



Multiple Sclerosis Trials Unpacked: Standards, Endpoints and Programming Experience

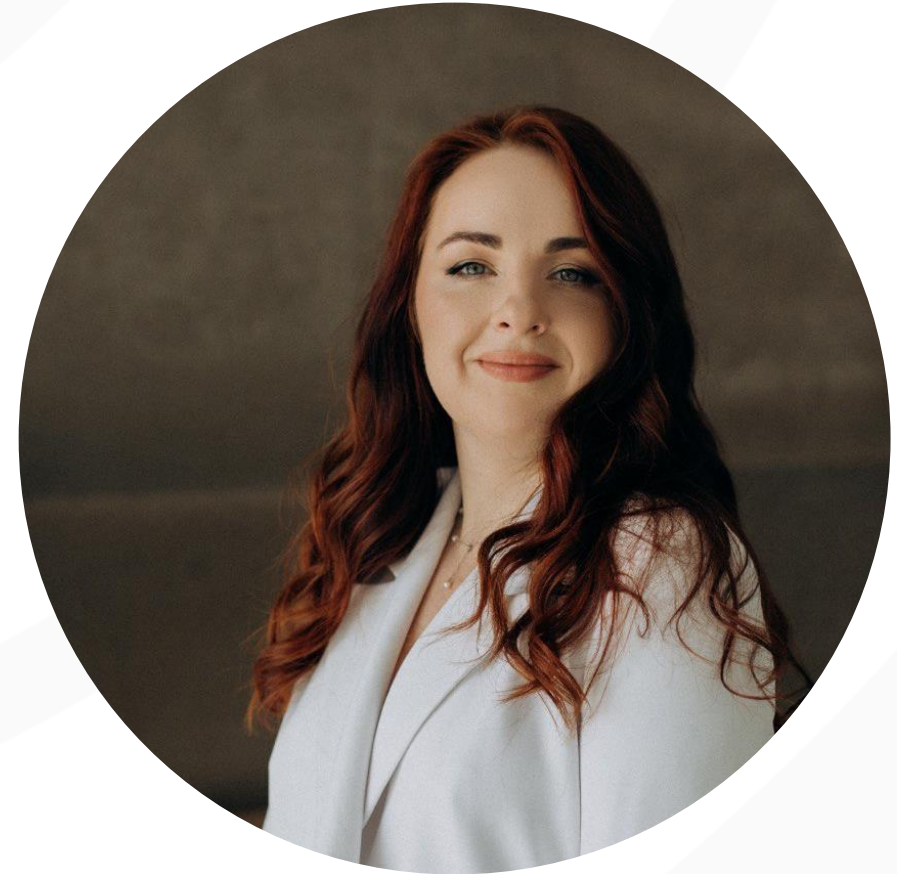
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PHUSE US Connect 2026

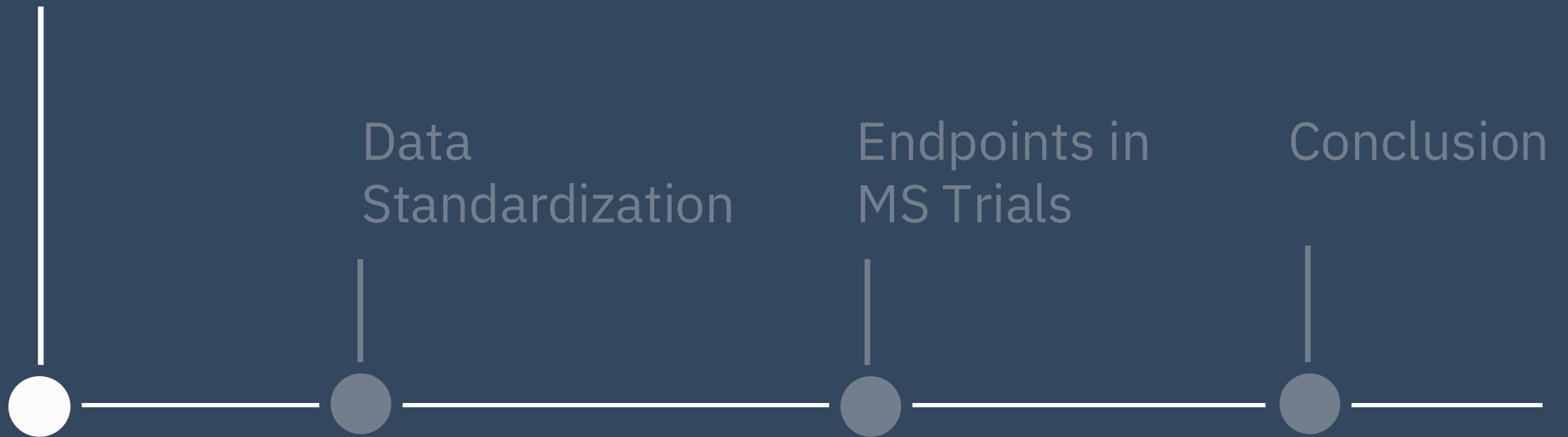
Agenda

- ✓ **MS Clinical Trials Overview**
- ✓ **Data Standardization**
- ✓ **Endpoints in MS Trials**
- ✓ **Conclusion**

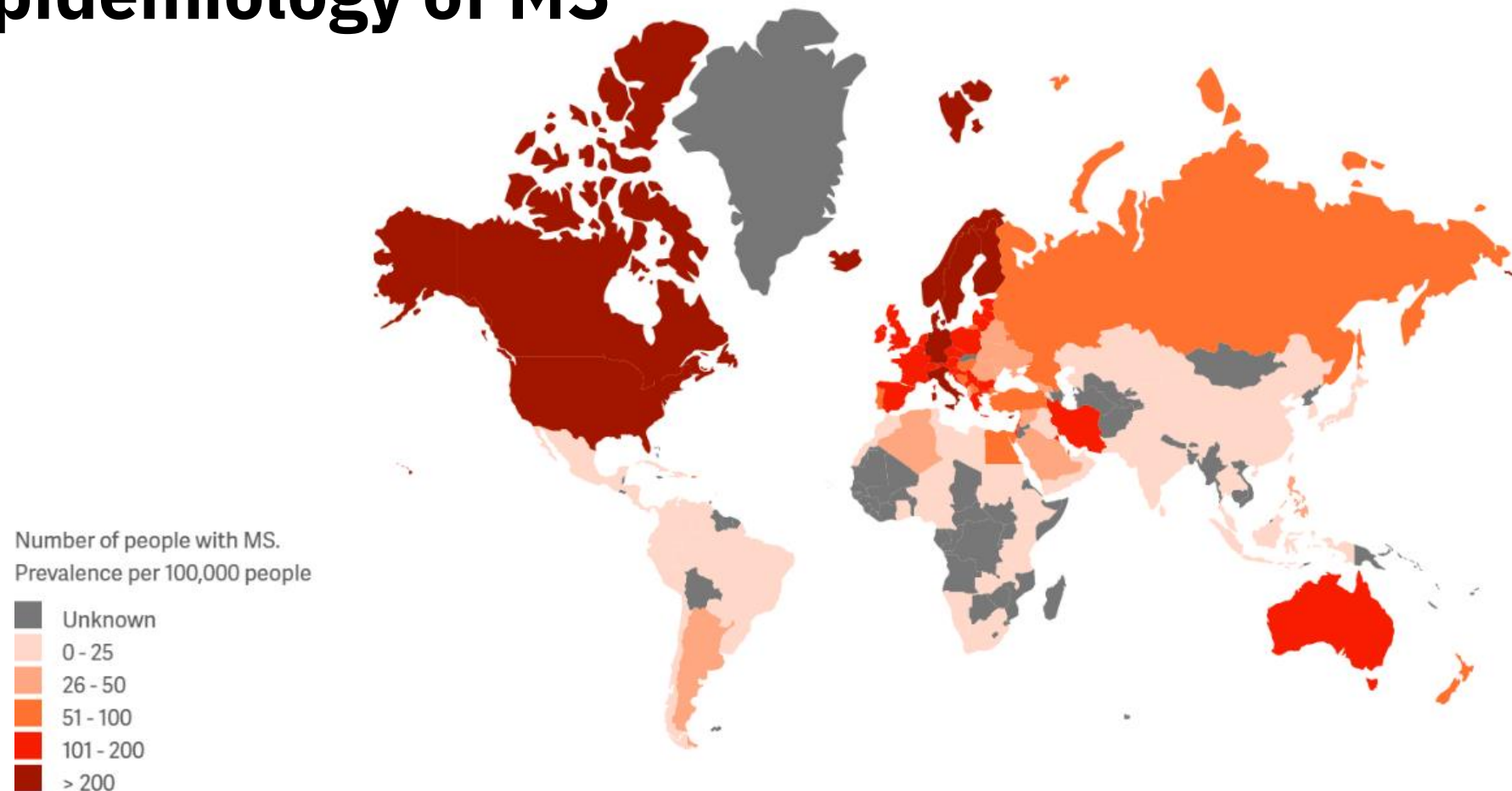


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MS Clinical Trials Overview



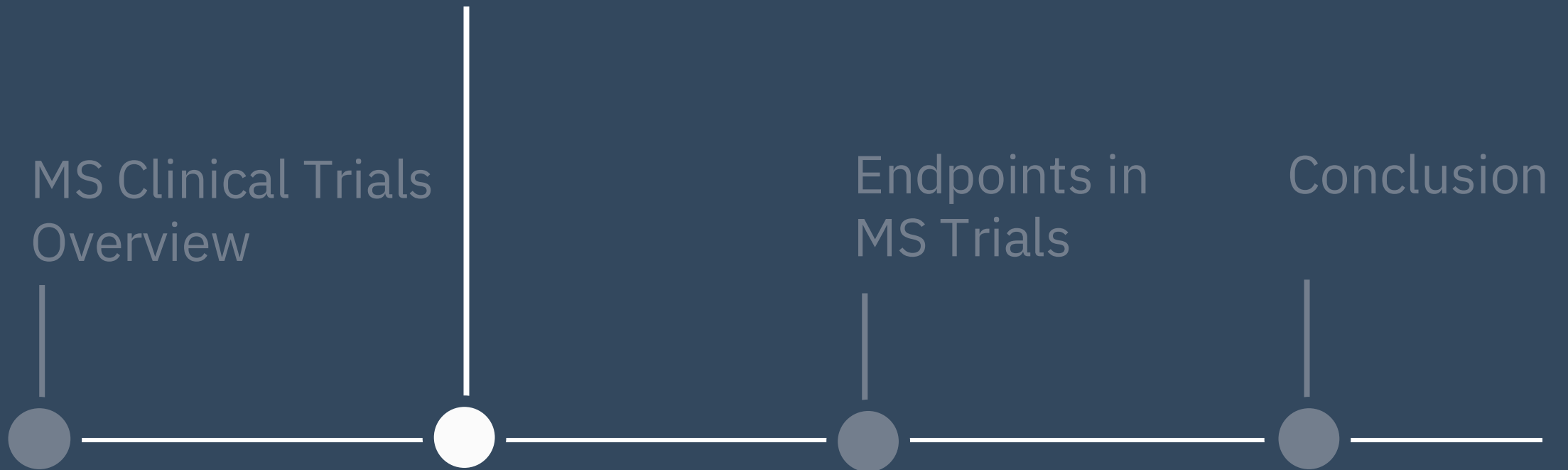
Epidemiology of MS



There are 2.9 million people living with MS worldwide.

According to the Atlas of MS the number of people with MS across the globe has increased from 2.3 million in 2013 to 2.8 million in 2020 and 2.9 million in 2023.

Data Standardization



Cornerstone



CDISC SDTM and SDTMIG
CDISC ADaM and ADaMIG
Define-XML
SDTM and ADaM CT
MedDRA and WHO Drug

Supplements



**Company-specific
standards**

**Multiple Sclerosis
TAUG v1.0**

**FDA Study Data
Technical
Conformance
Guide**

**Questionnaires,
Ratings and
Scales (QRS)**

Endpoints in MS Trials



Examples of Clinical Trial Endpoints used in MS

Relapses

- Relapse rate
- Annualized relapse rate (ARR)

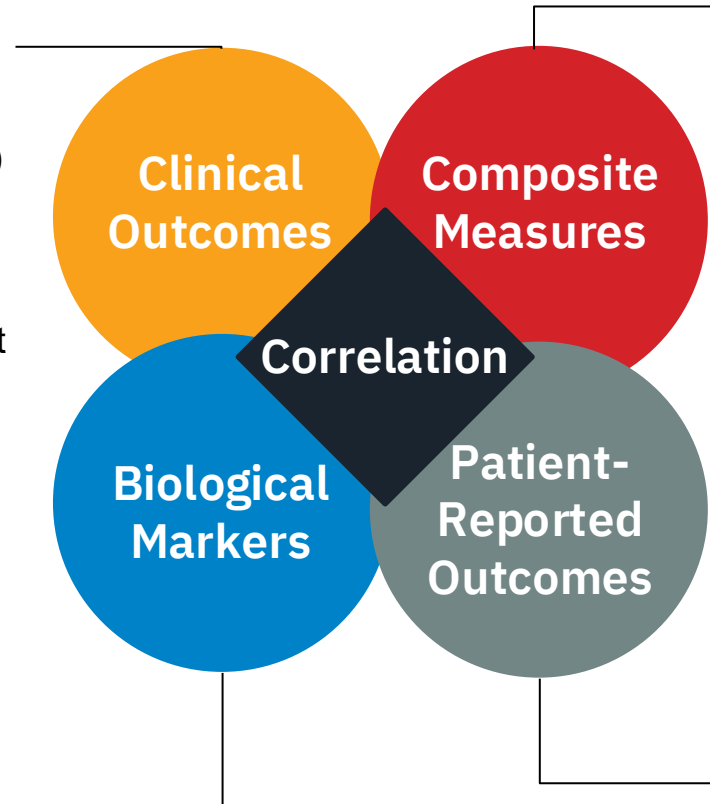
Disability

- Expanded Disability Status Scale (EDSS)
- Confirmed Disability Progression (CDP)
- Timed 25-foot Walk (T25FW)
- 9-Hole Peg Test (9HPT)
- Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)
- Hospital Anxiety and Depression Scale (HADS)
- Fatigue Severity Scale (FSS)

MRI Measurements

- Gd-enhancing T1 lesions
- T2 lesions
- Active lesions
- Combined unique active (CUA) lesions
- Brain volume
- Brain atrophy

Cerebrospinal fluid (CSF) oligoclonal bands
Neurofilament light chain (NfL) in CSF



- No Evidence of Disease activity (NEDA)-3
- NEDA-4
- No Evidence of Progression or Active Disease (NEPAD)
- Progression Independent of Relapses (PIRA), Composite PIRA (cPIRA), Modified composite PIRA (mcPIRA)
- Relapse Worsening Activity (RAW), Composite RAW (cRAW), Modified composite RAW (mc RAW)
- Confirmed disability accumulation (CDA), Composite CDA (cCDA), Modified composite CDA (mcCDA)
- Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54)
- Treatment Satisfaction Questionnaire Medication version 1.4 (TSQM v1.4)

Relapse

- new or clearly worsening neurologic symptoms
- Lasts for at least 24 hours
- is separated from a prior relapse for at least 30 days



SDTM representation

- **MH (Medical History):** MS onset and diagnosis history.
- **CE (Clinical Events):** represents the relapse as a clinical event
- **HO (Hospitalization):** hospitalization information for the relapse.
- **FA (Findings about):** additional clinical details (e.g., functional system affected, second attack, diagnosis date).
- Relationships across domains are documented in the **RELREC** dataset.



ADaM representation

- **OCCDS:** one record per relapse per subject, combining the relapse event data from multiple SDTMs.
- **BDS** for summary endpoints such as number of relapses, ARR, etc.
- **Alternative approach:** to store both the individual relapse records and the summary parameters in BDS.
- **ADTTE** for time-to-event analysis

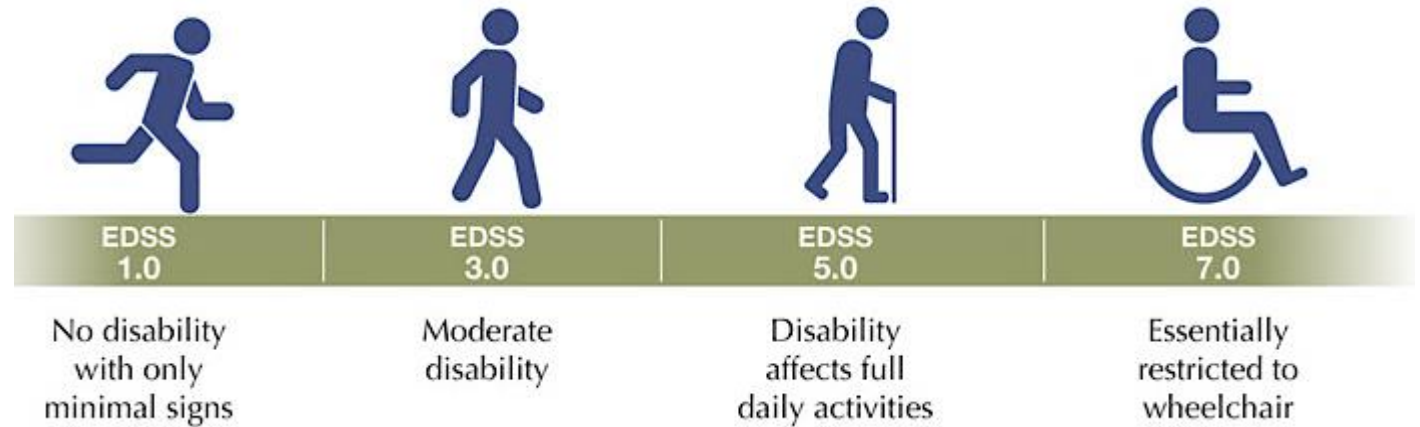


Key endpoints and analysis methods

- **Annualized Relapse Rate,** representing the average number of relapses a person experiences per year.
- **Poisson regression** for ARR commonly with log(follow-up time) as an offset and adjustment for baseline factors.
- **Survival analysis** for time to first relapse
- For recurrent relapses, **mean cumulative function** (MCF) approaches to summarize relapse accumulation over time.

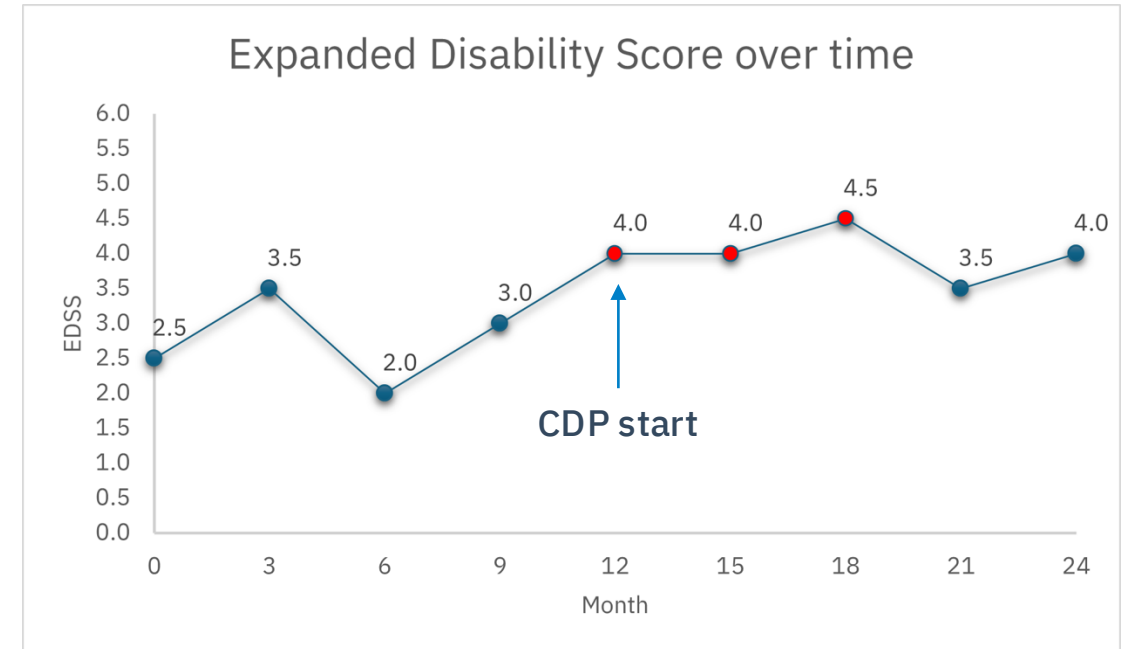
Disability Progression: EDSS

- Expanded Disability Status Scale
- introduced by Kurtzke in 1983
- remains a standard way to quantify neurologic disability over time
- is scored from 0 (normal neurologic exam) to 10 (death due to MS) in 0.5-step increments.
- SDTM representation: QS (Questionnaires). SDTMIG QRS supplement for EDSS released in 2013.
- ADaM representation: BDS dataset for EDSS over time.



Disability Progression: CDP

- Confirmed Disability Progression
- An increase of EDSS score from baseline of:
 - at least 1.5 points if the baseline is 0
 - at least 1 point if the baseline between 0 and 5
 - at least 0.5 point if the baseline 5 and more
- EDSS increase sustained for at least 3 or 6 months
- CDP is frequently analyzed as time-to-event (time to first confirmed progression), using standard survival methods.



Practical Challenges

- ☐ CDP definition is not fully standardized
- ☐ qualifying baseline assessment
- ☐ valid confirmatory assessment within the required timeframe
- ☐ missing visits and rare scheduled frequency

Functional Tests

9-Hole Peg Test (9HPT)

- standardized test of upper extremity function
- 2 trials per hand: dominant and non-dominant
- Analysis often uses mean time per visit

Timed 25-Foot Walk (T25FW)

- measures mobility and leg function
- 2 trials (out-and-back); assistive device may be used. Device changes vs baseline can bias interpretation.
- Analysis often uses mean time per visit

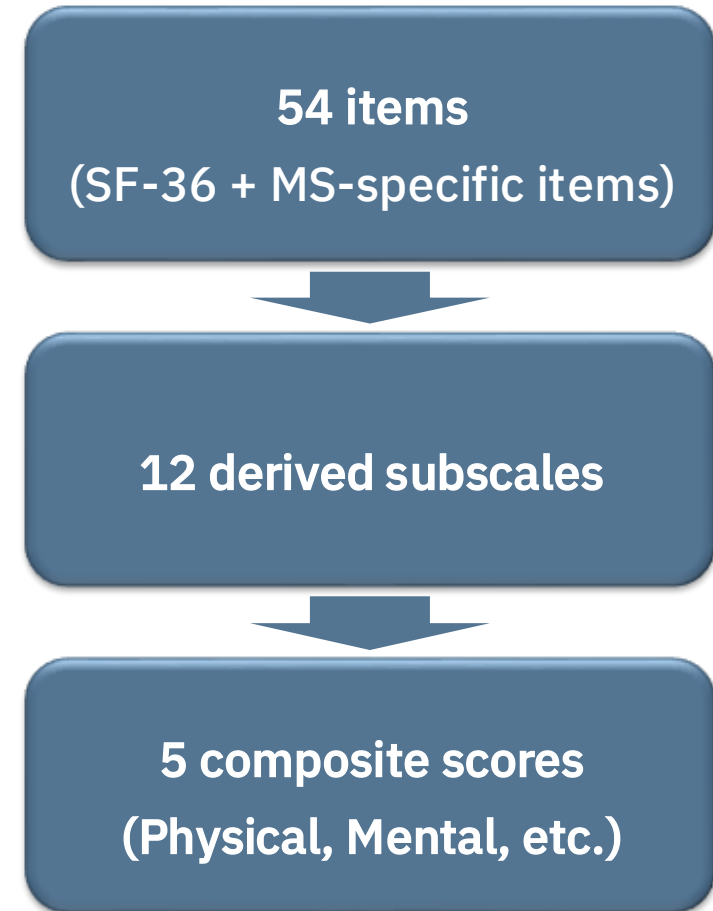
SDTM: Functional Tests (FT), Characteristics (SC) for dominant hand, SUPPFT for assistant device

ADaM: BDS (trial + mean) + 20% progression flags (if used)

Changes over time is analyzed using repeated-measures mixed models reporting estimated LS means

Patient-reported outcomes (PRO): MSQoL-54 example

- any report of a patient's health condition that comes directly from the patient
- SDTM: Questionnaires QS domain
- QRS supplement is available to help with controlled terminology and structure
- ADaM: BDS for derived subscales/composite scores (optionally keep item-level)
- analyzed using estimated LS means from a repeated-measures mixed effects model.

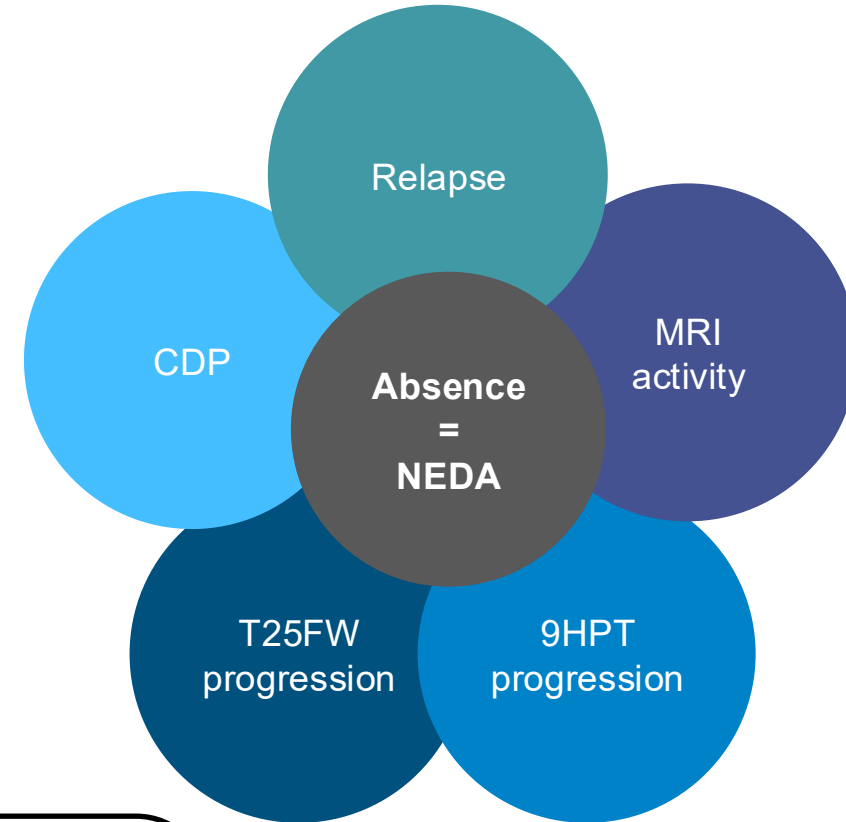
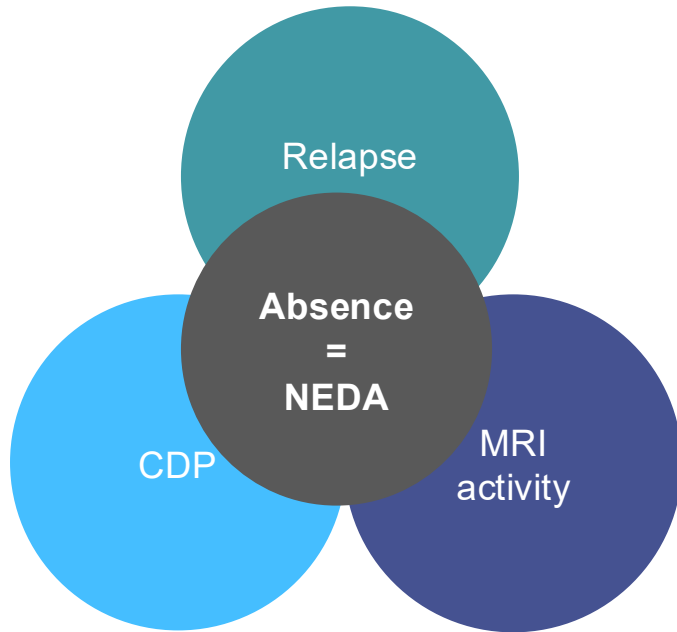


MRI: Magnetic Resonance Imaging

- key tool for assessing inflammatory activity and treatment efficacy in MS clinical trials
- Common MRI endpoints:
 - New/enlarging T2 lesion count
 - T1 Gd+ lesion count
 - CUA lesions
 - Brain volume change / atrophy
 - MRI activity flag (binary; used as NEDA component)
- analysis varies from Poisson or negative binomial regression for lesion counts to estimated LS means from a repeated-measures mixed effects model for continuous measures such as lesion volume or brain volume change.



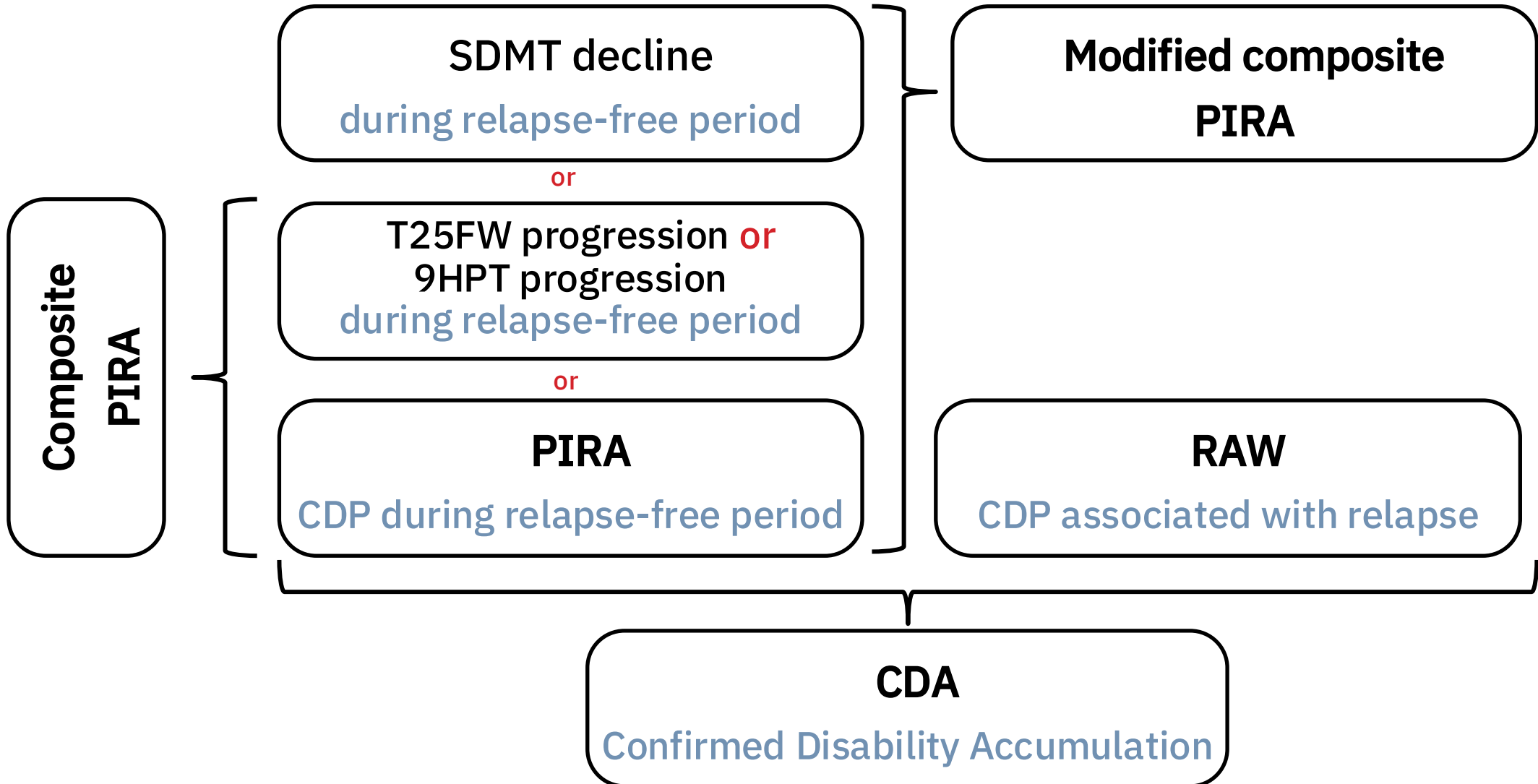
Composite endpoints



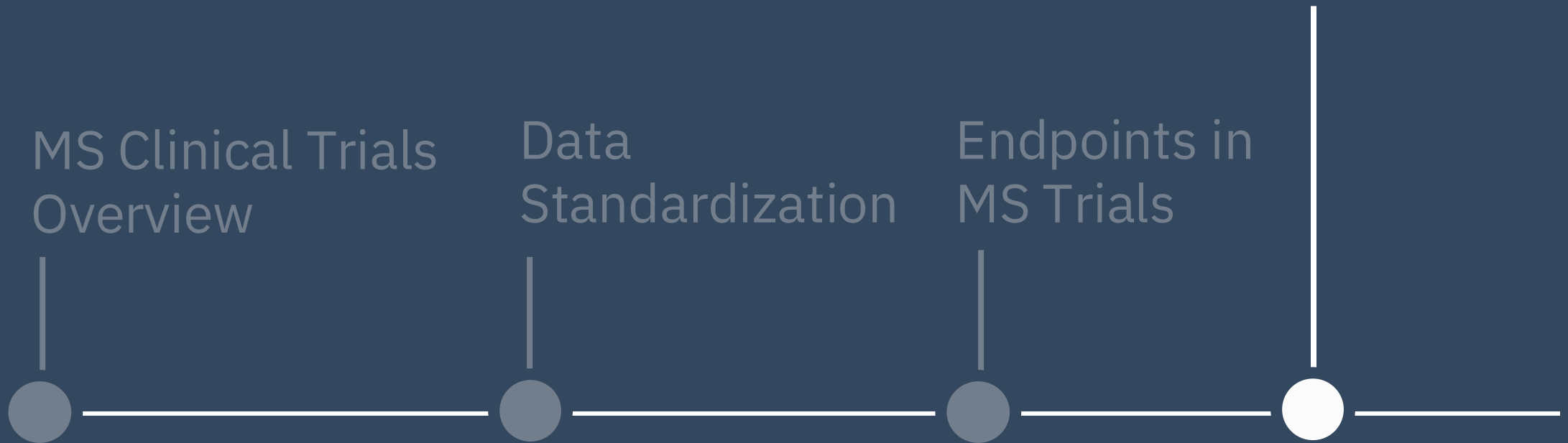
Practical Challenges

- Definition inconsistency
- Sensitivity over time
- Components frequency

Composite endpoints



Conclusion



Conclusion

- ✓ MS trials combine **multiple endpoint families**: relapses, disability, functional tests, MRI, PROs
- ✓ **Align early on the standards** to prevent rework and inconsistencies.
- ✓ Use **MS TAUG** as supportive guidance
- ✓ **Clear definitions + consistent derivations + transparent traceability** enables reproducible analyses and reviewer-ready submissions.
- ✓ Deliverables must be **clinically meaningful and technically traceable**.

Thank you for watching

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