Advancing our understanding of smouldering associated worsening (SAW) in Multiple Sclerosis (MS): The SAW index study

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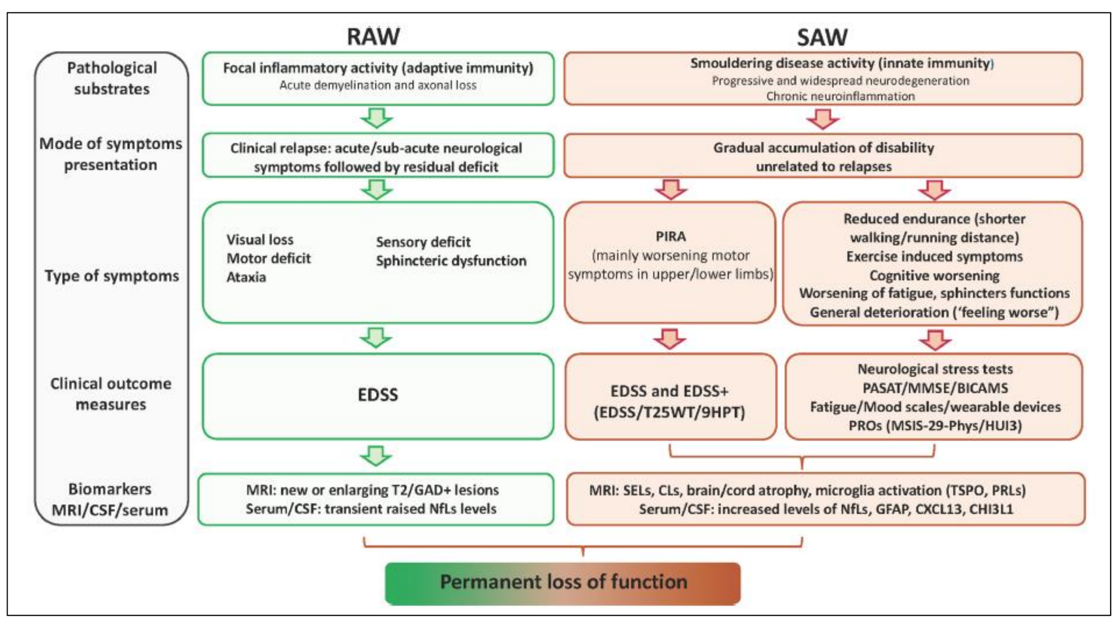
OBJECTIVE

- To describe the background & rationale of a study aimed at setting the foundations of an evidence-based SAW assessment & measurement framework.
- To highlight the requirement for detailed, targeted, longitudinal, patient-centric, qualitative research to underpin assessment & measurement instruments to enable proper assessment of SAW.
- To present the early results.

INTRODUCTION – An unmet need

- Figure 1 highlights that people with MS (pwMS) continue to experience subtle worsening across various domains despite the absence of acute inflammatory disease (relapses, new MRI T2 lesions).
- Traditional indicators insufficiently capture this worsening, which is increasingly attributed to smouldering pathological compartmentalised processes within the CNS present throughout the disease course.[1,2]
- Accurate SAW assessment and measurement – whether for identification, monitoring, treatment, or prediction – requires clarity on exactly what is changing, and in exactly what way. This is best derived first from pwMS.
- Forensic analyses of PRO measures highlight the importance of qualitative work and the need to test measurement hypotheses.
- Typically, progressive MS studies select relevant clinical variables as outcomes for measurement (e.g. disability) and then choose as outcome measures clinically relevant instruments (e.g. EDSS).
- Whilst this measurement strategy is logical, it is rarely, if ever, evidence-based enough given the magnitude of implications for pwMS and sponsors' investments.[3]
- Any measurement flaw, e.g., floor/ceiling effects, increases the probability that measured effects will underestimate true effects. [3] Moreover, the measured-effect-/-true-effect discrepancy is unquantifiable.
- This issue is less important when expected effects are large. However, if small, subtle, or slowly evolving changes and differences are expected, as manifest in SAW, misleading results and missed treatment effects are more likely.

Figure 1: Relapse and Smouldering associated worsening: The two clinical phenomena leading to permanent loss of function in MS[2]

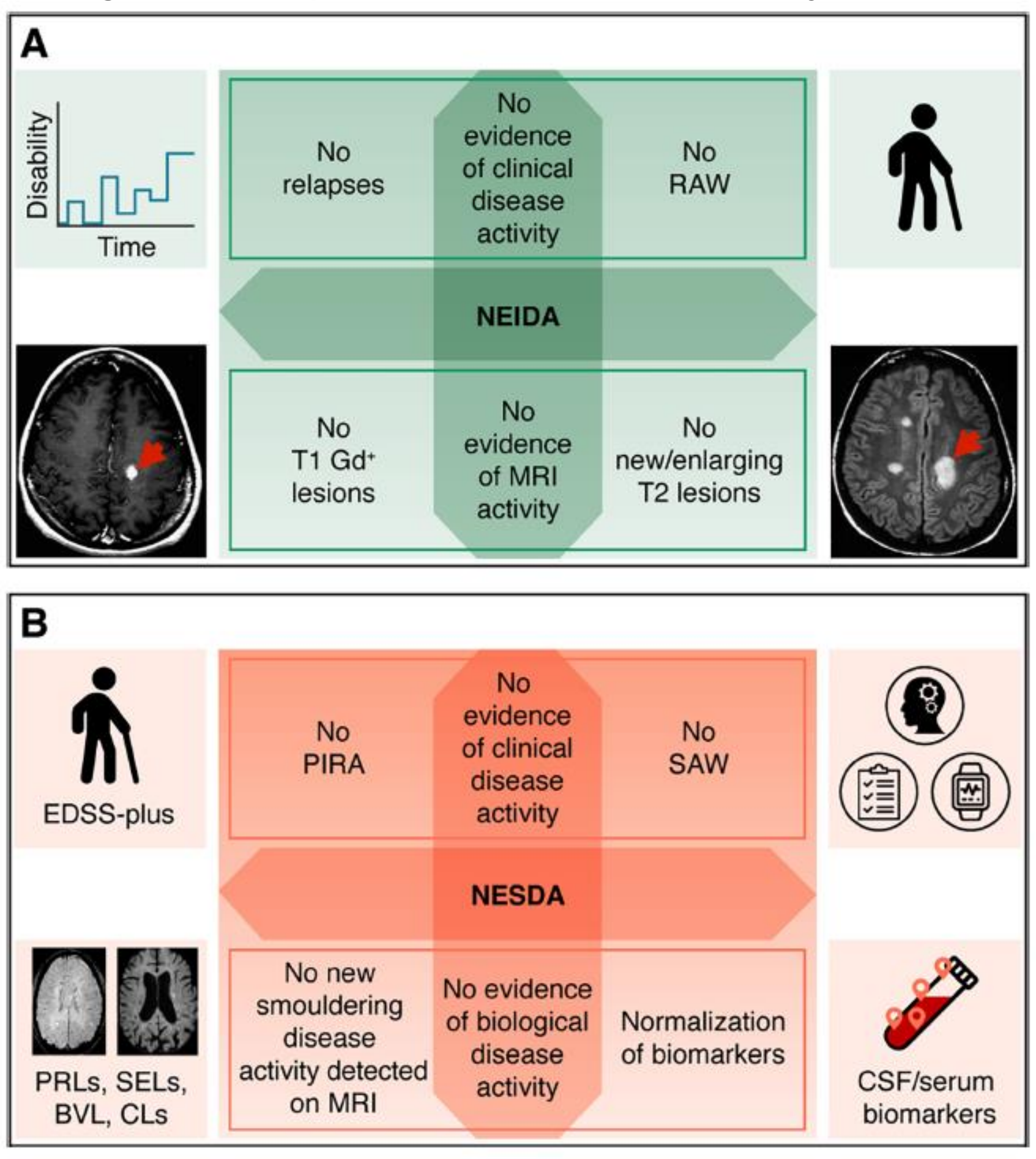


From Scalfari et al. Ann Neurol 2024;00:1–19.[2]

Different pathological substrates underpin RAW and SAW. They have different clinical manifestations. RAW can be detected with conventional methods. SAW encompasses progression independent of relapse activity (PIRA) which is restricted to changes in either EDSS scores, or performance times on the T25WT or 9-HPT. In contrast, SAW includes changes in other symptoms but requires more comprehensive monitoring and assessment not used routinely.

9HPT= 9-hole peg test; BICAMS = brief international cognitive assessment for MS; CHI3L1=chitinase-3-like protein; CLs=cortical lesions; CSF=cerebrospinal fluid; 1CXCL13=chemokine ligand 13; EDSS= Expanded Disability Status Scale GFAP=glial fibrillary acidic protein; HUI3= health utility index; MMSE=mini mental state examination; MRI=magnetic resonance imaging; MSIS-29= 29-item MS impact scale; NfLs= neurofilaments; PASAT=paced auditory serial addition test; PIRA= progression independent of relapse activity; PRLs=paramagnetic rim lesions; PRO= patient reported outcome; RAW=Relapse associated worsening; SAW=smouldering associated worsening; SELs=slowly expanding lesions; T25WT= 25-foot timed walk test.

Figure 2: Therapeutic control of disease activity in MS [2]



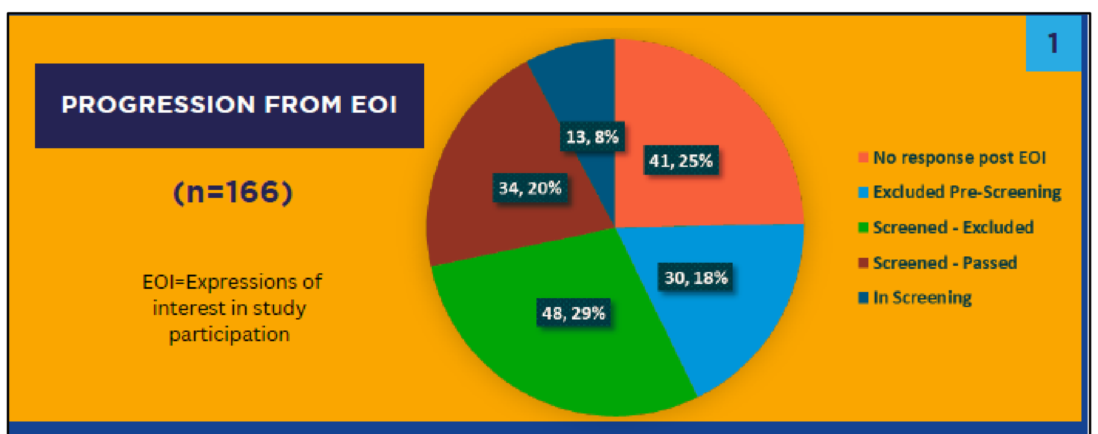
From Scalfari et al. Ann Neurol 2024;00:1–19.[2]

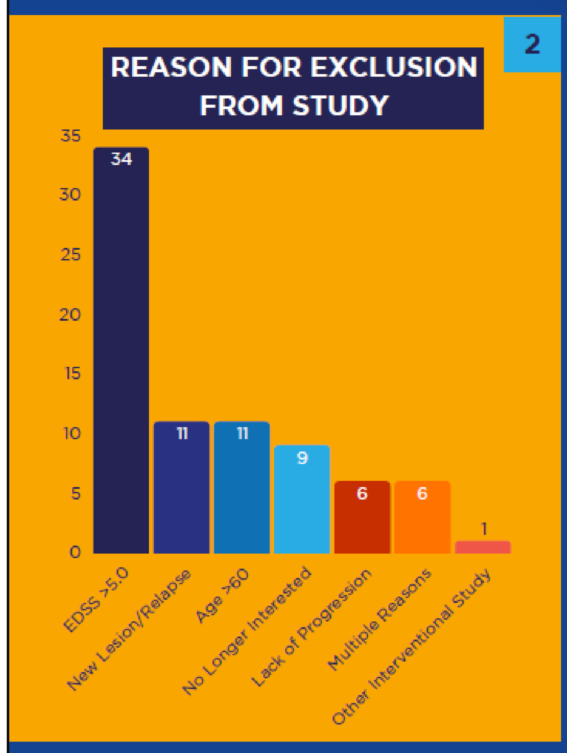
Figure 2 emphasises that future therapeutic strategies for MS will need to account for both inflammatory and smouldering disease activity; with the latter becoming the dominant goal.

A: NEIDA (No Evident Inflammatory Disease Activity) is defined as no new relapses nor MRI indicators of focal inflammatory activity (new or enlarging T2, or contrast enhancing T1 lesions).

B: NESDA (No Evident Smouldering Disease Activity) is defined as the absence of clinical evidence of SAW including PIRA. Changes related to SAW might be measured using PROs, cognitive or activity performance tests, or imaging and body fluid biomarkers; none currently widely used in routine practice.

BVLs= Brain volume; CLs=cortical lesions; EDSS-plus=EDSS + T25FW +9-HPT. PRLs-paramagnetic rim lesions; SELs=slowly expanding lesions.

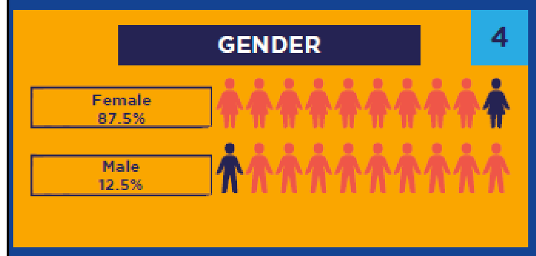




- 24 Recruited, 6 ICF's issued
- Overseas participants consented
- Additional recruitment activities underway
- EDSS >5 threshold remains recruitment challenge

ICF = informed consent form
EDSS = Expanded Disability Status Scale

DEMOGRAPHICS



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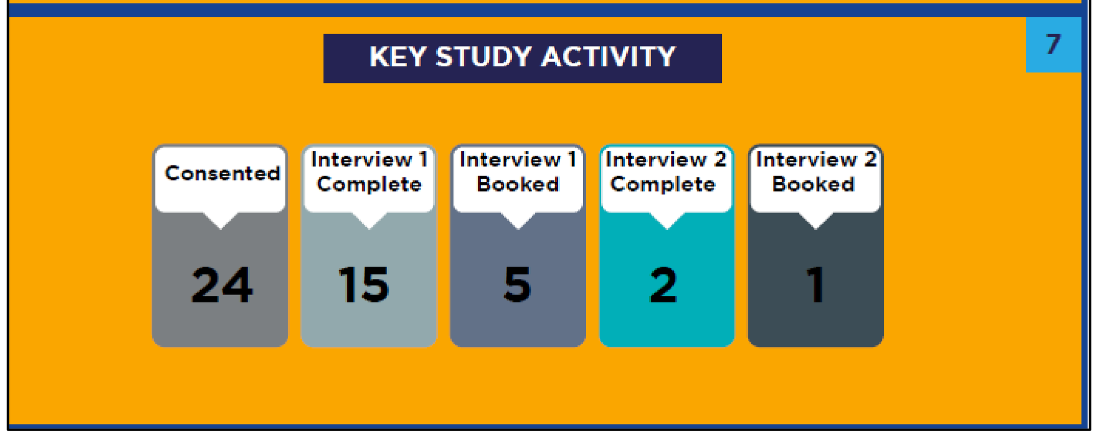
	Mean	Range
Age (Years)	49	34-59
Duration of MS (Years)	9.6	2-26
EDSS at Recruitment	4.0	2.0-5.0

RECRUITMENT GEOGRAPHY



References:
1. Giovannoni G et al. Smouldering multiple sclerosis: the 'real MS'. Ther Adv Neurol Disord 2022;15: 17562864211066752.
2. Scalfari A et al. Smouldering-Associated Worsening in Multiple Sclerosis: An International Consensus Statement on Definition, Biology, Clinical Implications, and Future Directions. Ann Neurol 2024;00:1–19.

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METHOD: Towards a methodological solution

- Detailed targeted longitudinal qualitative research – multiple interviews with multiple pwMS across multiple timepoints – offers a method for determining exactly what is affected and exactly how these change over time.
- This research method has the potential to establish evidence-based measurement frameworks, facilitate instrument choice, identify instruments limitations, inform clinically meaningful changes and differences, and provide a platform for instrument modification or development.

The SAW INDEX STUDY

- Detailed longitudinal qualitative work will be conducted in 40 pwMS and SAW across four timepoints.
- The time-points are monthly as this is a compromise between rapport building, information gathering, potential for change and the time available for the work. This also provides a cohort for continued interviewing over longer time periods.

INCLUSION CRITERIA

- Diagnosis of MS
- Age 18-60
- EDSS 2.0 to 5.0
- No relapses for 2 years or new disease activity on most recent scan

METHODOLOGICAL ADVANCES

- Typical health-related qualitative research consists of one-off interviews in a cohort of people continued to redundancy; defined as the emergence of no new concepts.
- Usually there is one interviewer, the interviews are analysed after batches or when all interviews are completed, and unclear quality control processes.
- We feel this process may be inadequate to gain the people's experience of subtle worsening across various domains.
- As such this study will:
  - ➢Have two interviewers at each interview to guide the interview process and review the information being gathered during the interview;
  - ➢Critique each interview immediately after its completion to aid development of the interviewing process.
  - ➢Edit the interview transcripts, synthesise the information for each participant, feed this back to patients to facilitate subsequent interviews.

RESULTS

- Figs 1&2 show the outcomes of those interested in participating. Many people with self-reported worsening had higher EDSS scores.
- Figs 3-5 show that 60% recruitment was achieved within 3 months and participant demographics were consistent with expectation.
- Figs 6-8 show international participation, recruits' interview status, and reported worsening was in diffuse domains and typically slight.
- These early findings are consistent with expectation implying the information gathered should provide the clearer understanding of SAW's clinical characteristics the study was intended to derive.
- Early interviews have confirmed the complexities of slow and subtle worsening in MS and the value of the methodological advances.
- Publication of the measurement framework is expected during 2025.

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