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Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials

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Study objective

To determine how eligibility criteria affect the exclusion rates, generalizability, and outcome heterogeneity of clinical trials investigating treatments for amyotrophic lateral sclerosis (ALS).

Summary results

The eligibility criteria exclude many patients with ALS, which reduces generalizability of trial results while only minimally improving the homogeneity of efficacy endpoints.

What is known and what this paper adds

ALS is a heterogeneous condition; clinical trial eligibility criteria are often designed to achieve a relatively homogeneous sample and thus improve the chances of observing treatment effects. This study provides evidence that these strict eligibility criteria are providing little benefit while potentially limiting the generalizability of results to an unacceptable extent.

Design, size, and duration

This study searched PubMed and Embase for randomized, placebo-controlled, clinical trials that evaluated the efficacies of single drugs in ALS. The publication window extended from January 2000 to November 2017. Phase I trials and trials initiated before 1996 were excluded. This study extracted the eligibility criteria and endpoint results from the selected trials. Based on the characteristics of a Dutch incidence cohort, this study determined the percentage of patients who would be excluded under each trial's eligibility criteria. Random-effects meta-analysis models were constructed to examine how eligibility criteria affected efficacy endpoints.

Participants and setting

The literature search yielded 38 suitable trials. The incidence cohort comprised 2,904 patients diagnosed with ALS between January 2006 and December 2016 in the Netherlands.

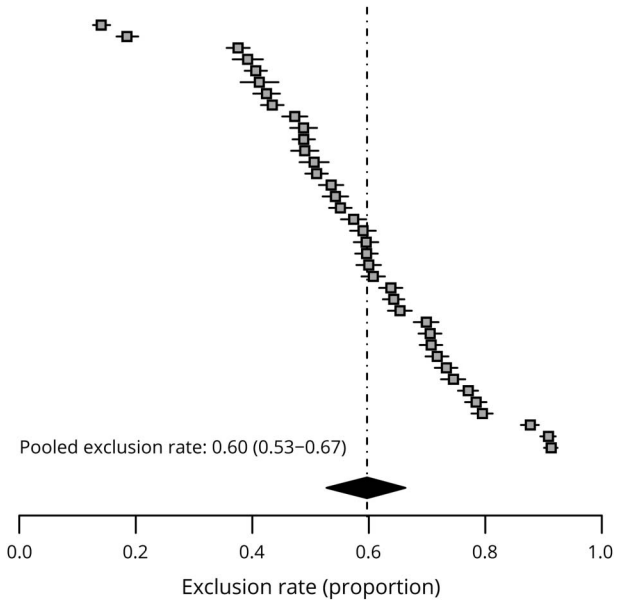
Primary outcome measures

The primary outcome was the mean estimated exclusion rate.

Main results and the role of chance

The mean estimated exclusion rate was 59.8% (95% confidence interval, 52.6%–66.7%). Various eligibility criteria neither reduced survival time heterogeneity ($p = 0.09$) nor affected between-patient variability in functional decline ($p = 0.25$).

Figure Estimated exclusion rates for 38 individual trials in a population-based cohort of 2,904 patients with ALS



Bias, confounding, and other reasons for caution

ALS is a complex disorder, and various concerns can have competing implications for eligibility criteria selection.

Generalizability to other populations

The use of a Dutch incidence cohort may limit the generalizability of this study's exclusion rate results.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

