radioligands with high affinity and low degree of homogenous nonspecific interaction.

IC-P-084 USE OF AN FDG-PET-DERIVED HYPOMETABOLIC CONVERGENCE INDEX ENRICHMENT STRATEGY TO REDUCE SAMPLE SIZES IN ALZHEIMER'S DISEASE CLINICAL TRIALS: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)

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Background: While the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is commonly used to measure cognitive decline in probable Alzheimer's disease (pAD) and mild cognitive impairment (MCI) patients, rates of decline vary. We previously introduced a single index, Hypometabolic Convergence Index (HCI), to characterize the extent to which the pattern and magnitude of cerebral hypometabolism in a person's fluorodeoxyglucose-positron emission tomography (FDG-PET) image corresponds to that in pAD patients. Here, we used data from ADNI to examine the extent to which 1) a person's baseline HCI predicts cognitive decline using the ADAS-Cog, Mini-Mental State Exam (MMSE), Clinical Dementia Rating-sum of boxes (CDR-SB) and Auditory-Verbal Learning Test (AVLT-Total), and 2) the HCI could be used to enrich clinical trials for clinical decline and reduce the number of patients needed to detect a treatment's clinical effects. **Methods:** Baseline HCIs were computed for 120 MCI and 54 mild AD patients who had up to 24-month data. We first characterized the extent to which HCIs correlated with 12-month and 24-month clinical declines. We then estimated the sample sizes needed to detect an AD-slowing treatment's effects on ADAS-Cog before/after enrichment for those patients with HCIs greater than the predetermined threshold of 13.82 for pAD and 8.19 for MCI (Chen et al., 2011, *Neuroimage*) with 80% power, 0.05 type-I error and a 25% treatment effect. **Results:** In pAD, HCIs correlated ($p <= 0.05$) with subsequent ADAS-Cog, MMSE, CDR-SB and AVLT-Total 12-month (24-month) decline ($r =$ 0.42(0.47), -0.35(-0.55), 0.28(0.29), -0.40(-0.43), respectively). In MCI, HCI also correlated with subsequent decline at 12-month (24-month) ($r =$ 0.33(0.32), -0.43(-0.50), 0.29(0.37), -0.17(-0.32), respectively). HCI enrichment is estimated to reduce the number of pAD patients needed per treatment arm to detect an AD-slowing treatment's effect on ADAS-Cog from 406 to 243 in a 12-month trial and from 168 to 137 in a 24-month trial. Similarly, it is estimated to reduce the number of MCI patients from 1,718 to 749 in a 12-month trial and from 926 to 374 in a 24-month trial. **Conclusions:** Baseline HCIs could be used to predict subsequent clinical declines in pAD and MCI patients and to reduce the number of patients needed to detect an AD-slowing treatment's effects in randomized clinical trials.

IC-P-085 TARGETED RECRUITMENT USING CSF BIOMARKERS: IMPLICATIONS FOR ALZHEIMER'S DISEASE TRIALS

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Background: Trials of therapies designed to target Alzheimer's disease (AD) pathology typically use clinical diagnosis as an inclusion criterion. Enrollment of patients without AD pathology may dilute treatment effects. Therefore there is interest in introducing biomarkers into trial entry criteria to reduce sample sizes. One possible biomarker is cerebrospinal fluid (CSF) Aß1-42, which is inversely related to deposition of amyloid protein in the brain and this is thought to be a sensitive biomarker early in the disease course. The aim of this study was to identify AD outliers based on CSF Aß1-42, to describe their characteristics and assess the implications of their exclusion on clinical trial sample sizes. **Methods:** Subjects with clinically-defined AD and baseline CSF were identified from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Using a previously-estimated CSF Aß1-42 cut-off (192pg/ml) we dichotomised this group into high-Aß-AD and low-Aß-AD subgroups. We compared high-Aß-AD individuals to the low-Aß-AD group using APOE e4 status. We estimated sample sizes for clinical trials based on brain and hippocampal atrophy rates, ventricular expansion rates, and ADAS-Cog 13 change calculated over 12 months with and without excluding the high-Aß-AD subjects. **Results:** Seven of 82 subjects were defined as high-Aß-AD. Only one of these seven was APOE e4 positive, compared with 76% of the low-Aß-AD group ($p < 0.002$). Change in MRI measures and ADAS-Cog 13 against CSF Aß1-42 are shown (figure). Sample size estimates based on atrophy rates were borderline significantly lower (9-12%) when excluding the high-Aß-AD individuals. Analogous estimates based on ADAS-Cog 13 were lower (6%) by excluding the high-Aß-AD subject, however this was not statistically significant (table). **Conclusions:** Clinically-diagnosed AD subjects with high CSF Aß1-42 levels may have atypical AD, or alternative underlying pathology. Using CSF biomarkers as inclusion criteria for AD may reduce required sample sizes and reduce the risk of exposing patients without amyloid pathology to treatment side-effects. However approximately 10% more subjects would need to be screened to allow for exclusion of high-Aß-AD individuals. This study provides support for the drive towards biomarker-led diagnostic and trial entry criteria.

Sample sizes for a trial to detect a 25% absolute reduction in atrophy rate / ADAS-Cog (13) with 80% power.

Outcome	Sample size (all ADs with CSF) (1)	Sample size (ADs with Aβ 1-42 $<$ 192 pg/ml) (2)	Ratio (2)/(1)
Whole brain	70 (52, 106)	62 (46, 95)	0.88 (0.63, 1.00)
Ventricles	108 (78, 160)	96 (70, 143)	0.89 (0.67, 1.00)
Hippocampi	77 (55, 112)	69 (49, 104)	0.91 (0.72, 1.01)
ADAS-Cog (13) [a]	544 (347, 1028)	513 (326, 984)	0.94 (0.74, 1.06)

95% BCa bootstrap confidence intervals in brackets

a, data unavailable for ADAS-Cog 13 in four (low-Aβ-1-42) subjects