ICAP Call Minutes

Monday December 8th, 9am EST

Hosts – [redacted] and [redacted] of ICAP

Alcohol Trial group attendees – [redacted] and [redacted]

Also attended by the industry leaders representing ABI, Suntory, and Heineken, among others

1. **RECAP FROM** [redacted]

- **Previous Research** - For 30-40 years people who drink alcohol in moderation have a lower risk of developing heart attacks and DM. The problem (meaning the reason this has not lead to medical recommendations) with those studies is that they are entirely observational. There have also been small and intermediate term trials, where alcohol level is dictated by the investigator. These have gone from as short as a couple of weeks to a year in duration. None have looked at heart disease since they have been too short and small. This is not considered gold standard evidence to lead the health recommendations .
- **NIAAA** – Is a branch of NIH that funds the largest amount of alcohol related research in the world. It is for this reason the preeminent funder anywhere. Much of the research is concerned with addictions and problems related to alcohol intake.

  They now want to investigate the relationship between alcohol intake and lowered cardiovascular and diabetes risk to see if it is casual. They have provided our team with two small planning grants which has allowed us to bring together a group of experts with whom we will work to determine how best to structure this project.

  Should it secure funding, it will release RFA to conduct a large clinical trial. NIAAA would be a partner in helping to run the trial. meaning we will need to undergo all of the standard scientific review required for all federally funded research in the US.

- **What would a trial look like? -** It would be a randomized, multicenter, trial. Individuals interested in the trail will come the field centers and sign a consent form. They will be at high cardiovascular risk (so we can conduct this in a 5yr period). They would fall in an intermediate category of drinking a little, but less than daily. They would be randomized to not drink at all or to drink daily for 5 years.

  We will provide support and monitoring to make sure they stay close to their assigned arm. It's ok if there is some decay, but we want to prevent this as much as possible. Over the course of their participation, we will monitor for primary and secondary outcomes and for safety outcomes.

Timeline - Each individual will be active in the study for 5 of the total 10yrs. There will be 6 months of ramp up. There will be a vanguard period, which means, for the first year, we will roll the trial out at a smaller number of sites and monitor recruitment rates. This gives us the opportunity to measure feasibility, and initiate course correction. (In a pilot study – you determine feasibility, but conclude and start the main study new, so all initial data is lost). There will be 3 years for enrollment, so the last person would finish the trail around year 8. The last two years are for data analysis and publication.

Making assumptions based on rates of the recruitment criteria and accounting for drop out and non-compliance, we will need to recruit 13,950. Ppts will come in every 6 months for biomarker measurement, and we will monitor hospitalizations. On a regular basis, we will administer (by web or phone), timeline follow back for alcohol consumption. We will also use GGT and HDL biomarkers to determine if the groups are different to the extent that we would expect. There will be compensation for ppts time and effort, and reimbursement for alcohol purchases.

External review board will monitor un-blinded data throughout the project to look for significant benefit/risk to the intervention and stop if in the best interest of the ppts.

Investigators on the team now, are the best people to help us build the protocol, and are not necessarily representative of all the sites we will involve. They have conducted very complex clinical trials to change diets or take combinations of various drugs.

2. QUESTIONS

- **ICAP, [redacted] – Can you clarify the role of fNIH and NIAAA?**

  [redacted] – We plan to follow the normal NIH procedures for funding a clinical trial. We will release an RFA calling for the consortium to respond to the request for this trial, and it will be reviewed by an external scientific committee.

  fNIH – Decides whether this is something that they would want to take on, and works with the funders to ensure that the contractual arrangements are mutually acceptable. When they acknowledge the funding, it will go to a NIAAA grant number. There may also be the opportunity to contribute fund directly to NIAAA.

- **ABI, [redacted]** –How does the vanguard model impact cost?

  [redacted] – There are two advantages of this "scale up" model. 1) The primary outcomein the vanguard would be hitting recruitment goals and broadly seeing difference in biomarker between the two groups. If we don't see convincing data then we stop the trial. The early years in a trial are usually more costly due to need to hire and build infrastructure, so the costs from launch through the vanguard would likely be similar to the yearly cost going forward. 2) This structure also allows course correction for the rate of of outcomes and its relationship to target recruitment numbers (ie. If the rate is higher we can adjust the total recruitment down and save $/time).

[redacted] - Also, each site will need to present their budget and justification at the outset of launch, and it will be reviewed/approved by NIAAA.

- **ICAP,** [redacted] – What is the anticipated timing of when it would come to NIAAA for review?

  [redacted] – It's likely that the funding opportunity will be released in early 2015, with the group funded by mid-late 2015.

- **ICAP,** [redacted] **–** Would you think that the CDC or someone else may pick up the idea and go a different way with it?

  [redacted] – Yes, we have been approached by different groups, and some of these groups have very different motives eg. investigating the relationships btwn alcohol and breast cancer.

  [redacted] – I am often defending the J shaped curve. Some people also want to prove there is no affect.

- [redacted] **, ?** – How will the monitoring and the screening work?

  [redacted] – Screening during the trial will occur every 6 months when we will measure information related to safety and outcome end points. In between visits, we will monitor for problems and encourage adherence by administering timeline follow-back. These will be proctored in the way that the ppts are asked trigger questions to help them recall relevant behavior . This practice is commonly used in alcohol addiction trials.

- **ABI,** [redacted] – What is the dissemination plan of releasing research results?

  Ken – This will depend on what happens during the trial. There will be a 1yr ramp up, 2-3 years of enrollment, 5 years of active intervention, followed by 2 years of analysis and publication. The protocol would be the only initial publication, along with some smaller ancillary studies. From the beginning of the vanguard period through year 8, we could publish studies on the physiological outcomes related to alcohol intake. However, we wouldn't have access to the data to publish final results, until the last few years of the study.

- **ABI,** [redacted] Can you describe the data availability to be shared with other researchers? What happens to the blinded data after the study? And will there be any differentiation btwn wine, beer, and spirits?

  [redacted] – We will need to make data available a year after the study concludes, and we can do so in the form of controlled data sets.

  The question we are asking is, "Does drinking one drink daily alter risk for heart disease and DM vs. not all?", so we will not separately randomize ppts to different alcoholic beverages (partly bc we believe that giving the ppts this freedom of selection will help with compliance). However, since we will be recording what people are doing, we will be able to ask the question of whether

there is a difference between the groups who consume different types of alcohol. If we were to separately randomize to different groups the study would need to be much larger/longer.

[redacted] Data would be deposited in a repository... (inaudible)

- **Suntory, ?** – Is the funding source going to impact the interpretation of the results by external agencies?

  [redacted] – We will be running the study in conjunction with NIH/NIAAA who is the biggest source of data for the WHO. As long as that firewall is established between industry, and the design/ management of the trial, it should remove doubt.

- **Suntory, ?** - Can you speak to the integrity of the self-reported data?

  [redacted] – That is the standard for how we conduct all stage 3 clinical trials. We do not observe the ppt receive the intervention, but rely on them to follow instruction and use reporting tools to provide compliance data.

- **Suntory, ?** – Is the intention to publish results even if they are less desirable eg. negative or mixed?

  [redacted] – Yes, however the peer review comments from the initial analysis of our study design were that we will most certainly see an impact for DM and we are not enrolling people of high risk for breast cancer.

  [redacted] (ICAP) - ICAP in principle requires that there be publication regardless of the results.