Participants:
Ray Anton, Medical University of South Carolina, Chair
Arnie Aldridge, RTI
Henri-Jean Aubin, Hôpitaux Universitaires Paris-Sud
Dan Falk, NIAAA
Deborah Hasin, Columbia University, Wednesday Only
Henry Kranzler, University of Connecticut Health Center
Raye Litten, NIAAA
Karl Mann, Central Institute of Mental Health
William Martin, Alkermes
Roger Meyer, Penn State Hershey College of Medicine
Charles O’Brien, University of Pennsylvania
Stephanie O’Malley, Yale University School of Medicine
Tanya Ramey, NIDA
Bernard Silverman, Independent Consultant
Maria Sullivan, Alkermes
Celia Winchell, FDA
Katie Witkiewitz, University of New Mexico
Lindsay Snyder, Parthenon Management Group

Summary of the Meeting:

1. New members and guests were welcomed to the meeting.

2. **Review/Highlights of NESARC – WHO Shift Data – New Findings:** D. Hasin provided an update on the cardiovascular outcomes by change in WHO risk drinking level, NESARC-III (2012-2013) cross-sectional data on differences in risk levels and multiple outcomes, and results of interaction tests of potential demographic and clinical moderators of results on shifts in WHO risk levels between NESARC Waves 1 and 2, and risk for alcohol dependence at Wave 2. **ACTION ITEM:** D. Hasin agreed she would explore creating cohorts of patients in a dataset of VA patients, although her work with these data is just starting under the auspices of a new study and so the idea of the cohorts cannot be completed immediately. **ACTION ITEM:** D. Hasin will circulate ideas and analyses for demographic and clinical characteristics as moderators of WHO shifts relationship to alcohol dependence data to the group and will address each set of these analyses separately during the future ACTIVE Steering Committee Calls. **ACTION ITEM:** D. Hasin will redo the analyses for blood pressure/hypertension.

3. **Review Highlights of WHO Drinking Level Change Stability Over Time:** K. Witkiewitz discussed that Boston University published a summary of her “Maintenance of World Health Organization Risk Drinking Level Reductions and Posttreatment Functioning Following a Large Alcohol Use Disorder Clinical Trial” article. The summary was published in the NIH-supported newsletter *Alcohol, Other Drugs, and Health: Current Evidence (AODH).* K. Witkiewitz discussed new findings on stability of WHO risk level reductions and (lack of) moderation by AUD dependence severity. **ACTION ITEM:** K. Witkiewitz will send a copy of the stability of WHO risk level reductions up to one year post treatment by AUD severity (COMBINE) to the group once it is completed. **ACTION ITEMS:** K. Witkiewitz agreed to analyze how the abstinent only and reduced-drinking patients, short of abstinence, differ on craving, as well as at other issues influenced by executive function, such as neuropsych testing. K. Witkiewitz also agreed to look at individuals who maintained treatment in 1-2 years and people who abstained.
4. **Discussion On the Level of Shift In Clinical Trials and Effect Sizes**: R. Anton discussed the level of shift in clinical trials and effect sizes. The group discussed effect size differences, sample sizes, and the meaning of more conservative findings being found that originally planned.

5. **Update on PRO Measures**: S. O’Malley updated the group on her planned phone discussion with Elektra Papadopoulos on PRO craving and alcohol consequence measures, including using existing PROMIS measures in trials as other measures mostly misses data on how people behave in clinical trials. The group discussed measures on consequences and alcohol use, including loss of control, craving, etc. as well as measures of use. The group agreed that there is need to come up with a way to capture data on craving and consequences from the patient’s perspective that that shows what the patient feels is distressful in an assessment in a way that is measurable and valid. The group agreed that more data on these assessments within the context of clinical trials is needed. in order to add alcohol use questions as an easier way to monitor drinking. A suggestion was made to addend the PROMISE questions (e.g., the Alcohol Use and Negative Consequences items) to some ongoing NIAAA funded studies.

6. **Follow Up of Initial FDA Meeting**: D. Falk provided an update on the FDA’s request for additional information on the Timeline Followback (TLFB) Measure. The initial dossier that included background material was submitted in November 2018. The FDA requested detailed information the TLFB from which WHO endpoints are derived. D. Falk and R. Litten worked with Mark and Linda Sobell, creators of the TLFB, to review and provide feedback on the response. ACTIVE submitted a Clinical Outcomes Assessment (COA) Qualification Plan on August 29, 2019 that included proposed use, context, how it was administered, as well as reliability and validity. D. Falk provided an overview of the TLFB, which is a widely used, self-report, retrospective, semi-structured interview to assess daily alcohol consumption in clinical trials. The group agreed that it is important to note that alcohol TLFB calendar methods are written in the EMA guidelines.

   **a. Next Steps**: D. Falk and R. Litten were told it would first be reviewed for “completeness” prior to any scientific review of it and that most submissions are returned for lack of completeness. On October 22, 2019, the FDA completed the initial assessment for reviewability and are currently drafting a response. Unfortunately, some key review team members were out of town at a conference until the end of the week, which caused some delays. As of November 12, 2019, the FDA noted that their response is being cleared so notification should be provided shortly (no response as of December 10, 2019).

7. **New Data on Employment and Labor Outcomes Related to WHO Risk Drinking Shift in the COMBINE Study**: A. Aldridge provided an update on analyses that evaluate the relationship between reductions in WHO risk drinking levels from baseline (pre-COMBINE treatment) to the treatment period and subsequent labor market outcomes. Samples from the COMBINE study were examined that were made up of participants in the eight pharmacological treatment arms, during and at the end of the 1 year period following COMBINE treatment (using sample 1) and over 3 years following randomization (using sample 2). **ACTION ITEM**: A. Aldridge will look at absenteeism and presenteeism and noted that it is a complicated relationship, as abstainers who do not drink can still state that they are missing work due to the disorder. **ACTION ITEM**: A. Aldridge will look at the distribution and remove abstainers from the data. This could potentially be a two-part analysis: 1) did you miss any days and, 2) of this smaller sample, how many days did you miss? The group discussed that this small group may not divide well into the WHO risk reduction groups.

   There was a discussion on obtaining population data from Denmark suggested by Dr. Mann. It was concluded that more information is necessary to determine if this data is germane to the ACTIVE mission and informs reduced drinking in relationship to improved health and economic issues. **ACTION ITEM**: A. Aldridge will contact the individuals with the Danish dataset, and K. Witkiewitz agreed to
assist. A. Aldridge will follow up with the group on next steps on a future ACTIVE Steering Committee Call.

2. **WHO Drinking Level Change and Economic Issues in the COMBINE Trial Paper Update:** A. Aldridge discussed target journals to submit the paper, including if it needs to be a narrower field journal. The group discussed potentially submitting to *Economics & Politics*, with a target audience of health services researchers, but the group was unsure if industry and industry consultants read the journal. The group discussed that a target audience might be health policy individuals, managed health professionals, and/or insurance companies. **ACTION ITEM:** A. Aldridge agreed to research the target audience for *Economics & Politics*. **ACTION ITEM:** A. Aldridge and R. Anton will contact ACTIVE participant Dr. Keith Isenberg, Anthem Health/Blue Cross Blue Shield, to solicit feedback on a potential journal, as he is likely the most familiar with readership and interests.

3. **Pharma Reps Discussion, Feedback and Thoughts:** The group discussed the that percentage of AUD patients receiving medications is around 9%; practitioners have various reasons for not prescribing medication to AUD patients, including VA practitioners. There was a wide ranging discussion on barriers to AUD medication use and how to find out more detail and specific specialty and health care site differences and a need to educate the public. Given the interest in vivitrol as a predicate FDA approved drug and the desire to evaluate trial length issues, the group discussed K. Witkiewitz conducting analyses on vivitrol similar to other studies. Dr. Sullivan indicated a willingness to discuss with her Alkermes colleagues whether the six month vivitrol registration trial could be made available. It would be useful even if the treatment groups would be blinded. The group discussed the dual diagnosis dataset, which is more contemporary and recently run. This data carried patients out an average of 9 months (6-15 months were included) and includes severe comorbidity. The group agreed that it may be useful to circulate what data we might be getting or will ask for, and this should show what Alkermes derived data is available or be useful.

The group then discussed new opportunities with naturalistic data that companies planned to collect. There could be a lot of opportunity with this data if analyzed with cooperation of ACTIVE members. Apparently there could also be access to VAMER and match claims data. Ideally, an evaluation of the availability of new datasets that could be made available to ACTIVE can be identified so the group can review and discuss next steps prior to the next March 2020 ACTIVE Workgroup Meeting. **ACTION ITEM:** W. Martin and M. Sullivan will get internal consensus from their colleagues on what they could provide and present at the March 2020 ACTIVE Workgroup Meeting. They will also inquire if the vivitrol dataset with blinded treatments can be provided to the ACTIVE group in general and Dr. Witkiewitz in particular to evaluate the WHO shift stability issue.

4. **Future ACTIVE Considerations:** The group discussed future ACTIVE considerations and focused on clinical trial length as well as if power is gained or lost in multisite trials.
   
a. **Clinical Trial Length:** The group discussed that another dossier or addendum to the current one, might be created for “clinical trial length”, depending on the FDA’s response. The group discussed a recent NIAAA gabapentin trial to use as individual level data that will be released within a week or so. The data needed is from a 6-month treatment study, and the group discussed what other analyses could be used for this data, potentially including Lundbeck or Otsuka datasets, now that nalmefene is approved in Japan. The group also suggested looking at previously presented ACTIVE dataset analyses. D. Falk and K. Witkiewitz previously looked at patterns and 80% of people were in the same pattern that they were going to be in by month 2. The group discussed potentially looking at this subset of individuals and analyzing data on their follow ups. **ACTION ITEM:** A half day will be scheduled at the March 2020 ACTIVE Workgroup Meeting to discuss the gabapentin six month study analyses, K. Witkiewitz’s new data, and perhaps also vivitrol if received. All of this is to evaluate trial length issues and
stability. The group agreed that a summary (table of analyses already done on trial length needs to be pulled together).

b. Power Gain or Lost in Multisite Trials – Does the number of sites matter in an AUD clinical trial? The group discussed that site variability matter in the COMBINE study and in almost all multi-site clinical trials. The group discussed that there might be a need for the field to have a tutorial paper on AUD multisite study issues in regards to treatment effect variability across sites, as it does not seem to have been done before. This paper could include distribution of outcomes, missing data, level of attrition, and number of sites, including both the amount of missing data and sources of variable data that can have an influence. The group agreed to revisit this at a later date.

c. Use of Biomarkers in Clinical Trials

d. PRO and Craving Measures

e. Adaptive Designs

f. Dual Diagnosis Considerations

5. Discussion of Future Presentations: The group discussed future presentations, including the following:

a. ASAM 2020 Meeting: April 02 – 05, 2020 in Denver, Colorado. R. Anton submitted a session with S. O’Malley, D. Falk, and Richard Saitz, ASAM member and editor of the Journal of Addiction Medicine. R. Saitz will serve as the discussant and can serve as a bridge between ASAM membership and ACTIVE. This session was accepted for presentation.

b. Volterra Alcohol Conference: May 5-8, 2020 in Volterra, Italy. K. Witkiewitz submitted a clinical symposium. This conference included many US based attendees. It is unclear if this conference is the best fit for this presentation and acceptance is not assured.

c. RSA/ISBRA: June 20-24, 2020 in New Orleans, Louisiana. The group agreed that both K. Witkiewitz and D. Hasin will have plenty of new data by this meeting. ACTION ITEM: S. O’Malley will check with D. Hasin on if J. Knox or M. Wall is available to present. S. O’Malley will send an email to organize the submission, as well as organize a lunch/dinner meeting while the group is at RSA/ISBRA.