MSR268

Latent similarity matching for external control arms:
A preregistered target trial emulation reproducing a randomized spinal cord injury placebo arm

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Can **registry-derived external controls** reproduce the placebo recovery trajectory of a spinal cord injury trial?

Study population

European Multicentre Study about Spinal Cord Injury (EMSCI) registry [1]
7,416 participants before eligibility

Randomized placebo arm from the Nogo Inhibition NISCI trial [2]
48 participants before eligibility

Target-trial eligibility criteria [3]
Age 18–70, traumatic cervical SCI, severity AIS A–D, baseline at 16–27 days after injury, eligible predicted recovery, complete covariates.

501 registry donors
37 trial participants
Eligible cohorts for matching

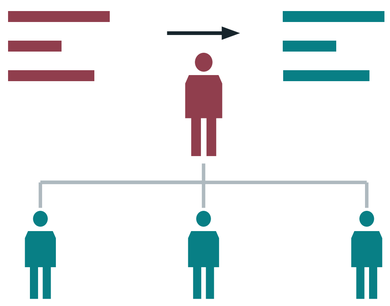
Matching

Different matching specifications

Latent Similarity Matching (LSM), PSM, CBPSM, KNNM, MDM, CEM

Baseline covariates are used to match

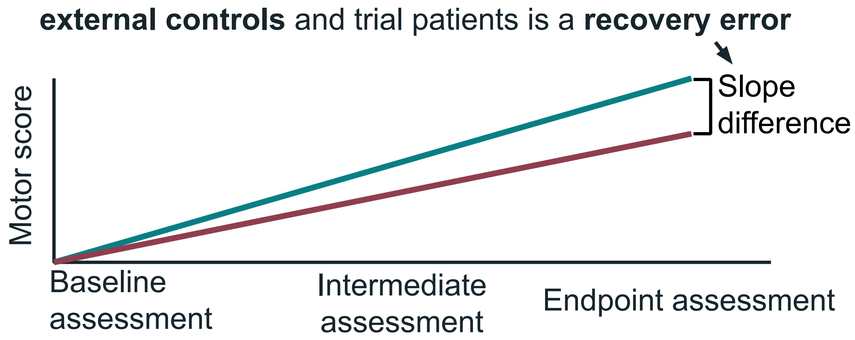
Age, severity AIS grade, UEMS, LEMS, TLTL, TPP, neurological level of injury, days after injury at baseline



≤3 matched donors per trial participant to form an **external control arm**

Recovery comparison

The **difference in modelled average improvement** in upper extremity motor score from baseline to 168 days after between **external controls** and trial patients is a **recovery error**

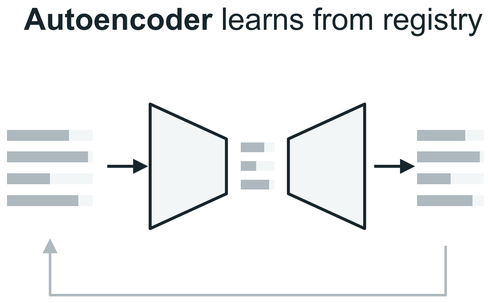


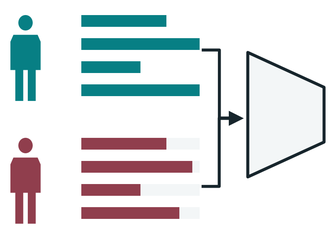
Point estimate of zero suggests no difference. **Equivalence** is established when 90% CI falls within ±4 motor score points [4].



Latent similarity matching uses an autoencoder trained on registry baseline covariates to project placebo patients into a latent space for nearest-neighbour matching.

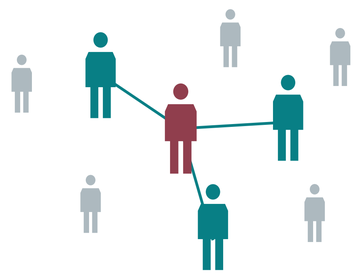
Autoencoder learns from registry



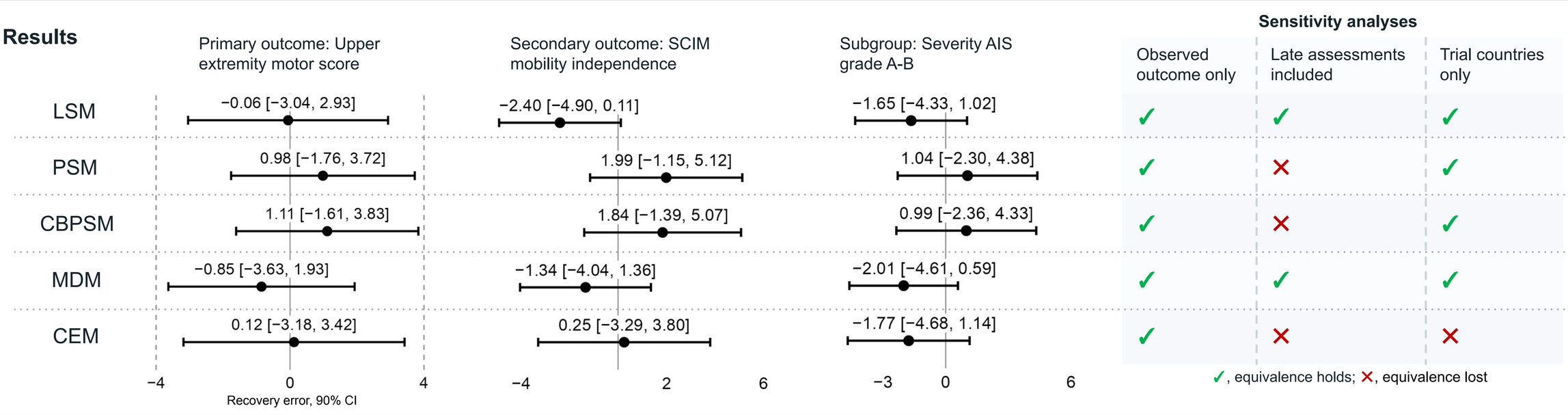


Trial participants and donors are projected on the **latent space**

Matched donors are selected based on **latent proximity**



Results



Sensitivity analyses

	Observed outcome only	Late assessments included	Trial countries only
LSM	✓	✓	✓
PSM	✓	✗	✓
CBPSM	✓	✗	✓
MDM	✓	✓	✓
CEM	✓	✗	✗

✓, equivalence holds; ✗, equivalence lost

Takeaways

- EMSCI-derived external controls reproduce the mean modelled recovery of NISCI placebos across matching methods, given eligibility, measurement, and outcome harmonization.
- Assessment timing, missing follow-up, and uncertainty estimation condition equivalence.

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[1] Bourguignon L, et al. International surveillance study in acute spinal cord injury confirms viability of multinational clinical trials. BMC Med 2022.
[2] Weidner N, et al. Safety and efficacy of intrathecal antibodies to Nogo-A in patients with acute cervical spinal cord injury: a randomised, double-blind, multicentre, placebo-controlled, phase 2b trial. The Lancet Neurology 2025.
[3] Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol 2016.
[4] Fehlings MG, et al. Rho Inhibitor VX-210 in Acute Traumatic Subaxial Cervical Spinal Cord Injury: Design of the SPinal Cord Injury Rho INhibition InvestiGation (SPRING) Clinical Trial. Journal of Neurotrauma 2018.