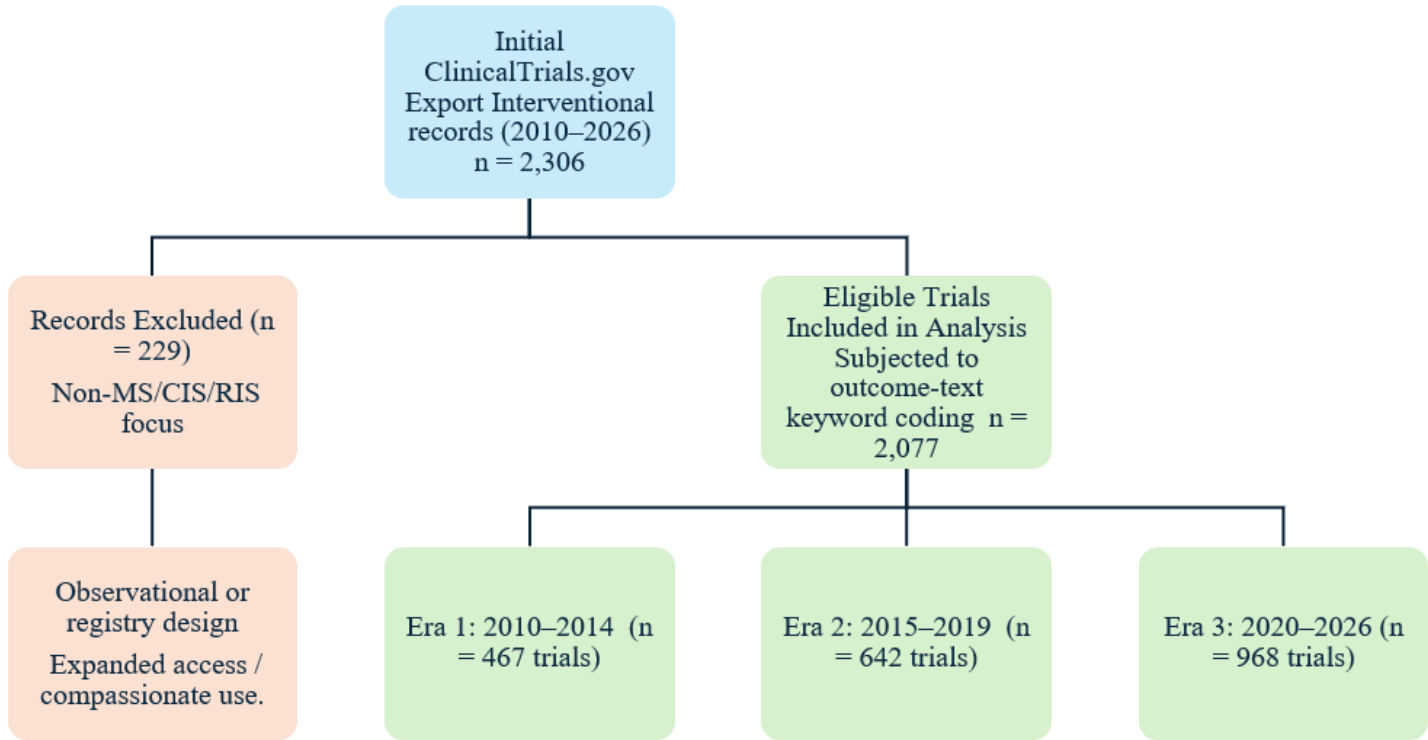


Figure 1

Flow diagram of ClinicalTrials.gov record selection for the registry analysis.

Figure 2

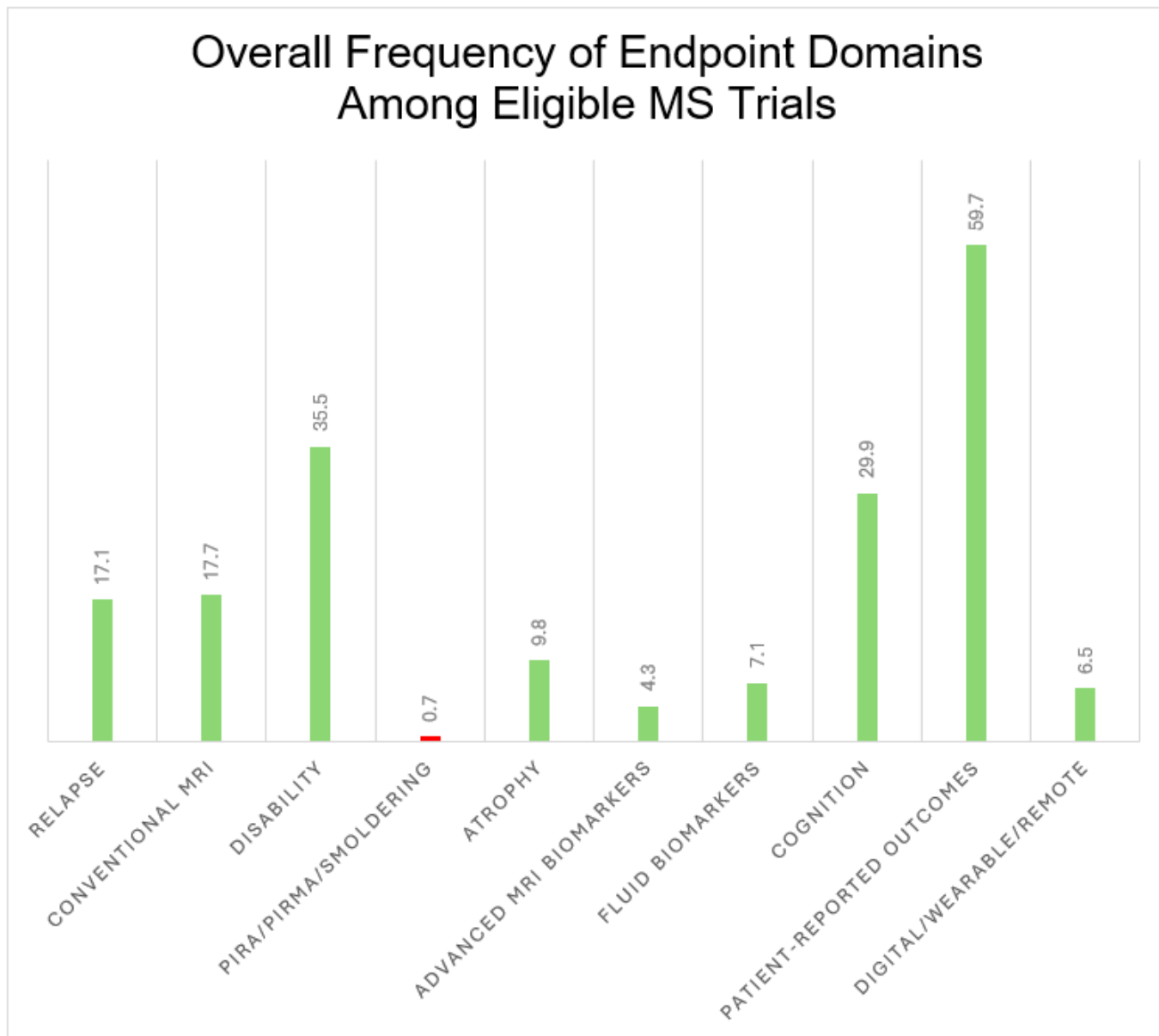


Figure 2

Overall Frequency of Endpoint Domains Among Eligible MS Trials.

Figure 3

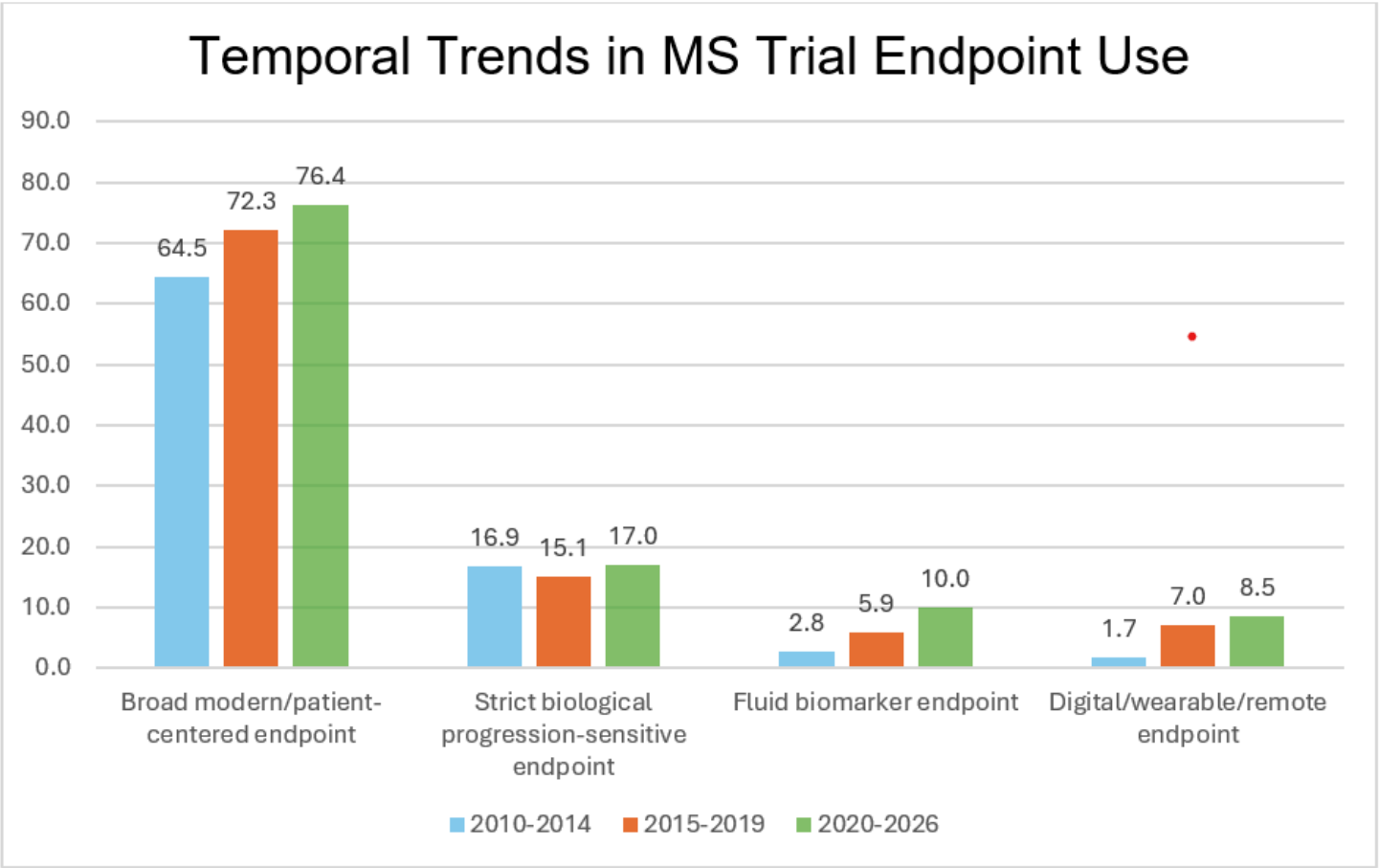


Figure 3

Temporal Trends in MS Trial Endpoint Use

Supplementary Files

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