Leveraging External Controls from PRO-ACT for Exploratory Efficacy Assessment in Early-Phase ALS Trials

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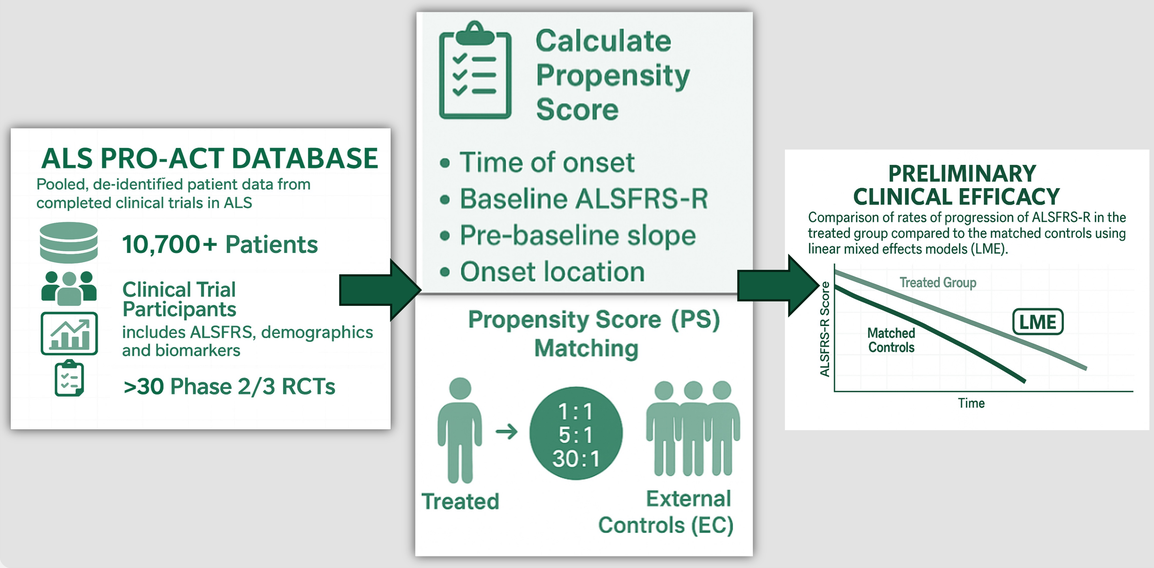
Assessment of feasibility of using external controls derived from the PRO-ACT database to facilitate preliminary efficacy assessment in early-phase, single-arm ALS trials. Through a case example with NUZ-001 and a simulation study, EC methods achieved covariate balance and yielded interpretable treatment effect estimates, supporting their role in strengthening early clinical development.

Background

- **ALS is a progressive, fatal neurodegenerative disease** with limited treatment options, highlighting a high unmet need.
- **Early-phase trials in ALS (especially Phase 1)** are designed for safety and pharmacokinetic evaluation but are increasingly expected to provide **preliminary efficacy signals.**
- These trials are often **single-arm and open-label**, making efficacy interpretation challenging without concurrent controls.
- **External controls (ECs)** using historical trial data provide a potential solution to improve comparative context.
- The **PRO-ACT database** contains participant-level data from >30 randomized Phase 2/3 ALS trials, serving as a valuable source for EC construction.
- **Propensity score (PS) methods** can adjust for population differences, improving comparability and reducing bias in EC analyses.

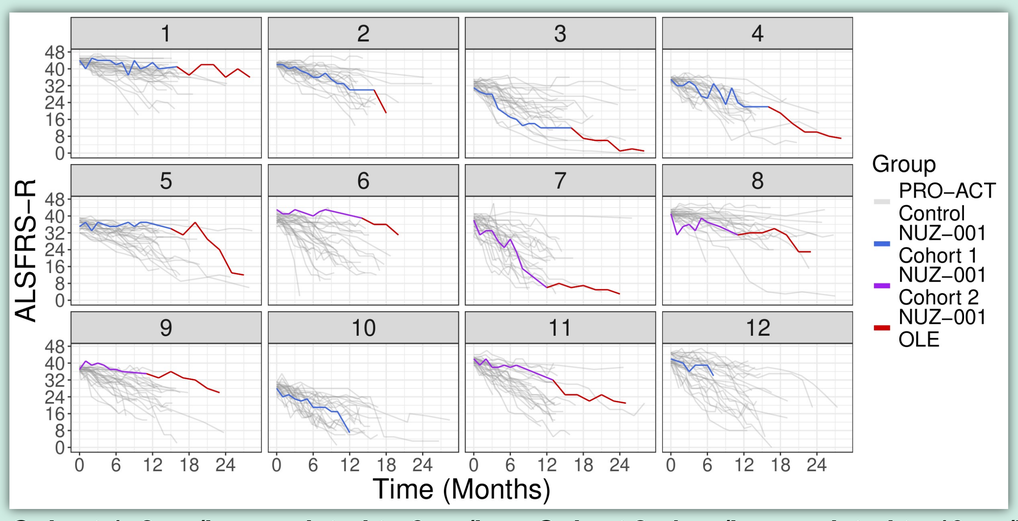
Matching procedure + Preliminary Efficacy Analysis



Motivating Example: NUZ-001 Integrated Preliminary Efficacy Analysis

- N=12 NUZ-001 treated participants from Phase 1 + OLE compared to PS matched EC from PRO-ACT
- Baseline covariates are well balanced after matching

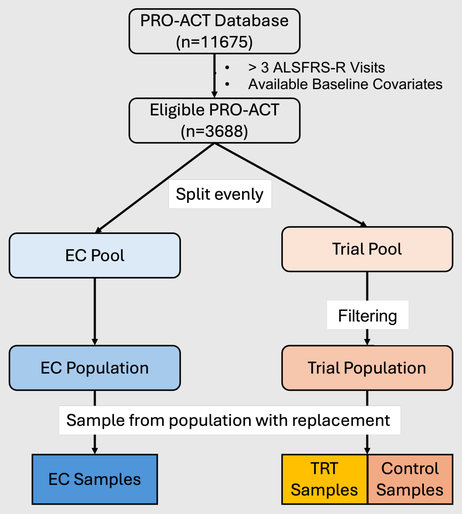
	PRO-ACT Controls (N = 360)	NUZ-001 (N = 12)
Time since Onset (Months)		
Mean (SD)	15.3 (7.27)	14.7 (8.38)
Median [Min,Max]	14.5 [3.8, 35.8]	13.9 [3.6, 34.0]
Baseline ALSFRS-R		
Mean (SD)	37.9 (4.64)	38.2 (5.10)
Median [Min,Max]	38.0 [24.0, 46.0]	39.5 [28.0, 44.0]
Pre-Baseline Slope		
Mean (SD)	0.786 (0.438)	0.826 (0.461)
Median [Min,Max]	0.733 [0.11, 2.14]	0.739 [0.21, 1.48]
Onset Location		
Bulbar	60 (16.7%)	2 (16.7%)
Other	300 (83.3%)	10 (83.3%)



Cohort 1: 2mg/kg escalated to 6mg/kg Cohort 2: 4mg/kg escalated to 10mg/kg

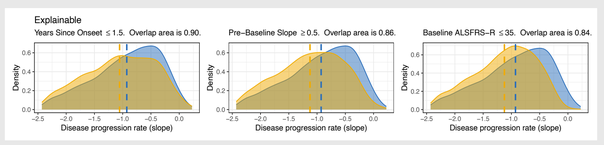
Matching analysis	PRO-ACT Control Slope	NUZ-001 Slope (N=12)	Between-group Difference	P-value (one-sided)
30:1	-1.21 (-1.30, -1.11)	-0.83 (-1.33, -0.34)	0.37 (-0.13, 0.88)	0.0725
5:1	-1.28 (-1.49, -1.06)	-0.83 (-1.33, -0.34)	0.44 (-0.05, 0.94)	0.0380
1:1	-1.26 (-1.66, -0.86)	-0.83 (-1.33, -0.34)	0.43 (-0.13, 0.99)	0.0645

Simulation Study using PRO-ACT

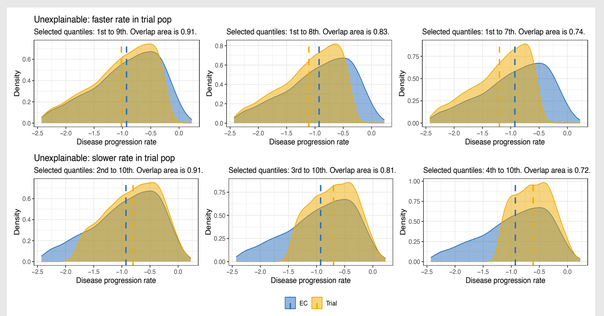


Trial population is ***filtered*** to mimic scenarios where there are ***differences in ALSFRS-R rates of progression*** compared to EC.

Explainable Differences: Filter based on baseline covariates



Unexplainable Differences: Filter based on ALSFRS-R slope quantiles



- Single arm analyses with different matching ratios are compared to RCT and naïve historical benchmark
- N=12 for single arm trial vs. N=24 (1:1 ratio) in RCT
- Treatment effects include no difference in slope (Null) and a difference in the slope of 0.40
- Average operating characteristics reported: effect estimates, power/type I error (one-sided alpha = 0.05)

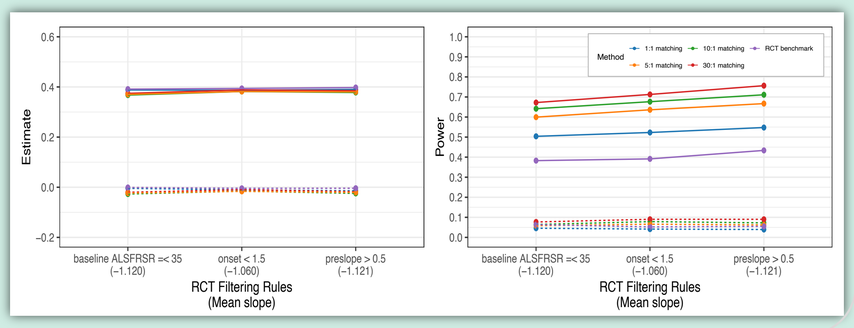
Simulation Comparison: Single Arm + EC vs. RCT for Small Phase 1 studies (N=12)

Matching results in unbiased estimates & controlled Type I Error

Power using matching increased over RCT in studies with small N. Likely due to potential for covariate imbalance in RCT.

Power increases with matched ratio.

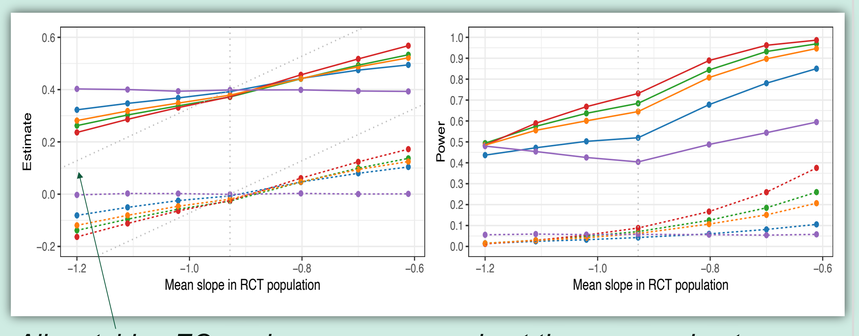
Explainable Differences between EC and Trial Population



Matching results in biased estimates & inflation in Type I Error

- *Bias small under 1:1 matching. Effect estimates range from 0.31 to 0.50 under alternative and -0.09 to 0.09 under null. Type I error increases from 5% to 10%.*
- *Bias increases with matched ratio.* *Note: May not translate to what is often done in practice where matching ratio is chosen dynamically to achieve covariate balance*

Unexplainable Differences between EC and Trial Population



All matching EC analyses are more robust than comparing to a naive historical benchmark with reductions in total potential bias of up to 67%.

Conclusions

External controls (ECs) from PRO-ACT can facilitate preliminary efficacy assessments in early-phase, single-arm ALS trials

Strengths

- PRO-ACT is a rigorously collected clinical trial database where endpoints are measured consistently with clinical trial standards, reducing potential measurement bias.
- Large pool of EC enables robust matching on key prognostic covariates.
- Known prognostic factors in ALS progression are well studied, supporting reliable adjustment methods.
- PS methods provide robust results if differences in EC and trial population are explained by covariates.
- Under the assumption of unmeasured confounders, formal matching analyses are more robust than naïve historical benchmark comparisons

Limitations

- Potential unmeasured confounders (e.g. regional differences, differences in Phase 1 and 2/3 populations) could result in unexplained differences between EC and trial data.
- In the presence of unexplained differences, PS matched analyses can result in biased estimates of treatment effects and inflated type I error. Quantification of the potential bias relative to the estimated effect size is important.
- Given the small sample size of early phase studies, preliminary efficacy analyses are underpowered and should be interpreted with caution.
- Future work is needed to explore optimal EC methods and prognostic baseline covariates

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