Study Title: Antidepressant Response in the Treatment of Depressive Symptoms and Frailty Characteristics in Older Adults

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**Statistical Analyses:**

The data analyses utilize linear mixed effects regression since this approach can handle missing data and the correlation of repeated measurements within the individual. Mixed effects models using maximum likelihood estimation provide valid inferences in the presence of ignorable nonresponse. I will be trained by Dr. Marcus to use Supermix software written by Donald Hedeker and Robert Gibbons for the analysis of longitudinal data using mixed-effects linear regression. To test Hypothesis 1, I will use linear mixed effects regression of depression score across time as a function of frailty deficit group (those with specific frailty deficits=1, those without deficits=0), 3 time dummy variables (time1=1 for week 8 and 0 otherwise, time2=1 for 6 months and 0 otherwise and time3=1 for 12 months and 0 otherwise) and the interaction of group by time dummies, with a random effect for repeated measures within the individual. I will use a contrast within this model to estimate and test the significance of the difference in outcomes between those with and without deficits at the end of the Acute Phase (8 or 16 weeks). Hypotheses 2 (outcome: total frailty characteristics) and 3 (outcomes: WHODAS2.0, SPPB, ECog, actigraphy scores; IL-6, CRP, serum albumin levels) will be tested in a similar way. The contrasts to test Hypothesis 3 will evaluate the deficit vs. non-deficit differences at 6 months and at 12 months (end of the Follow-up). The relationship between baseline impairment in domains of cognition and frailty characteristics will also be explored.

The power analysis for Aim 1 and Aim 2 is based upon the calculations for longitudinal models given by Hedeker and colleagues, with 4-time points assumed (0, 8 weeks, 6 months and 12 months) for the trend line. A two-group design and a random-effects structure with random slope, residual term and autocorrelated residuals, ICC=0.3 and a 5% attrition rate between each pair of assessments are assumed. Tests are 2-tailed with $\alpha = .05$. To test a between groups linear trend effect, 30 subjects per group at baseline will provide sufficient power to test for a moderate effect (a between groups difference increasing linearly from 0 at baseline to .6 SD units). I recognize the limitations of using pilot studies to guide power calculations for future R01. The proposed study however will be sufficiently powered to determine whether the effect size is clinically meaningful, i.e. an effect size that is somewhat larger than moderate is likely to be clinically meaningful.