Risk Evaluation and Education for Alzheimer's Disease – the Study of Communicating Amyloid Neuroimaging (the REVEAL-SCAN Study)

Statistical Analysis Plan

April 29, 2021

National Institutes of Health/National Institute on Aging: RF1 AG047866

ClinicalTrials.gov Number: NCT02959489

REVEAL SCAN Analytical Strategies
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Aim 1: To determine whether disclosure of elevated brain amyloid will bias ADCS-Preclinical Alzheimer Cognitive Composite (ADCS-PACC) test results and subjective memory.
Study Subjects: Those who are Amyloid positive (A+)
Outcome: ADCS-PACC, measured twice (6 wks., 6 mos.) (primary), and subjective memory measures Metamemory in Adulthood Questionnaire and Memory Functioning Questionnaire (secondary), measured twice (6 wks., 6 mos.)
Primary Hypothesis 1.1: At 6 months after disclosure, ADCS-PACC scores will be lower among A+D+ participants than A+D- participants.
Primary Analysis 1.1: For this aim we focus on one outcome, ADCS-PACC, and thus use an alpha level of 0.05 to determine statistical significance. First, we will obtain descriptive statistics for those who are in the D+ and D- groups among A+ subjects. Then, we will compare ADCS-PACC scores between D+ and D- groups among A+ subjects using a two-sided test of means. Next, we will compare D+ and D- groups on potential confounders. We will initially consider confounders due to the Covid-19 pandemic (as described below) and then consider other confounders (including age, education, premorbid function, experiences of discrimination). If any are significantly different between the two groups ($p < 0.05$), despite randomization, we will conduct regression analysis adjusting for those confounders that are different. Analyses will be repeated measures (6 wks. and 6 mos.) adjusting for baseline measure at time of randomization. We will focus on 6 month differences, but also check for time-averaged differences between D+ and D- groups. Check ADCS-PACC for normality. If normal, linear regression analysis for repeated measures can be used, specifically a mixed-effects model with repeated measures (MMRM). If not normal, we will use an appropriate transformation to make the distribution more normal. We will also conduct an Intention-to-Treat (ITT) analysis, which will incorporate information from those who drop out over the 6 months, assuming missing at random. This analysis will have better control of type 1 error and power. We will model time as a categorical measure, and the primary outcome will be the estimated difference (contrast) between the two groups (D+ and D-) at 6 months and secondarily the time-averaged difference. We will also apply a model with 3 repeated measures (baseline, 6 wks., 6 months) without adjustment for baseline ADCS-PACC to examine the full trend over time, but this will be a secondary analysis.

Analysis 1.1 if we do not reach planned sample size: Our plan for this study is to recruit 270 subjects who would be randomized equally to D+ and D- groups. With 10% loss, we expect 120 subjects in each group with about 50% being A+ due to enrichment of *APOE* e4+ participants. Thus, there would be ~60 people in each of the four groups: A+D+, A+D-, A-D+, A-D-. For Aim 1, we powered the study to detect a difference between the A+D+ and A+D- groups. With 60 subjects in each of these two groups, we have 80% power to detect a difference of 1.15 ADCS-PACC points. After pursuing this plan for several years we found that the expected 50% split between A+ and A- participants was too optimistic and in fact we found that the proportion of A+ subjects enrolled in the study was hovering between 25% and 30%, thereby reducing the numbers available for evaluation of Aim 1, the primary research question for the study. In June, 2018, we applied for a supplement to this research project to aid us in attaining needed sample size for Aim 1. We revised our estimated sample size needed for Aim 1 to be 50 in each group (A+D+, A+D-), determining that we could detect a moderate meaningful difference of 1.2451. If we are not able to attain the sample size that we expect (~50 in each group), we will conduct an analysis of the existing sample. If the result is significant, we then had more power than we thought we might; that is, the difference between the two groups was greater than 1.2451. If the difference between the two groups is not significant, we will examine the confidence interval for the difference to obtain a range of estimates of possible differences, given our sample size.

Outliers: Components of the ADCS-PACC and the overall score will be examined for outliers. We will exclude values that are more than 2 standard deviations from expected mean values (based on the literature). In addition, we will consult visit notes and TOMM scores to see if anything unusual might be a factor in the outliers.

Missing PACC data: Some participants may be missing or have invalid components of the PACC. If missing more than 1 of the PACC components, the participant will be excluded from analysis. If missing 1 or fewer of the PACC components, we will conduct multiple imputation analyses to fill in missing values. Multiple imputation datasets will be derived and analyses will combine results over the imputed datasets, following standard procedures for imputation. For a sensitivity analysis, we will also conduct an analysis excluding these individuals.

Adjusting for Covid-19: The Covid-19 virus impacted the tail end of our study; as a result some visits did not occur when planned. For example, the 6 month visits ranged from 3 months to 14 months. Thus, our primary analysis will adjust for the actual time of the visit. In addition, we will include a dichotomous variable indicating whether the visit occurred after March 15, 2020 or not, since the existence of the Covid-19 virus, a widespread, acute psychological trauma, may have affected the study participants' responses. We will examine the impact of the Covid-19 virus prior to considering other confounders that might impact the results. As a benchmark of comparison, we will also conduct an analysis using the categorical times of the planned visits. Likewise, we will also conduct an analysis that excludes observations after March 15, 2020.

Secondary Hypothesis 1.2: A+D+ participants will have higher scores on scales of subjective memory complaints than A+D- participants.
Secondary Analysis 1.2: Two instruments have measured subjective memory: (1) Metamemory in the Adulthood Questionnaire (108 questions) with two subscores and (2) Memory Functioning Questionnaire (64 questions) with 5 subscores. Thus, these two questionnaires result in 7 different scores. Results from all 7 are summarized in Lineweaver et al paper (2014). Lineweaver et al used two-way MANOVA on all 7 and then proceeded to two-way ANOVA for each of the 7. We plan to conduct this same analytical plan.

Exploratory Hypothesis 1.3: Differences in PACC scores between disclosed and non-disclosed will be larger for African American participants than all other race groups combined.
Exploratory Analysis 1.3: The analysis will be the same as the primary analysis, but now conducted only in the African Americans in the study. If the hypothesis is true, we expect a larger difference, but the study is not powered for this subgroup analysis. To formally test whether African Americans have a greater response, we will perform analyses of the full group of A+ individuals, adding an interaction term to the model for race * disclosure group.

Aim 2: To determine whether disclosure of elevated brain amyloid will cause psychological distress.

Study Subjects: All Study Participants and the subgroup of A+ subjects
Outcomes: IES (Impact of Event Score), measured twice (6 wks., 6 mos.), and INI-AD, measured twice (6 wks., 6 mos.)
Hypothesis 2.1: At 6 weeks after disclosure, A+D+ participants will have greater IES scores and INI-AD scores than A-D+ or D- participants.

Analysis 2.1: Analysis will generally use the same methods as Aim 1. For this Aim, IES is the primary outcome for which we will use an alpha level of 0.05. INI-AD is a secondary outcome. Our main focus for this aim is contrasting scores between the A+D+ and A-D+ groups. We will also contrast the A+D+ and the D- groups (as long as the A+D- and A-D- exhibit similar outcomes). As in Aim 1, we will obtain

descriptive statistics between the two groups (A+D- and A-D+ for the first contrast and then A+D- vs the D- group). We will also evaluate the confounding effect of Covid-19 as described in Aim 1 and subsequently other potential confounders for these contrasts and incorporate if needed in further regression analyses. Note that there is no IES at baseline. So there is no adjustment for a baseline measure. The same holds true for INI-AD. One major difference here is that the IES and INI-AD are not normally distributed and cannot be transformed to become so. Thus, we will use generalized linear models fit with generalized estimating equations using a log link and a gamma distribution. If needed, we will add a value of 1 to all scores to shift the distribution away from zero and use a log transform on the data. We will focus on the differences at 6 weeks, but also evaluate the time-averaged differences.

Exploratory Hypothesis 2.2: Comparison of outcomes at 6 weeks and 6 months after disclosure will show African Americans to be equally vulnerable to psychological distress as measured by IES and INI-AD after amyloid imaging compared to all other racial and ethnic groups.

Exploratory Analysis 2.2: Analyses will be the same as described above for IES and INI-AD applied to the subgroup of African Americans. To formally test whether effects are the same, we will add an interaction term to the model for race to evaluate whether African Americans experience similar distress as those in the study who are not African American.

Aim 3: To explore how amyloid imaging disclosure will impact preventative health behaviors, advance planning for health (e.g. long-term care insurance decisions) and well-being (e.g. stigma, quality of life and relationships).

Study Subjects: All Study Participants, contrasting D+ and D- participants. Additionally, we will compare the A+D+ subjects to the A-D+ subjects.
Outcomes: We will focus on outcomes at 6 months of follow up after disclosure.

Measures: We have several categories of behavior to examine.

1) Preventive Health Behaviors: diet, vitamin intake, physical exercise and mental exercise, medication changes
2) Advance Planning: long-term care insurance decisions, other insurance decisions, completion of advance directives
3) Well-being: stigma, quality of life and relationships, sharing of information

Aim 3 Hypotheses:

Preventive Health Behaviors:
D+ individuals will show equivalent probability of undertaking preventative health behavior changes as D- individuals.

A+D+ individuals will show a higher probability of undertaking more preventive health behavior changes than A-D+ individuals.

Advance Planning:
Advance planning will occur with a similarly low frequency in D+ and D- individuals.

Advance planning will occur more frequently for A+D+ individuals than A-D+ individuals.

Well-Being:
D+ individuals will report more sharing of information than D- individuals.
Sharing of information will not differ between A+D+ and A-D+ individuals.

D+ individuals will report more stigma compared to D- individuals. This effect will be modified by amyloid status. A+D+ individuals will report more worries about stigma than A-D+ individuals.

D+ individuals will report similar QOL compared to D- individuals. This effect will be modified by amyloid status. A+D+ individuals will report lower levels of quality of life than A-D+ individuals

Aim 3 Analyses: While we will examine each measure individually, our primary analysis will focus on aggregate summary measures for: 1) any preventative health behavior changes made over 6 months since disclosure that the participant reports, and 2) any advanced planning measures taken over the 6 months since disclosure. Separate bivariate analyses will be conducted for each of these summary measures. For 1) and 2), we will contrast the D+ and D- groups using chi-square statistics. We will also contrast the summary measures in the disclosed group by those with elevated and not elevated brain amyloid. We will conduct multivariable logistic regression analyses to control for any variables that appear to be confounders. We will use follow-up analyses to elucidate factors driving significant main effects.

For 3) Well-being, we will examine group differences in each stigma, quality of life and relationships, sharing of information at 6 months post disclosure. We will examine mean differences between groups on two measures of stigma (AD concern since learning risk/amyloid & Social Impact Scale) and conduct outlier analyses to identify potential predictors of extreme responses. We will use ordinal logistic regression to examine differences in quality of life as measured by an estimate of the impact of risk estimate/PET. To examine relationships and result sharing, we will use two-stage models to examine (a) decisions to share with others and (b) levels of satisfaction with this sharing. Analyses of decisions to share information will include a participant's sharing of each a risk estimate and an amyloid test result. Binary outcomes will be examined using unadjusted proportions and adjusted odds ratios. Analyses of satisfaction will include rank ordered levels of satisfaction with decision to share, of sharing a risk estimate, and of sharing an amyloid result. We will contrast groups defined by disclosure and amyloid status.

Adjusted models will control for measured factors unbalanced across study groups and baseline values will be assessed as predictors of Aim 3 outcomes. All Aim 3 analyses will be conducted in the full group and also in the subgroup of disclosed study participants. Prior to analysis we will check that all model assumptions are adequately met. If not, we will adjust the analysis plan accordingly. Since these are exploratory analyses, we will use an alpha level of 0.05 to assess statistical significance. We will report estimates and their respective 95% confidence intervals.