**Participants:**
Ray Anton, Medical University of South Carolina, Chair
Arnie Aldridge, RTI
Anne Andorn, Indivior
Henri-Jean Aubin, Hôpitaux Universitaires Paris-Sud
Yangchun Du, Alkermes, Thursday Only
Dan Falk, NIAAA
Joanne Fertig, NIAAA, Wednesday Only
Jay Graham, Indivior
Ralph Gueorguieva, Yale University
Deborah Hasin, Columbia University, Thursday Only
Hank Kranzler, University of Connecticut Health Center
Raye Litten, NIAAA
Karl Mann, Central Institute of Mental Health
Didier Meulien, Lundbeck
Roger Meyer, Penn State Hershey College of Medicine
Martin Mumenthaler, Amygdala Neurosciences
Charles O'Brien, University of Pennsylvania
Stephanie O'Malley, Yale University School of Medicine
Tanya Ramey, NIDA, Wednesday Only
Bernie Silverman, Alkermes
Peter Strumph, Amygdala Neurosciences
Celia Winchell, FDA, Thursday Only
Katie Witkiewitz, University of New Mexico
Gary Zarkin, RTI
Lindsay Snyder, Parthenon Management Group

**Summary of the Meeting:**

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

2. Discussion of a workgroup paper, first authored by Dr. Dan Falk of the NIAAA, showing how the World Health Organization (WHO) drinking risk level reduction could be used in clinical trials of AUD was conducted. **ACTION ITEMS:** The goal is to submit the paper by the end of the year.

3. A discussion on the problem of missing data and revisited the possible alternatives for missing drinking data on which WHO shift outcomes are based.

4. A discussion on the objective of the WHO drinking level change and economic issues in the COMBINE trial and an update on planned analyses to evaluate the relationship between shifts in WHO drinking risk categories and subsequent health care costs or broader social costs. **ACTION ITEMS:** In general, the economic data should focus on healthcare costs while analysis of other social costs e.g. crime and motor vehicle accidents be undertaken separately. There was also general agreement that labor costs/employment (although more complicated) should also be analyzed and discussed.

5. A discussion on WHO drinking levels and physical harms including a number of medical outcome measures e.g. blood pressure, liver function tests (AST, ALT) GGT, %CDT and ER/Urgent Care visits
in the COMBINE study. In general, these analyzes support the meaningful use of the WHO drinking risk level shift in clinical trial outcomes.

6. A discussion on the ways to operationalize and evaluate stability of treatment response to how long a treatment trial should be:
   - Agreement (kappa) of Early response with Later response
   - Agreement (i.e., kappas) of response between Consecutive months (Witkiewitz et al., 2017)
   - Prevalence of monthly response patterns across treatment
   - Compare responses at end of treatment (e.g., 3- vs 6-months) with long term follow-up response

In general, data analysis to date suggest a trial length of 3-5 months appears adequate for response stability. Further discussion is needed if and when a meeting with the FDA is planned whether the focus should be only on WHO drinking levels or do we also include trial length data.

7. A discussion on a proof of concept studies is needed during medication development and also what role craving plays in alcohol treatment. The workgroup discussed if ACTIVE should have a full day symposium in conjunction with the NIAAA at the March ACTIVE Meeting or whether there should be an ACTIVE sponsored symposium prior to RSA. There was discussion regarding whether “other abused drug” clinical lab studies should also be included. The consensus was 1) not do a symposium in conjunction with RSA, but also 2) March would be too soon to do an independent workshop and 3) that alcohol lab studies are plentiful enough to initially focus on and that is also consistent with the ACTIVE mission. There was concern on where to find funding. There was also varied opinion on who should be invited to present and attend in general? More open, focused, or closed?

**ACTION ITEM:** The ACTIVE Steering Committee will further discuss the symposium and report back to the workgroup. Options for financial support from FDA sources might be explored. Whatever is done has to be coordinated with NIAAA who is already funding studies in this area.

8. A discussion on the NESARC-III findings for the Waves 1 and 2 of the WHO Drinking Risk Levels & Alcohol Consequences as indicated by AUDIT scores, as well as levels of anxiety and depression. In general, there again is association between WHO drinking risk category reduction and reduction in AUDIT scores and levels of anxiety and depression. A discussion on possible two papers, one focusing on AUDIT change and one on Psychiatric Symptom Change will be considered. In addition, K. Witkiewitz and D. Hasin will look to combining the Clinical trial health consequences (e.g. liver enzyme) change and the NESARC liver outcome change with the WHO risk level shift into another paper focusing on Health Consequences.

9. A discussion on group sequential design, sample size increase, a case study in alcohol dependence, and sequential parallel comparison design (SPCD).

**ACTION ITEM:** This topic will be included in future meetings and steering committee calls.

10. The French (Ethypharm sponsored) Baclofen study (recently published) was presented as a case study of public interest, government encouragement, and ultimately a negative clinical trial. It highlighted the need for proper dosing, need of a double blind trial prior to approval for treatment, and public awareness influencing treatment and regulatory decisions.

11. A discussion on the design and results from the randomized, double-blind, parallel group, placebo-controlled 6-month study conducted in Japan. The emphasis was on how the WHO drinking risk category shift would perform in a clinical trial. It appeared to be a good outcome marker which
differentiated active treatment from placebo, supporting previous historical work done by ACTIVE and the EMA’s guidelines for use of the WHO measure as an outcome indicator.

12. A discussion on the summary of findings from WHO shift endpoint was provided. The workgroup reviewed the document that would be submitted to the FDA to request a meeting on the WHO risk drinking category shift as endpoint in AUD clinical trials. The workgroup agreed that this should NOT be separate from the clinical trial length considerations but should be but SHOULD be separated from discussions with the FDA on use and type of PRO and craving measure in clinical trials. R. Litten discussed the process of scheduling a meeting with the FDA, including the proposal application that will be submitted by NIAAA. The workgroup discussed what focus should be included in meeting; e.g. WHO categories based on drinks per day versus drinks per drinking day? The industry caucus also agreed that industry representation could/should be included when the ACTIVE group meets with the FDA. If accepted, the meeting will be 60-90 minutes with the agenda/slides will need to be provided two weeks before the meeting date.

**ACTION ITEM:** R. Litten will submit the application to the FDA as soon as possible with ACTIVE input, and in the submission request, that if they do not agree to have a meeting, what they might recommend as a course of action. Dr. Anton summarized the group discussion that, irrespective of the FDA meeting plans, papers will be written and probably a consensus paper summarizing all of the work will be needed.

13. The industry caucus met during lunch and agreed once again that a clinical laboratory symposium is needed and that it might be beneficial to expand to include NIDA and other NIH institutes. The workgroup further discussed potential avenues of funding, including if the FDA or NIH has funds for this type of symposium. There is an ACTION group that handles other types of substance abuse and may be a resource of funding if the symposium to broadened beyond alcohol. The consensus is that the clinical laboratory symposium should occur, but it is not feasible to happen at the March 2018 ACTIVE Meeting. The industry caucus also agreed that industry representation should be included when the ACTIVE group meets with the FDA if possible. NIAAA agreed to explore this possibility. Dr. Anton later added that perhaps the EMA should be made aware of this meeting with the FDA, and if allowed perhaps they should be included in the discussion.

14. Future directions of ACTIVE inquiry occurred. A short list included more work on: Danish healthcare registry data, papers including a featured piece in JAMA Psychiatry or elsewhere, and meeting presentations.

15. The group was reminded about an NIAAA/ACTIVE symposium at the ASCP meeting in May. Sponsored by NIAAA, Dr. O’Malley once again agreed to chair this symposium with the focus on WHO drinking risk category shift and relationship to drinking consequences in clinical trials and the general population.