#3080 Title: A systematic review of extra-motor symptom evaluation in clinical trials for amyotrophic lateral sclerosis.

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Background:
Amyotrophic lateral sclerosis (ALS) is increasingly recognised as a multi-system disorder, presenting with extra-motor symptoms which arise secondary to motor degeneration or are indicative of wider pathophysiology. Extra-motor symptoms such as cognitive impairment, behavioural change, neuropsychiatric symptoms, sleep disturbances, fatigue, sialorrhea, and pain are common in, and impactful upon, people with ALS.

Aim/Hypothesis:
We aimed to systematically review historical clinical trials in ALS to identify if extra-motor features of ALS were explored as outcome measures and if so describe the tools used. We hypothesise that assessment of extra-motor symptoms has been largely neglected in trial design and that where evaluated, it has been with assessment tools which are not designed to evaluate these symptoms in people with ALS.

Methods:
We reviewed clinical trials of investigative medicinal products in ALS, since the licensing of riluzole. Trial registry databases including WHO International Trials Registry, European Clinical Trials Register, clinicaltrials.gov, and PubMed were systematically searched for Phase II, III or IV trials registered, completed or published between 01/01/1994 and 16/09/2020. No language restrictions were applied. We evaluated the use of assessment tools to investigate extra-motor symptom as outcome measures.

Results:
237 clinical trials were included in this review for use of outcome measures. These trials evaluated cognitive impairment (16 trials, 6.8%), behavioural change (38, 16%), neuropsychiatric symptoms (75, 32%), sleep disturbances (12, 5%), fatigue (18), 8%, saliva (182, 77%) and pain (55, 23%). 29 trials (12%) did not include any assessment of extra-motor symptoms. 51 versions or combinations of assessment tools were utilised in these trials. The most commonly used primary outcome measure in ALS trials, the ALS-FRS(R), is a physical functioning assessment with one sub-domain item assessing saliva. The ALS-FRS® accounted for the full number of trials assessing saliva in this review. 6 instruments used were ALS-specific (designed and validated specifically for people with ALS), 14 were symptom-specific, 4 were both, and 9 were generic (evaluated the symptom within a general measure, eg QoL).

Conclusions:
Extra-motor symptoms have been under-evaluated in trials for people with ALS. Where evaluated, this has been primarily using assessment tools which are not specific to ALS or the extra-motor symptom, which may affect the validity of conclusions drawn regarding the impact of candidate drugs.

PROPSERO registration: CRD42020223648