SITE PERFORMANCE IN AN INVESTIGATOR-RUN MULTIPLE SCLEROSIS CLINICAL TRIAL

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INTRODUCTION

The Avonex Combination Trial (ACT) was an industry-sponsored, investigator-run clinical trial that evaluated oral methotrexate and intravenous methylprednisolone as adjunctive therapies for relapsing-remitting MS patients with continuing disease activity on interferon beta-1a monotherapy. ACT observed 313 subjects for one year at 72 clinical sites.

Inclusion of community-based clinicians is a component of the NIH Roadmap for Medical Research. Although community practices increasingly are included as sites in MS clinical trials, there are few published data on their performance.

METHODS

Site Categorization

Sites were categorized as a university based clinic (n=28), multispecialty group (n=7) or community-based Neurology solo or group practice (n=37) based on Henry K, Lawyer BL, Member Demographics Subcommittee of AAN. Neurologists 2004. St. Paul: American Academy of Neurology, 2005. If there was uncertainty concerning categorization of a site, the Principal Investigator was queried.

Site Performance Measures

- Start-up speed = time from signed confidentiality agreement to site activation
- Cost = negotiated cost-reimbursement per subject
- Subject recruitment-retention (adjusted for time available for the site to enroll) = patient-days of trial participation/time from site activation to termination of ACT enrollment
- Protocol deviations = deviations per subject-year follow-up
- Data quality and responsiveness to queries = (data queries/100 case report forms) x site's mean query response time

Analytic Strategy

- The coordinating center site (Cleveland Clinic Foundation, a multispecialty group) was excluded from the analysis.
- The analytic approach utilized was intended to limit errors due to multiple comparisons
- Factor analysis for data reduction:
  - Account for variability and correlations among 5 performance measures by fewer latent variables, ignoring site type
  - Principal factor analysis, initial commonality estimates from squared multiple correlations, number of factors by Eigen value/SCREE plot, varimax rotation
  - Generate estimated scores of retained factors
- Multivariate analysis of variance (MANOVA , exact Wilks' lambda) for tests of differences of scores among 3 site types
- Step-down multiple comparison permutation sampling-adjusted comparisons of single factors and measures across site type pairs

DISCLOSURES

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See the AAN listing for detailed Conflict of Interest information.

RESULTS

Table 1. Comparison of subject baseline characteristics and on-study activity.

	University based clinics (n=28)	Multispecialty groups (n=6)	Community practices (n=37)
Patients enrolled (total, mean per site)	115, 4.1	22, 3.7	154, 4.2
Age (y, mean ± SD)	40.5 ± 6.8	42.4 ± 8.4	42.9 ± 7.5
Sex (% female)	73.9	95.5	79.2
Years from onset (mean ± SD)	8.8 ± 6.5	8.9 ± 6.9	10.4 ± 7.3
Years from diagnosis (mean ± SD)	5.7 ± 4.8	5.8 ± 4.1	7.5 ± 5.9
EDSS (mean ± SD)	2.5 ± 1.1	2.7 ± 1.5	2.8 ± 1.1
MSFC:			
T25FW (sec, mean ± SD)	5.7 ± 2.7	7.6 ± 7.7	6.7 ± 4.4
9HPT (sec, mean ± SD)	22.5 ± 5.4	24.1 ± 9.4	22.3 ± 5.6
PASAT3 (# correct, mean ± SD)	48.5 ± 11.8	48.5 ± 10.4	44.7 ± 13.9
Relapses prior 3 years (mean ± SD)	2.4 ± 1.6	2.1 ± 1.4	2.5 ± 1.5
Qualifying event:			
Relapse only (%)	60.9	50.0	60.4
GdE MRI brain only (%)	8.7	18.2	13.0
GdE MRI spine only (%)	0.9	0.0	0.7
Relapse and GdE MRI brain /spine (%)	29.6	31.8	26.0
MRI measures:			
T2-volume (cm^3, quartiles)	1.72, 5.67, 12.39	0.70, 2.24, 7.38	1.33, 4.26, 11.90
T1-volume (cm^3, quartiles)	0.21, 0.99, 3.26	0.13, 0.40, 1.28	0.14, 0.67, 2.96
BPF (mean ± SD)	0.816 ± 0.024	0.819 ± 0.025	0.814 ± 0.024
GdE lesion number (mean ± SD)	0.58 ± 1.82	0.36 ± 1.14	0.53 ± 1.50
Percent with ≥1 GdE lesion	20.0	14.6	22.4
N/E T2 lesions (mean ± SD)[9]	2.0 ± 3.2	1.9 ± 3.1	1.2 ± 2.7
Relapse rate (pooled estimate ± SE)[9]	0.37 ± .07	0.68 ± .14	0.35 ± .06

[9]From multiple imputation of missing or incomplete data.

Figure 1. Comparison of site performance (1=university, 2=multispecialty, 3=community).

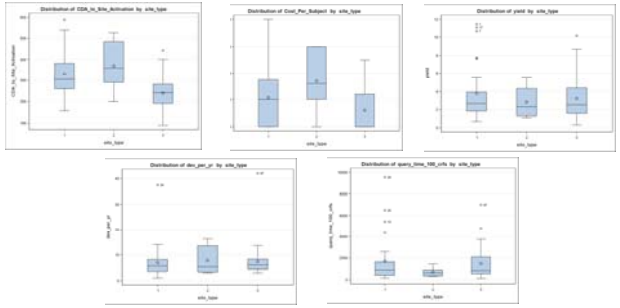
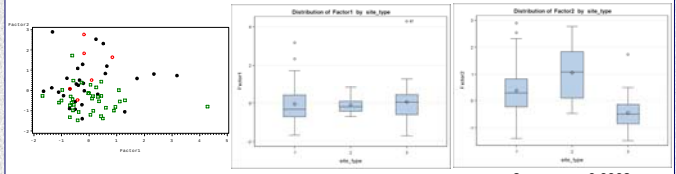


Figure 2. Factor Analysis identified two latent factors.
- Factor 1 "Study execution" was high when enrollment-retention low, protocol deviations high, queries high/response slow.
- Factor 2 "Pre-study" was high when start-up speed was slow and cost per subject was high.

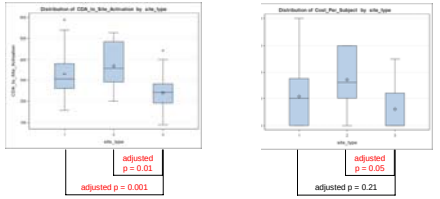


3-group p = 0.89 3-group p = 0.0003

Table 2. Factor 2 differences are from community neurology practices.

Permutation-adjusted site-type joint comparisons of Factor 2 (start-up speed and per-subject cost)		
Site types compared		p - value
University-based	Multispecialty	0.33
University-based	Community neurology	0.004
Multispecialty	Community neurology	0.003

Figure 3. Community practices vs. other site types on Factor 2 performance measures.



CONCLUSIONS

- Although subject baseline characteristics were comparable at university-based clinics, multispecialty groups, and community neurology practices, on-study activity differed.
- Aggregate performance did not suggest systematic differences in simple measures of site performance based on subject recruitment-retention, adherence to protocol, and data quality and responsiveness to queries .
- Community practices initiated more rapidly than university-based clinics and multispecialty groups and accepted lower per-subject reimbursement than multispecialty groups.