ACTIVE Workgroup Meeting
November 19 – 20, 2024
Virtual Live Meeting

Minutes

Participants:

Maryam Afshar
Arnie Aldridge
Ray Anton
Henri Jean Aubin
Dan Falk
Michaela Hoffman
Terry Horton, Day 1
Zachary Illg, FDA Guest
Bruce Imbert, Day 1
Raye Litten
Jaromir Mikl, Day 1
Karl Mann
Stephanie O'Malley
Valentine Pascale
Lara Ray
Joe Schacht
Chamindi Seneviratne, NIH Guest, Day 1
Bernard Silverman
Maria Sullivan, Day 1
Konstantinos Tsilkos
Garth Whiteside
Katie Witkiewitz
Conrad Wong
Constance Zou, FDA Guest
Joanna Gupta, Association Manager

Tuesday, November 19, 2024

1. ***Welcome:*** R. Anton welcomed the group, introduced new and continuing corporate support, and mentioned new meeting attendees. 2024 marks the 15th year of ACTIVE; The workgroup began in 2009. Around 17 – 18 companies have supported this initiative throughout the years. Current meeting attendees include eleven academic experts (two from Europe), five members of the FDA, three NIAAA personnel, and eight pharma representatives. New corporate supporters include Eli Lilly and Imbrium, with continued corporate support from Indivior. New attendees include J. Gupta, Executive Office Manager; J. Schacht, guest presenter; J. Mikl, guest presenter; V. Pascale, Imbrium; G. Whiteside, Imbrium; K. Tsilkos, Eli Lilly; M. Sullivan, Eli Lilly; C. Wong, Eli Lily; and C. Zou, FDA.

   R Anton discussed confidentiality and brought up a slide that helped him emphasize the importance of recognizing that information presented at this meeting is shared among group members, as it includes pre-published data and other confidential information. Therefore, all information is for the benefit of the group and should not be shared without explicit permission.

   R. Anton also reviewed the meeting agenda and provided an overview of current and new directions. Current and new directions for the ACTIVE workgroup include 1) finalizing the World Health Organization (WHO) Reduced Drinking Level (RDL) outcome metric, which is waiting on FDA review and decision; 2) Focusing on AUD RCT trial length issues to potentially inform trial length guidance, perhaps through regulatory channels; 3) accelerate the simulation project; 4) studying sub-populations of AUD patients for pharmacotherapy (e.g. those with Obesity, Sleep Disorders, Alcohol Withdrawal Symptoms, Psychiatric Diagnoses); 5) focusing on biomarkers (e.g., biochemical, genetic, identified through neuroimaging, etc.) as predictors, moderators, indicators of treatment response, etc.; and 6) considering non-pharmaceutical treatments for AUD. (e.g., TMS, ultrasound, etc.)

2. ***How we spent our last six years: Evaluating a new outcome measure for AUD clinical trials:*** R Anton provided a history of ACTIVE's involvement with validating a WHO reduction in drinking metric. This

included both associations with Alcohol related behaviors and physical measures. It also included work showing how it performed relative to other FDA endorsed measures in several clinical trials.

R. Anton then provided an overview of the WHO Risk Drinking (RDL) qualification plan. It was submitted by NIAAA to the FDA in the spring of 2020. This submission was in response to a meeting in 2019 between the FDA, ACTIVE members, and NIAAA. The workgroup received a preliminary reviewability memorandum in May 2022 and a final reviewability memorandum in November 2023. Notification of a final decision process is pending.

Finally, R. Anton discussed highlights from the executive summary. This overview included the fact that AUD is ubiquitous and carries high morbidity and mortality, is undertreated with few medications approved for use, and often patients want to reduce drinking rather than achieve complete abstinence. The WHO-RDL is related to important outcomes, including how patients feel and function across various physical and socio-behavioral measures and patient improvement in RCT AUD clinical trials.

3. ***Informing AUD Clinical Trial Length via Sustainability Analyses:*** K. Witkiewitz presented how to determine the length of a clinical trial for AUD. In their draft guidance, the FDA stated that 6 months is an ideal trial length. This recommendation was based on the idea that drinking patterns recorded for a period shorter than six months may not be stable enough to predict behavior at later time points. K. Witkiewitz drafted questions to consider when determining trial length. Namely, 1) when are drinking patterns shown to be stable and representative of future experience? and 2) what short-term outcomes predict outcomes at long-term follow-up? K. Witkiewitz analyzed data from Project MATCH, COMBINE study, and Horizant to answer these questions. Results revealed that data collected at time points short of 6 months generally predict later drinking behavior

   How do these findings compare with studies referenced in FDA guidance? Overall, drinking patterns are stable and representative of future experience. Using methodologies like those cited by the FDA in their guidance, we find that WHO risk level reductions in a 3-month and 4-month trial are stable and representative of future experiences and outcomes. This suggests that trial length can be shorter than currently thought. Discussion highlighted that shorter trial length would have greater acceptability to subject/patient participation, less drop out, better compliance etc. However, safety evaluations might need to be longer depending on knowledge of the medication/drug involved.

4. ***Neuroimaging as a Response Biomarker in Medications Development for Alcohol Use Disorder:*** J. Schacht spoke on using functional neuroimaging (i.e., functional magnetic resonance imaging, or fMRI) in alcohol medication development. He stated that neuroimaging can be used as a response biomarker for medication development, focusing specifically on the alcohol cue reactivity paradigm, studies assessing a variety of drugs through this paradigm, and comparing self-reported craving to fMRI alcohol cue reactivity. J. Schacht then recapped this paradigm of alcohol cue reactivity and craving: When researchers expose participants to alcohol-related cues that elicit cravings, participants say they want to drink. This paradigm is a strong predictor of relapse in real-world clinical settings. Characterizing the underlying neural substrates of this paradigm will help identify medications that can modulate these substrates. For example, alcohol cues strongly and consistently activate the ventral striatum and other reward-related brain areas (Schacht et al., 2013). Work done with naltrexone (one of the few FDA approved medications for AUD) has shown that reduced alcohol cue-elicited activation of the ventral striatum early in treatment predicted naltrexone-induced reductions drinking during the following 4 months of treatment. For prospective AUD medications, reduction of alcohol cue-elicited brain activation could serve as a go/no-go signal for further development of the medication. Dr. Anton pointed out, however, that the alcohol cue brain activation paradigm might be germane to only drugs that reduce

reinforcement and craving. Drugs that work through other mechanisms, such as normalizing brain function, AW symptoms, or sleep, might need other types of pre-study evaluation.

5. ***Alcohol Use Relapse Among Patients with AUD Presenting with Insomnia in the Merative Market Scan database from 2008 – 2022***: J. Mikl presented on how sleep pathology contributes to AUD pathology and vice versa. (Merative is the name of the vendor and more information is available here.) He reported on a retrospective case-control study comparing the real-world odds of return to alcohol use among adults with AUD in remission who either did or did not receive pharmacotherapeutic intervention for insomnia. The baseline characteristics between cases and controls were generally similar by demographics. The odds of a return to alcohol use were 21% lower in treated compared to untreated patients. After adjustment for confounders, the odds of a return to alcohol use in treated patients compared to untreated patients slightly decreased to 19%. The use of treatments approved for insomnia among adults with AUD in remission was associated with reduced odds of alcohol use relapse.

6. ***Discussion on Sleep Disorder as a Predictor or Moderator of AUD Treatment Efficacy. Could This Be a Pharmacological Target?*** M. Hoffman discussed sleep as an important target or modifier in AUD clinical treatment. Insomnia improved in subjects treated with gabapentin (60.6% reduction) compared to those treated with placebo (37.8% reduction). For participants with gabapentin, those with higher baseline insomnia improved more in their drinking measures. Insomnia was a significant independent predictor of drinking improvement that did not moderate gabapentin's effectiveness. Gabapentin impacts both sleep and alcohol use, and its effect on drinking is not completely dependent on sleep change.

Wednesday, November 20, 2024

7. ***Synopsis of the Previous Day and Review Daily Agenda***: R. Anton reviewed the previous day's discussions and presented the agenda for day two of the meeting. He then discussed current and new directions for ACTIVE, including finalizing the WHO RDL outcome metric, focusing on AUD RCT trial length issues, accelerating the simulation project, and focusing on biomarkers of AUD.

8. ***Update on the Use of the PROMIS and Craving Measures as an Explanatory Endpoint in AUD Clinical Trials***: S. O'Malley presented on patient-rated outcomes (PRO) focusing on negative consequences of drinking and craving. PROMIS was an NIH roadmap initiative designed to improve self-reported outcomes using state-of-the-art psychometric methods. There are 7-item short forms for each unidimensional construct measured by PROMIS. Validation studies to detect change over time showed that PROMIS' negative consequences subscale can detect changes in negative consequences that are associated with reductions in alcohol consumption. It seems to be suitable for use in AUD trials; Dr. Falk indicated that it is being considered/used in some NIAAA sponsored trials.

   S. O'Malley's discussed her work related to craving focused on opiates, stimulants, alcohol, nicotine, and cannabis. She and her colleagues at Yale performed an extensive systemic review to identify craving items from questionnaires published in the literature. Her team also utilized focus groups to inform item development and identify gaps in the definition of craving. The next steps involve field testing of the final item pool to determine whether a single measure/scale can be developed that is invariant across substances in addition to developing substance specific measures.

9. ***Initial Questions and Insights from the Combined Multisite AUD Clinical Trial Database:*** M. Hoffman spoke on the need to improve AUD clinical trial design and predicted outcomes. One way is to evaluate both individual and together the number of factors that can impact the statistical power (odds of finding a drug effect) of studies. Researchers and pharmaceutical companies must make decisions when developing the protocol for a clinical trial that affects this power. The decisions include sample size, trial

duration, and various demographic and drinking differences in AUD clinical sample makeup. She assessed data from five studies: COMBINE, HORIZANT, Levetiracetam study, Quetiapine study, and Varenicline study. She did this to assess study design effects (i.e., sources of variation). For example, considering the degree of variability at a one study site within a multisite trial might impact decisions on sample size. M. Hoffman also assessed abstinence before randomization as a predictor of outcomes. There is a negative correlation of -.27 between abstinence before randomization and drinking at the end of the study (i.e., more prestudy abstinence days predicts less drinking during the study) perhaps leading to increased type 2 error estimates. The next steps involve potentially adding single-site studies to increase the database, looking for other potential baseline predictors, and incorporating this information into a larger simulation project (algorithm development that can be used in clinical trial study design).

10. ***Does Variability in Key Study-Site Characteristics Influence Empirical Success of AUD Multisite Pharmacotherapy Trials?*** A. Aldridge discussed the challenges of identifying factors related to individual study sites that impact the success of AUD multisite trials. Successful trials should be able to find an effect if a true effect exists, find it statistically significant, and ensure the estimate a researcher gets is accurate. However, study design choices can impact the success of a trial, including sample size, number of sites, number of participants, missing data, trial duration, and sample makeup (e.g., comorbidities). A. Aldridge and colleagues used a simulation model to see how varying the number of sites, the likelihood of balanced sample sizes across sites, etc. impact findings. Site factors associated with moderating the treatment effect include site sample size, unbalanced randomization, and unbalanced missing data. This was a proof-of-concept exercise and sets the stage for more advanced analysis.

11. ***Discussion, Plans for Further Analyses, and Future Directions:*** R. Anton discussed future directions for ACTIVE, including producing a summary paper on the WHO Risk Drinking Level metric for AUD trials. He reviewed some of the future goals alluded to in his introductory presentation. There was general agreement that the goals were worthwhile but need to be prioritized going forward. He thanked that the attendees for their ACTIVE participation during this virtual meeting. He especially thanked the presenters for their efforts in producing targeted and thoughtful presentations that led to meaningful questions and discussions.

12. **Wrap-up:** The group learned that the next ACTIVE meeting will be in person in March 2025. A venue within the Maryland suburbs of Washinton, D.C., will be selected for this spring meeting.