ACTIVE Virtual Workgroup Meeting
November 20-21, 2025
Minutes

Participants:

Arnie Aldridge, *Academic*
Ray Anton, *ACTIVE Chair*
Patrick Bach, *Academic*
Dan Falk, *NIH/NIAAA*
Michaela Hoffman, *Academic*
Dylan Kirsch, *Academic Guest*
Raye Litten, *Advisor*
Karl Mann, *Academic*
Stephanie O'Malley, *Academic*
Lara Ray, *Academic*
Joe Schacht, *Academic*
Chamindi Seneviratne, *NIH/NIAAA*
Nelson Sessler, *Imbrium*
Bernard Silverman, *Consultant*
Maria Sullivan, *Eli Lilly*
Garth Whiteside, *Imbrium*
Katie Witkiewitz, *Academic*
Conrad Wong, *Eli Lilly*
Rachel DeAngelo, *PMG Association Manager*

Thursday, November 20, 2025

1. **Welcome, Overview, and Important Facts:** R. Anton welcomed the group, new attendees and introduced continued corporate support. 2025 marks the 16th year of ACTIVE. Roughly 18 companies have supported this initiative throughout the years. Current meeting attendees included academic experts (two from Europe), NIH/NIAAA personnel, and pharma representatives. Unfortunately, invited FDA participants had conflicts with the schedule and would try to join if possible. Corporate supporters included Eli Lilly and Imbrium. Indivior has supported ACTIVE for the past 2-3 years but has since decided to no longer attend the meeting because they currently suspended their interest in this space. New attendees include R. DeAngelo, Executive Office Manager; P. Bach, Academic Member from Germany; N. Sessler, pharma representative from Imbrium substituting for Val Pascale; and Dylan Kirsch, Academic Presenter from UCLA. R. Anton mentioned that Henri-Jean Aubin retired from his position and will no longer be participating in ACTIVE meetings. A new EU member has been suggested and will be reviewed by the coordinating committee.

   R. Anton discussed confidentiality and explained a shared slide that helped 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.

2. R. Anton reviewed the meeting agenda and provided an overview of ACTIVE's role in evaluating the FDA and approval of the WHO-risk drinking metric for AUD clinical trials. R. Anton went on to explain important facts and talking points 1) FDA and NIAAA participation in ACTIVE during the time of developmental work and papers on the WHO-RDL was done under a Public-Private Partnership (agreement) with appropriate FDA guidelines followed; 2) FDA, NIAAA and NIDA (for some of the time), as well as Academics and Pharma reps participated in ACTIVE's work as members of the PPP; 3) Pharma companies supported the work of ACTIVE through grants/funding to Parthenon Mgmt Group (PMG) which acted under the auspices of the American Society of Clinical Psychopharmacology (ASCP); 4) Neither pharma nor ASCP provided prior directives to ACTIVE - all work was generated by discussions and ideas presented openly at the biannual ACTIVE meetings; 5) ACTIVE published its work in peer review journals and presented at professional scientific and clinical conferences; 6) the WHO-RDL metric was chosen partially based on its current use in the EMA regulatory approval process; and 7) after the initial meeting between FDA staff, NIAAA, and ACTIVE academic members, the FDA requested a submission of a Full Qualification Plan for the WHO-RDL metric change for use in pivotal clinical trials targeting patients diagnosed with AUD; 8) The COA

subsequently reviewed the FQP and suggested changes which were accepted by ACTIVE/NIAAA; 9) **NIAAA in collaboration with ACTIVE** submitted the data/dossier of its analytic work on the WHO-RDL for the FQP to the COA. Raye Litten was the designated submitter; 10) The COA asked for further analyses of the data submitted and their staff subsequently repeated, and extended, analyses based on the FDA's internal committee requests; and 11) Raye Litten (NIAAA staff) received an approval letter in January 2025.

3. **JAMA Psychiatry ViewPoint Paper: Overview and Response:**
   R. Anton gave a brief overview of how this paper came to fruition in JAMA Psychiatry alongside the OverView paper authored by K. Witkiewitz. Both papers were published online in September and will take about 6-9 months to come out in full press. R. Anton participated in an interview and a publication in a weekly substance newsletter that is distributed to substance abuse treatment facilities and directors. R. Anton hoped that discussion throughout the day would include how we can reach other groups, including European groups, and potential publication in a European journal.

4. **Baseline Predictors of Drinking Outcomes During 5 NIAAA Sponsored Clinical Trials:** M. Hoffman presented her work on publicly available AUD clinical trial datasets for alcohol use disorder, focusing on baseline predictors of study drinking outcomes (total abstinence, no heavy drinking days, and WHO-RDL reduction). She analyzed data from five placebo-controlled trials, identifying that 1) days since last drink prior to randomization (first study drug day) and 2) baseline WHO risk drinking level were significant predictors for various outcomes. The presentation of data analysis, particularly regarding the impact of pre-randomization abstinence on trial outcomes, was discussed. More than 3 days of abstinence significantly increases the possibility of a placebo response based on the drinking outcome measures utilized and guided by the FDA. cutoff for study inclusion criteria. The group discussed the practical challenges of assessing participants with high levels of pre-randomization abstinence, including logistical issues for pre-study clinical assessment with active drinking participants.

5. **Relationship between WHO-RDL shift and other drinking outcomes in the 5 NIAAA Funded Multisite AUD Pharmacotherapy trials:** M. Hoffman continued her presentation on an analysis exploring the relationship between WHO risk drinking levels and percent heavy drinking days. She demonstrated how heavy drinking days are calculated and discussed the lower bounds for different WHO risk drinking categories. It was clarified that this analysis was a "lower bound" mathematical investigation rather than a reflection of clinical reality. M. Hoffman further presented actual data showing the average percent of heavy drinking days for subjects in different WHO risk categories by the end of the clinical trials, as well as changes in heavy drinking days over time. The analysis suggested that percent of heavy drinking days could be a useful proxy for other outcome variables in early studies. M. Hoffman also examined the IMBIBE scale as a validation measure, finding that participants who met the two-level shift criteria but had heavy drinking days still showed improvements in negative drinking consequences. The group discussed the need for standardization in clinical trial designs (including participant selection criteria, pre-study drinking levels, clinical trial length, alcohol severity measures, and craving (to name a few), noting progress has been made over the years but highlighting that variability still requires careful consideration. Dr. Anton urged NIAAA to do more to standardize these issues in its early pharmacotherapy clinical trial program as well as urging academic and SBIR investigators to use these standard methods unless otherwise justified.

6. **Examining the Impact of Clinical Trial Length on Detecting Medication Treatment Efficacy for Alcohol Use Disorder:** L. Ray presented a meta-analysis of 139 clinical trials examining the impact of trial length on detecting medication effects for alcohol use disorders. The analysis found no significant differences in effect sizes across trial lengths for both abstinence and drinking reduction endpoints, even when limited to FDA-approved medications. While the study suggests that trial length may not strongly influence the likelihood of detecting medication effects, L. Ray acknowledged that other factors such as participant variability and retention rates should be considered in clinical trial design. The discussion highlighted that

while longer trials (6+ months) are often required by regulatory agencies, the data suggests that shorter trials might be sufficient for some treatments, though this needs further investigation.

7. **JAMA Psychiatry OverView Paper (REF?): Summary and Response:** K. Witkiewitz highlighted the decade-long work on the WHO risk drinking levels since 2015. In the beginning, there was very limited information on this topic which led to the first two papers in 2017 and many more over the last 10 years. This paper was a systematic review of 34 studies. The review found strong associations between reductions in WHO risk drinking levels and improvements in various domains such as AUD symptoms, psychiatric symptoms, and mortality. The group discussed the adoption and education of the WHO drinking risk level endpoint in clinical practice, noting that while pharmaceutical companies have received FDA approval to use it in regulatory trials, there is a need to educate primary care physicians and the public about its clinical meaningfulness. They explored various educational opportunities through existing professional societies, highlighting the Prescriber Clinical Support System as a valuable resource.

8. **Brief Remarks on Important AUD Clinical Trial Design Issues that Still Need to Be Considered:**
   R. Litten reviewed the following topics that may be of interest to the FDA and pharma (unfortunately FDA representatives were not present to offer their opinions) to help facilitate the discussion for the remaining agenda items:
   1) Expand/improve FDA guidelines in conducting alcohol clinical trials. These include length of alcohol clinical trial, grace periods, and other outcomes (e.g., craving, continuous measures);
   2) Determine the validity of preclinical animal models and human laboratory paradigms to predict efficacy in alcohol clinical trials;
   3) Advance precision medicine. Discover, develop, and validate molecular biomarkers (including alcohol consumption lab tests, genetic predictors or medication response, and perhaps brain scanning measures);
   4) Implement evidence-based alcohol screening and treatment interventions in all medical settings

   They examined the predictive value of preclinical models and human lab paradigms, proposing a high-throughput screening tool to evaluate more compounds and combinations. Precision-medicine approaches were highlighted throughout, including integrating biomarkers and clinical factors, improving alcohol screening and treatment in medical settings, and identifying subgroups most likely to benefit from therapies. The conversation addressed initiatives within ACTIVE such as continued focus on analyzing existing trial data and inviting researchers to share emerging findings with pharma and the FDA. A major theme was the challenge of defining, validating, and communicating clinically meaningful endpoints. The group discussed the WHO-RDL as a potential “gold-standard measure” and explored expanding FDA-qualified endpoints, including harm-reduction and craving-related metrics. They noted the FDA’s analyses showing strong correlations across drinking measures and considered how to make nuanced precision-medicine findings more accessible to providers and patients.

   As an example, the group noted that CDT is an FDA qualified as a heavy-drinking biomarker but not used yet for drug-efficacy claims. They explored what additional data would be needed to bridge that gap. They also discussed the potential role of neuroimaging, and the importance of identifying biomarkers that predict treatment response in heterogeneous populations. They also discussed practical challenges—such as funding validation studies, collecting biomarker data in large trials, and engaging FDA effectively.

   A wide-ranging discussion ensured that they touched on the following various topics. Unfortunately, the lack of input from individual staff working with the FDA in these discussions was unfortunate and could have added a wider perspective to these discussions.

9. **What New Information/Analyses Might Be Useful for Pharm Companies in the Design and Implementation of AUD Regulatory Clinical Trials?**

10. **What New Information/Analyses Might Be Useful for the NIAAA and FDA to Help Inform Guidance to Pharma Companies During Development of AUD Pharmacotherapy?**

11. **Discussion Regarding How to Inform Interested Parties (Treatment Providers, Pharm Companies, The Public) on the New Drinking Reduction Endpoint for AUD Clinical Trials?**

    Many ideas were shared on the above issues and caveats mentioned. There were limitations as to what ACTIVE itself could do, as well as individual academic investigators. This is particularly important in reaching clinicians and the public. It would likely have to be a multi-pronged effort by NIAAA and Pharma Companies. This could include presentations at scientific meetings, but also most importantly, direct communications through published/web-based guidelines, marketing of new (and perhaps older) medications, etc. R. Anton pointed out that while, historically, most clinical/public information/education has been done by pharma companies government agencies and professional society guidelines also have a role to play. For example, the ACTIVE group might have an opportunity to reach out more to the professional and lay press after the two *JAMA Psychiatry* articles appear in print in 6-9 months. A consensus agreed that preparation for that should proceed well ahead of time.

Friday, November 21, 2025

12. **Synopsis of the Previous Day and Review Daily Agenda**: R. Anton reviewed the previous day's discussions and presented the agenda for day two.

13. **Prediction and Monitoring of AUD Medication Effects as Reflected in Neuroimaging Results – The European Perspective:** P. Bach shared neuroimaging results showing that brain responses to alcohol cues generally decline over time within a six-minute MRI scanner cue presentation paradigm, particularly in the ventral striatum, and that importantly this reduction aligns with decreases in craving. While most individuals showed reduced activation over time in the scanner, roughly 30–40% did not; importantly, those with increasing activation tended to have more severe and longer-standing AUD. These patterns indicate the potential of fMRI paradigms for predicting daily cravings and clinical outcomes, though individual-level cutoff values are still needed. The group then discussed how fMRI might forecast relapse risk and treatment response. P. Bach presented evidence that ventral striatal activity predicts severe relapse more accurately than a prior measured AUD related behavioral and drinking models. He reviewed a study showing that naltrexone prevented increases in cue reactivity observed in treatment-as-usual, with the strongest benefit among people with high baseline cue reactivity. P. Bach also summarized several neuroimaging studies, including a replication of K. Mann's 2014 work and a small naltrexone crossover trial, demonstrating correlations between shifts in ventral-striatal activation and changes in craving and related behaviors. He also explained that many of the studies relied on abstinent inpatient samples, making it difficult to link findings to changes in drinking patterns. Dr. Anton pointed out he and Dr. Schacht had done a study showing that the magnitude of naltrexone-induced reduction in fMRI ventral striatum alcohol cue reactivity was associated with better clinical outcome in an outpatient recently drinking AUD treatment seeking population. The consilience between German and American investigators is a powerful replication of this concept, supporting clinical relevance. The promises and limitations to the use of this technology for drug development ensued.

14. **The Alcohol Cue-Exposure Paradigm as a Screening Tool for Alcohol Use Disorder Medication Development: A Critical Review:** D. Kirsch presented a review of alcohol cue-reactivity paradigms, highlighting their role in medication development for alcohol use disorder. The review aimed to refine and standardize the paradigms for better early efficacy screening. D. Kirsch discussed the sensitivity of cue-reactivity to various medications, including those that target craving and non-craving mechanisms. Meta-analytic findings suggested a correlational link between medication effects on cue-reactivity and drinking

outcomes, particularly for heavy drinking. The review concluded that while the paradigms show promise, additional longitudinal within-subject data is needed to strengthen their predictive value for medication development. D. Kirsch presented on fMRI-based alcohol exposure research, highlighting that alcohol cues reliably activate reward-related brain regions and showing promise as a biomarker for AUD. D. Kirsch also reviewed current practices in implementing this paradigm in AUD pharmacotherapy studies, noting substantial variability in methodology that could contribute to mixed findings. She emphasized the need for standardization of methodology to improve interpretability of findings and offered recommendations for refining the paradigm, particularly focusing on behavioral cue-reactivity tasks administered outside of MRI contexts. The conversation ended with a discussion on the potential of this paradigm to be qualified as a drug development tool, with suggested collaboration with the FDA to achieve this. Several members remarked that the actual use of alcohol consumption paradigms rather than cue paradigms per se would likely be more sensitive and ecologically relevant to the prediction medication effects in AUD clinical trials. However, it was also pointed out that reasons for drinking, reinforcement vs. normalization or Alcohol Withdrawal or Cognitive effects might need to be taken into account when choosing what sort of clinical lab surrogate paradigm to implement.

15. **Overview of Study Design and Early Results of a Phase-2 Semaglutide Study. Models of Early Phase 2 Clinical Trials in AUD:** J. Schacht presented findings from a Phase 2 trial of oral semaglutide for AUD. The trial, which was completed in October, was funded by an NIAAA R21 grant and philanthropic foundations. J. Schacht highlighted the drug's potential effects on AUD, noting that while it is not yet approved for this indication, early data suggest promising results. Initial trial data, which lasted 8 weeks, showed reductions in alcohol consumption. J. Schact suggested that longer treatment durations might be needed to fully assess the drug's effects. The study was praised for its rapid data turnaround and transparency. Participants discussed potential areas for further analysis and emphasized the importance of brain imaging studies and future analyses.

16. **Discussion: How do Pharma Companies View Human Clinical Lab Studies and Early Phase 2 Trials for AUD Medication Development. How can NIAAA and Academics Inform This Process?:** The discussion focused on how pharmaceutical companies perceive human lab studies, with C. Wong explaining that while large companies may not conduct these studies directly, they value the scientific literature generated by academic researchers. The group discussed the potential value of human lab studies in drug development, emphasizing their importance in dose selection and early drug elimination. The group agreed that while cue-reactivity data is valuable, significant changes in drinking behavior are crucial for advancing a drug candidate, as most companies require a high level of confidence in a drug's potential success before investing heavily in development. It was agreed that alcohol drinking lab studies might be better predictors of treatment outcomes than self-reported craving measures, as mentioned in previous discussions.

    The discussion continued with questions about FDA considerations about AUD clinical lab studies for medication development The group moved on to discuss the potential use of lab studies and imaging techniques, such as fMRI, in early-phase clinical trials for novel drugs targeting alcohol use disorder. C. Wong emphasized the need to organize existing scientific literature to make a compelling case to the FDA about using fMRI as a biomarker for accelerated approval, similar to how amyloid biomarkers are used in Alzheimer's trials. The discussion highlighted the challenges of using imaging studies in drug development for alcohol use disorder and the need for further evidence to convince regulatory authorities of their value. They explored how these studies could provide valuable data for small biotech companies, potentially saving time and money, but emphasized that fMRI or other neuroimaging data would likely be ancillary rather than critical for drug approval. The participants agreed that while human lab studies could help in early drug development, more work is needed to validate any biomarkers or imaging techniques as predictive of clinical outcomes. They also discussed the importance of including naturalistic drinking follow-up periods in these studies and the need for standardized pipelines in neuroimaging research.

Several members encouraged NIAAA to take the lead perhaps working with the FDA in organizing and funding efforts for standardization, synthesis, and communication of results of neuroimaging studies and biomarker studies (similar to what was recently done with clinical lab models). ACTIVE members likely could be involved in this process.

17. **Discussion, Plans for Papers and Further Analyses, Future Directions, and Possible Addition of Other Academic Members:** R. Anton thanked the attendees for their participation during this virtual meeting. He especially thanked the presenters for their efforts in producing targeted and thoughtful presentations that led to questions and discussions. R. Anton also asked participants to keep in mind any individuals who may be a good fit to join the ACTIVE group whose ultimate goals are to improve AUD clinical trial design, to maximize the ability to detect a positive effect of new medications, and to inform regulatory guidelines in the spirit of accelerating the discovery and approval of new medications. He reminded participants that the sanctioned Public Private Partnership (PPP) under which ACTIVE operates has been a positive effort in moving in those directions, which ultimately should alleviate the public health burden of heavy alcohol use and its disorders.