**DIABETES COG**

**Statistical Analysis for Specific Aim 2:**

We will address Specific Aim 2 using a modified version of the Specific Aim 1 approach, including Phase 1 summary statistics and Phase 2 statistical models. We will test **Hypothesis 2**, whether there is a significant effect of race on the slope of cognition after adjusting for cumulative mean hemoglobin A1c levels and other covariates, by fitting linear mixed effects models to assess change in cognitive function over time using pooled data from three clinical trials. GCP will be treated as the primary outcome and EF and Memory as secondary outcomes. The main effect of interest when testing **Hypothesis 2** will be associated with a race by time interaction and whether this effect is attenuated by introducing a cumulative mean hemoglobin A1c by time interaction into the basic model.

**Assessing treatment effects:** We will determine whether the effect of cumulative mean hemoglobin A1c on cognitive slope differs by sex, age, diabetes treatment type (none, metformin, insulin or other) or clinical trial by introducing interaction terms into the basic model.

**Missing Data:** The clinical trials made significant effort to minimize participant loss, including the implementation of monitoring activities and development of retention subcommittees. Some covariate and outcome data is still missing due to non-response and selective attrition. We will impute missing covariate data under the assumption that it is MAR and investigate how the analyses could be affected by MNAR data (Little and Rubin, 2019) We will also identify covariates associated with time-to-death to include in our models and perform sensitivity analyses to model the effects of non-response bias, missing covariates and death.

**Statistical Power Considerations:** Power calculations for Hypothesis 2 were performed using the approach proposed by Galecki and Burzykowski (2013) and Stroup et al. (2018). Given that data from ACCORD, DPPOS and GRADE were not available, variance components associated with harmonized GCP needed for calculations were obtained using the pooled cohort data identified in Aim1. The estimates of standard deviation are: =0.09 for random slope,=4.8 for random intercept and =3.4 for residual error. With the projected sample size of more than 8,588 adults and an average of 2 observations per adult, we estimate more than 90% power (alpha=0.05) to detect an anticipated attenuation by 0.01 points per year of a difference between the GCP slopes of Blacks and Whites by adding A1c by time interaction term into our basic model.This effect on a difference in slopes can also be expressed as a ratio relative to the corresponding standard deviation of the slope variation (0.11= (0.01/0.09)). Considering a decline of ≥0.5 standard deviations in harmonized GCP to be clinically meaningful [refs needed], we are well positioned to detect the effect of interest.

**C2c. Potential Problems and Alternative Strategies to Achieve Aim 2**

We may be unable to account for all cultural, economic, educational and biologic factors that contribute to racial differences in cognitive trajectories. However, we will account for proxies of education quality, socioeconomic status and vascular risk factors to the best of our abilities. Adherence was self-reported in ACCORD and GRADE, although each trial educated participants on the importance of taking medication as prescribed and collected actual glucose levels over time. Pill containers were inspected in DPPOS, with 72% of participants adhering to metformin. Dementia data was not initially collected in any clinical trial but may become available for us to examine as a secondary outcome. ApoE genotype was assessed in DPPOS and will be examined as a covariate in sensitivity analyses. Sensitivity analyses examining duration of insulin use at baseline (<10 vs ≥10 years) and excluding participants with moderate microvascular disease at baseline will also be performed. Hispanic participants will be excluded from the pooled clinical trials. Racial differences in attrition and number of cognitive assessments could influence cognitive trajectories and will be examined.