

ACTIVE Workgroup Meeting #20
March 14-15, 2018
Sheraton Rockville
Location: Kings AB

Participants:

Ray Anton, Medical University of South Carolina, Chair
Anne Andorn, Indivior
Jay Graham, Indivior
Deborah Hasin, Columbia University, Thursday Only By Phone
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
Stephanie O'Malley, Yale University School of Medicine
Tanya Ramey, NIDA, Wednesday Only
Bernie Silverman, Alkermes
Peter Strumph, Amygdala Neurosciences
Celia Winchell, FDA, Wednesday Only
Katie Witkiewitz, University of New Mexico, Wednesday Only
Gary Zarkin, RTI, Wednesday Only
Lindsay Snyder, Parthenon Management Group

Minutes:

1. R. Anton welcomed the group and provided an overview of the program. The first day will be dedicated to planning the meeting with the FDA.
2. **Overview of WHO Clinical Trial Paper and Submission Plans:** O'Malley provided an overview of the *Reductions in World Health Organization WHO Drinking Risk Level as Outcomes in Alcohol Pharmacotherapy Trials* paper and results. **Action Item:** S. O'Malley will circulate the final draft for quick approval from the ACTIVE group.
3. **Review Highlights of WHO Drinking Level Change and Social and Physical Consequences from the COMBINE Study and others:** K. Witkiewitz provided an overview on drinking reduction endpoints.
4. **Review/Highlights of NESARC – WHO Shift Data:**
 - a. R. Anton discussed D. Hasin's data on alcohol dependence at a 3-year follow-up by change in WHO Risk Drinking Category between Wave 1 and Wave 2 data. The group discussed that focus should be on the very high risk drinking group or only the Alcohol Dependence Group. **Action Item:** Further discussion is needed on why models did not converge on the AUDIT-C scores.
 - b. R. Anton also discussed the SF12v2 mental component summary (last 30 days) at least 1 SD below the mean by change in WHO risk drinking category. **Action:** Further discussion is needed on if the 1-shifts include the 2-shifts or is only people with 1 shift?
Data collection method is very important as well as recommendation to the FDA on which method should be used for clinical trials. Discussion of this data in more depth with Dr. Hasin was scheduled for the following day.
5. **WHO Drinking Level Change and Economic Issues in the COMBINE Trial – Review and Update:** G. Zarkin recapped how modifications to the main model impacted the relationships between drinking risk level shifts and healthcare costs. **Action Item:** A discussion ensued on whether quantity frequency drinking data could be substituted for TLFB daily drinking data. K. Witkiewitz will evaluate Q/F in the

COMBINE Study from OCDS questions and compare to TLFB derived WHO categories. This could provide RTI with the new variable data to use in its analysis.

6. Preparation for FDA Meeting. Data, Ideas, Structure:

- a. FDA Meeting Overview:** R. Litten provided an update that NIAAA/ACTIVE submitted a meeting request to the FDA and the request was initially moved to the biomarker division but then back to the CPIM division. The meeting will likely be scheduled within the timeframe of May 2018 through the end of July 2018. This meeting will be ninety minutes total with no more than 20-30 minutes of preliminary slide presentation followed by discussion with the FDA representatives who potentially could provide feedback with items they would like to see for a future meeting. The entire agenda, all presentations, speaker text with glossary terms and background are due two weeks prior to the CPIM Meeting. Reference materials are very beneficial to provide prior to the meeting so background presentations do not take up the time. Ultimately, the FDA representatives, if in agreement with the data, could recommend that the WHO drinking risk category shift be acceptable as an outcome measure for AUD clinical trials **and added to an FDA guidance.**
- b. EMA:** The group agreed that once the dossier is created, ACTIVE will send the information to EMA to keep them informed of the work of ACTIVE and regulatory discussions in the United States. **Action Item:** ACTIVE will send the March 2018 Workgroup Meeting Minutes to Michael Buehlen of the EMA with a cover letter that details the progress toward the CPIM Meeting.
- c. Industry Involvement:** The group discussed if industry should be involved and agreed that it is important to provide a variety of industry participants to show the global support of this effort. **Action Item:** R. Litten will see if NIAAA has any regulations regarding including industry representatives at the FDA CPIM Meeting.
- d. Clinical Trial Length Considerations:** The group agreed that this discussion should be separate, but that this may be needed when discussing endpoints and their stability. The CPIM Meeting is a chance for them to provide guidance and ask questions to assist with next steps, and they may encourage adding additional considerations in this area. The group discussed whether trial length issues should not be considered at all during the initial CPIM Meeting.
- e. How to Measure/Quantitate Drinking (TLFB vs. Q/F measures):** The group agreed to move forward with drinks per day at the primary metric on which to base WHO drinking risk categories. The group should also consider how TLFB data correspond to Q/F data both in clinical trials and possible in the NESARC data. NIAAA does have timeline data with quantity frequency that has not been published and will look into presenting that data.
- f. WHO Risk Drinking Category Shift as Endpoint in AUD Clinical Trials:** The group agreed to overview the traditional outcome variables, the problems with using them, and then introduce the concept of drinking reduction in the background package.
- g. Presentations:** The group agreed that the presentation should only be 20 minutes and 15 data-oriented slides. FDA will need to
 - i. K. Witkiewitz:** The overview graph and text slides should be presented, and the data from clinical trials should be very focused. The group agreed that there should not be too much data in these slide presentation; there should be much time for discussion. Present only 2-shift data verbally but the 1-shift data might be included in the dossier with backup slides, in case 1-shift is of interest to the FDA.
 - ii. S. O'Malley:** S. O'Malley will look at the 2-shift, and not include any 1-shift. The group discussed looking at changes in how others feel and function. The dossier should include the presented table #3 as well as the graph data for the dossier.
 - iii. Participants:** There should be one or two presenters (e.g. Litten, Anton, Witkiewitz) to lead the presentation with additional representatives as references in the meeting: Debbie Hasin, Gary Zarkin, Katie Witkiewitz, Dan Falk, Stephanie O'Malley. The group agreed that the data should be simple enough for one presenter to present all information.

1. 1 Background Presenter – Raye Litten, NIAAA
2. 1 Data Presenter – Ray Anton to overview the work of ACTIVE and state the case for the need for harm reduction and possibly presenting NESARC data.
3. All participants should be there for discussion and questions.

Action item: An outline should be created ASAP and then circulated so the work can be divided with the goal of having everything ready by May 1.

7. Continuation of Discussion and FDA meeting planning:

- a. D. Hasin: The group previously discussed the need to focus on only drinks per day and those with alcohol dependence, as well as questions of how the drinking data was collected. As previously discussed, the focus should be on the subset of people with AUD at Wave 1. The group reviewed the simplified adaption of Dawson ADV (method 2) that included quantity frequency.

Action Items:

- i. D. Hasin will re-run the analyses for AUDIT-C, liver disease, any affective/anxiety disorder, any other substance use disorder among a subset of participants limited to those with alcohol dependence at Wave 1.
- ii. D. Hasin will re-run the analyses for these outcomes +alcohol dependence where the possible levels are 1 and 2 or more, not 1, 2, or 3 levels. D. Hasin will provide the algorithm (scoring guideline) for how the WHO risk levels were defined, and the questions used to provide the information for that, for the full Dawson method, and the simplified method that I presented in November, 2016.
- iii. D. Hasin will see if one of her clinical studies has TLFB data and Q/F questions on alcohol consumption to see how these measures compare.

8. Financial Summary of ACTIVE and Future Plans: R. Anton discussed the financial summary and future plans. He indicated that current funding would allow for only one more 2-day in person meeting under the historical cost analysis. The group finally agreed that the biggest goal and focus should be the WHO endpoint measure with the FDA CPIM Meeting and resources should be focused in this area and no other spending plans should be considered until that goal was accomplished.

9. Overview of Trial Length Analyses: R. Litten discussed the treatment response stability. The group discussed at least 4 ways to operationalize and evaluate the stability of response to treatment:

- a. Agreement (kappa) of Early response with Later response
- b. Agreement (i.e., kappas) of response between Consecutive months (Witkiewitz et al., 2017)
- c. Prevalence of monthly response patterns across treatment
- d. Compare responses at end of treatment (e.g., 3- vs 6-months) with long term follow up response

Dr. Litten said that a recently completed 6-month clinical trial by NIAAA could provide further data on WHO drinking risk stability. Dr. Falk will be leading this effort going forward.

10. Clinical Laboratory Symposium Plans: The group discussed the Steering Committee’s recommendation to have the clinical laboratory symposium in conjunction with the ACTIVE Meeting at the NIAAA office. The group wondered whether NIDA may be interested in co-sponsoring a clinical laboratory symposium. The group agreed that the FDA and pharmaceutical companies should be invited. **Action Item:** T. Ramey and R. Litten will look at the feasibility of a co-sponsored clinical laboratory symposium. It was decided that while this is an extremely important topic that the focus right now should be on the FDA meeting to discuss the WHO risk reduction measure as a clinical trial endpoint.

11. Clinical Trial of a mixed opiate antagonist compound (samidorphan) in an AUD population: B.

Silverman discussed samidorphan (ALKS 33): a new chemical entity that, in vivo has been demonstrated to function as a μ -opioid antagonist.

12. Discussion of Future Directions:

- a. Danish Registry Data:** K. Mann discussed the Danish Research Group data for healthcare costs.
Action Item: R. Anton asked K. Mann to inquire from the Danish group if they have drinking data on this cohort either at baseline or end that could be used to categorize the WHO risk drinking. If not, it is questionable how this data would be useful to us at this time.
- b. AAAP Meeting, December 6-9, 2018:** The group agreed that Ray Anton, Stephanie O'Malley, Dan Falk, and Bernard Silverman can assist with creating a proposal for the AAAP Meeting. There was consensus that a final paper presenting the work of ACTIVE might be useful once the FDA meeting(s) occur.