estimates. Iteration continues until convergence. We extend this algorithm to include nonlinear effects on each outcome for age, gender, education, APOE4 genotype, A β, tau, and their interactions. Covariates are selected for each outcome at each stage of the iteration based on the Akaike Information Criterion using a generalized additive model approach. Outcome measures considered include assessments (ADAS13, MMSE, FAQ, and RAVLT), MRI brain volumetrics (hippocampus, ventricles, and entorhinal cortex), CSF (A β, tau, p-tau), and PET (PiB, Florbetapir, and FDG). **Results:** Similar attempts at this estimation have stratified by covariates or ignored them altogether. Our current approach will allow closed form, as opposed to bootstrap, estimation of important covariate effects for each outcome. Covariate adjustment for age is particular important since our progression curve estimates span 20 years. **Conclusions:** The proposed method provides improved estimates of long-term progression curves, interrogation of covariate effects, and inspection of different patterns of progression.

F3-02-03 OPTIMALLY WEIGHTED ENDPOINTS FOR CLINICAL TRIALS IN MILD COGNITIVE IMPAIRMENT AND PRE-CLINICAL ALZHEIMER'S DISEASE

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Background: Composite endpoints formed by combining scales or subscales from existing clinical, functional, and neuro-psychometric assessment batteries have been proposed as primary endpoints for clinical trials of mild cognitive impaired (MCI) as well as pre-clinical Alzheimer's disease. However, composites constructed by a simple summing or averaging of the component scale scores may fail to properly utilize information contained in the subscale data compared to optimally weighted composite scales determined through reference to formal statistical models. **Methods:** We present an approach for determining optimal composite weights that maximize the signal-to-noise ratio of change score outcome measures. The algorithm assigns weights to the different components by taking into account trial design, the correlation structure among the component scales, and the longitudinal progression rates of the individual components. We illustrate by way of example the potential improvement in efficiency of optimally weighted composite endpoints versus other proposed or implemented composites using placebo arm data from the Alzheimer's Disease Cooperative Study (ADCS) clinical trial of donepezil and vitamin E in MCI subjects [N Engl J Med 2005;352]. Efficiency is characterized as the relative statistical power or sample size required to detect treatment effects assuming a mixed model repeated measures analysis of a two arm clinical trial with equal allocation to both arms. **Results:** Optimally weighted composites consistently outperformed composites constructed using alternative weights. For example an optimally weighted composite of the Clinical Dementia Rating scale sum of boxes (CDR-sb) pooled with items 1, 4, 7, and 8 of the Alzheimer's Disease Assessment Scale (ADAS) reduced sample size required to power a 36 month trial by 14.4 percent compared to the unweighted composite score. **Conclusions:** Formal statistical metrics that characterize the relative performance of outcomes measures can be used to derive optimally weighted clinical trial endpoints. Such optimally weighted composites can substantively improve the efficiency of clinical trials, reducing the sample size or trial duration required to establish a treatment effect and increasing the probability that effective treatments will be identified.

F3-02-04 USE OF INTRA-INDIVIDUAL DISTRIBUTIONS OF DAILY ACQUIRED HOME-BASED MEASURES INCREASES RCT SENSITIVITY

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Background: Trials in Alzheimer's disease are increasingly focusing on prevention in asymptomatic individuals. This poses a challenge in examining treatment effects since currently available outcome measures are not optimally sensitive to detect cognitive decline or trial-induced improvements. Consequently large sample sizes are required for randomized controlled trials (RCTs). More sensitive outcomes and better statistical approaches are needed. We aimed to develop a new metric sensitive to improvement/decline in functional outcomes by using individual-specific distributions (as opposed to group-norms). We used unobtrusively monitored in-home data, which allows us to collect enough data points to generate individual-specific distributions of functional outcomes such as computer usage and walking speed/variability within a short duration of time (e.g., 3 months). Our objective was to compare sample sizes required to achieve sufficient power to detect prevention trial effects in two scenarios: (A) annually assessed neuropsychological test scores modelled as a function of time using mixed effects models (a conventional approach), and (B) the likelihood of hitting subject-specific low performance thresholds modeled as a function of time using generalized mixed effects models. **Methods:** 114 subjects enrolled and followed over 3 years in the Intelligent Systems for Assessing Aging Study at Oregon Health & Science University. Using the difference in empirically identified time slopes between those remaining normal during the follow-up (normal control, NC) and those who transited to mild cognitive impairment (MCI), we estimated sample sizes required for achieving 80% statistical power for detecting 20% (i.e., the difference in time slopes between NC and MCI will be reduced by 20%), 30% and 40% treatment effects. **Results:** Sample size estimates indicated approximately 2000 subjects with a follow-up duration of 3 years would be needed to achieve 30% effect size if the outcome is memory test scores (Logical memory scores). If the outcome is hitting low threshold of walking speed (10 th %tile of individual-specific walking speed), 262 subjects are required. For computer use (40 th %tile low use) 26 subjects are required. **Conclusions:** Individual-specific thresholds of low functional performance based on high-frequency in-home monitoring data distinguish trajectories of MCI from NC and could reduce sample sizes in prevention RCTs.

TUESDAY, JULY 15, 2014
FEATURED RESEARCH SESSIONS
F3-03
TRAUMATIC BRAIN INJURY AND NEURODEGENERATIVE DISEASE: FROM EPIDEMIOLOGY TO BIOMARKERS

F3-03-01 TRAUMATIC BRAIN INJURY AND DEMENTIA RISK: AGE AND SEVERITY MATTER

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Background: There is conflicting epidemiological evidence regarding the importance of traumatic brain injury (TBI) as a risk factor for dementia. Few prior studies have used non-TBI trauma (NTT) patients as controls and age/severity stratification. **Methods:** In this retrospective cohort study, we assessed dementia-free survival in adults diagnosed with TBI versus NTT. Using a California state-wide emergency department (ED) and inpatient database, we identified all patients aged $\geq$55 diagnosed with TBI (based on ICD-9 code Center for Disease Control (CDC) definitions) or NTT in 2005-2006 who survived the hospitalization. Subjects with baseline dementia (based on validated inpatient ICD-9 code definitions) were excluded. The primary outcome was a new ED or inpatient ICD-9 code diagnosis of dementia $\geq$1 year after the initial trauma during the follow-up period ending in 2011. The association between TBI and dementia was estimated using Cox proportional hazard models before and after adjusting for known dementia predictors and pre-specified interactions and also stratified by TBI severity (mild vs. moderate/severe based on ICD-9 code CDC definitions) and age category (age 55-64, 65-74, 75-84, and 85+). **Results:** The cohort included 165,655 trauma subjects, of whom 51,792 (31%) had TBI. Over the study period, 9.2% of TBI patients developed dementia versus 6.2% of