Summary of discussion from EC meeting on 5/5/16 and additional thoughts.

- Need to know the effect of vitamin D on everyone (n=2400) to conduct the necessary subgroup analyses.

- 25OHD level stabilizes within 6 months. M12 is the best time-point to assess change in 25OHD, which is also before most of the outcomes develop.

- 25OHD assay is stable and standardized, and differences are expected to be large between placebo and intervention groups. However, running all time-points (e.g. BAS, M12) in the same analytical run is always preferred.

- In a representative subgroup [N=1200, 1/2 of the cohort], we can check 25OHD at BAS, M12 and M24 to demonstrate stability over time and to use in relation to other outcome (e.g. Cholesterol change). **This is something we can do now** ~$72k without indirects). That would be good use of the ADA grant money (also, overhead is low for ADA so a grant dollar stretches further…). Per protocol, results will not be provided to participants. The BAS result from the 1200 participants can enter Table 1 Participant Characteristics for the combined cohort (what everyone sees) and by group (what the DSMB sees) to determine whether our predictions for baseline 25OHD level were correct and 25OHD is the same between placebo and vitamin D. Change over time will not be disclosed unless the DSMB needs that information during interim analysis of the primary outcome.

- In the remaining participants (N=1200), we will run the 25OHD measurements at BAS and M12 visits only. This will be done in 2 batches as sub-cohorts of 600 participants each complete the M12 visit.

- We will split a few control samples and run them at each run to control for any changes – this may not be necessary as the lab likely does this (will get info and find out CV for between assay of total 25OHD)

- Consider measuring cholesterol profile in the same sub-cohort (N=1200, BAS, M12 and M24), ~$40k without indirects and hsCRP (don't know cost). These can all be done at Tufts at the same time as 25OHD.

- What else can we measure in this sub-cohort?
  - Measurement of labs (vitamin D [intervention], cholesterol, hsCRP, insulin [outcomes]) at M12 or M24?

- M12 advantages
  - Obtain data (e.g., CRP, disposition index) before disease manifests and competing events (e.g., statin use, metformin use) influence results
  - Ability to compare to other studies in the literature. Many stop at M12.
  - Allows for earlier data analyses and publications (relevant only if analyses are robust)

- M24 advantages

    - Longer follow up and exposure to vitamin D will provide better data on efficacy (compared to M12). Based on Tromso study and other studies, long-term exposure is required to alter pathophysiology.
    - Earlier time points (e.g. M12) will be influenced by the effect of weight loss on both vitamin D and outcomes of interest. Therefore, the full effect of vitamin D supplementation may not be appreciated.
    - More stable data (effectiveness over efficacy)
    - Still adequate time for data analyses and publications

- Measuring both M12 and M24 advantages
    - Measuring half of the cohort (in a representative way that reflects the characteristics of the entire cohort) for the same cost as a single time point (M12 only),
    - Power likely adequate (1200 vs. 2400)
    - Repeated measures may provide a statistical advantage.