ACTIVE Spring Meeting
Hilton Washington DC Rockville Hotel
Rockville, MD
March 24-25, 2026
Minutes

Participants:

Maryam Afshar, *FDA*
Arnie Aldridge, *Academic*
Ray Anton, *ACTIVE Chair*
Patrick Bach, *Academic, Day 2 Virtual*
Mehdi Farokhnia, *Eli Lilly*
Michaela Hoffman, *Academic*
Raye Litten, *Advisor*
Zachary Illg, *FDA*
Patrick O'Connor, *Academic, Day 2 Virtual*
Stephanie O'Malley, *ACTIVE Vice Chair*
Valentine Pascale, *Imbrium*
Chamindi Seneviratne, *NIH/NIAAA, Day 2 Virtual*
Elizabeth Sharpe, *FDA*
Bernard Silverman, *Consultant*
Maria Sullivan, *Eli Lilly*
Melissa Weimer, *Academic Guest, Day 2*
Garth Whiteside, *Imbrium*
Katie Witkiewitz, *Academic, Day 1*
Conrad Wong, *Advisor*
Constance Zou, *FDA*
Rachel DeAngelo, *PMG Association Manager*

Tuesday, March 24, 2026, 1:00 PM – 5:30 PM

1. **Welcome and Overview:** R. Anton welcomed the group, and each attendee introduced themselves. 2026 marks the 17th year of ACTIVE. Roughly 18 companies have supported this initiative throughout the years. Current meeting attendees included academic experts, FDA personnel, and pharma representatives. Unfortunately, invited NIH/NIAAA participants could only present and join virtually for a short amount of time on Day 2. Corporate supporters include Eli Lilly and Imbrium. New attendees included R. DeAngelo, Executive Office Manager (first in person meeting); E. Sharpe, FDA representative; M. Farokhnia, pharma representative from Eli Lilly; and Melissa Weimer, Academic Presenter from Yale. Dr. Anton announced the recent decision to phase out of his leadership role within ACTIVE. Dr. O'Malley has accepted the role of Co-Chair and will work closely with Dr. Anton over the next 6-7 months and assume the Chair position by the virtual meeting in November. Dr. Anton plans to stay involved with ACTIVE as a member, maintaining his intellectual contribution to the group. The group congratulated Dr. Anton on this tremendous achievement and welcomed Dr. O'Malley to her new role.

   As a reminder, it was emphasized 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 evolution of ACTIVE from early challenges in 2007 to current progress over the years, highlighting improved momentum but ongoing barriers. Key historical issues included limited regulatory clarity, lack of guidance, little assistance on endpoints, and minimal pharma engagement. Today, ACTIVE is focused on new directions:
   - Clinical Trial Length Considerations (including "Grace Periods")
   - Baseline Predictors of Placebo Response and Effects on Trial Length
   - Place of Drinking Biomarkers (Lab Tests) in AUD Trials
   - Secondary Outcomes/Endpoints (How to Choose and Define Them)
   - Place of Craving in AUD Trials and Endpoints (Translational Value)
   - Ongoing Dialogue with NIAAA and FDA to Accelerate Issues germane to AUD Clinical Trials

- Dissemination/Education of Reduced Drinking Outcomes for AUD Trials (including Interactions with the EMA)

3. Dr. Anton reviewed issues related to AUD trial length which included:
    - Participant/Patient drop-out rates e.g., 20% for 3–4-month trial vs. 40% for six-month trial
    - The need to impute or estimate missing drinking data from those who drop out of the study.
    - The cost associated with longer trials from medication, CRO, lab, trial data collection personnel, and the need for enhanced samples sizes to make up for the drop out loss of data and standard error increase leading to reduced effect size estimates.
    - Potential concerns about treating patients for extended periods who are not getting better from participation.

4. **Overview of Trial Length in Other Psychiatric or Behavioral Component Disorders**: This presentation by R. Litten summarized FDA guidance across multiple disorders including major depressive disorder, bipolar disorder, obesity, and addiction. The summary concluded the following: 1) The proposed duration of treatment with the drug, as well as the type of disorder, can influence study design of pivotal trial including the length of study.; 2) FDA guidance describes two types of pivotal phase trials: short-term treatment (usually 3 months) to decide if the drug works and long-term treatment (6 to 12 months) to determine relapse prevention and safety; 3) "Grace periods" (early weeks of the study where outcome is not counted in the final analysis) are allowed in several disorders; 4) The FDA is now requiring one well-controlled pivotal trial instead of two with confirmatory evidence. The presentation continued with a summarization of Alcohol Use Disorder (AUD) from FDA guidance in 2015. Current data is now available, including newer data sets from well-designed clinical pharmacotherapy trials, more sophisticated analyses, and new information on reduced drinking. However, there are still some remaining questions related to FDA study design of alcohol pivotal trials and guidance.

5. **Overview of WHO-RDL Reduction Stability Over Various AUD-RCT Treatment Periods:** K. Witkiewitz presented data from previous ACTIVE presentations including studies between the years of 2017 and 2024.This presentation reviewed evidence supporting the WHO risk drinking level (RDL) reduction as a stable and meaningful endpoint in alcohol use disorder trials, showing that reductions in drinking observed as early as 3-4 months are strongly predictive of long-term outcomes (up to 10 years) and comparable to traditional endpoints like abstinence. The findings question the need for the current 6-month FDA trial requirement for drinking efficacy endpoints, suggesting shorter trials may still capture reliable, clinically meaningful changes, especially since reduced drinking is more acceptable and sustainable for patients. These findings could inform decisions about trial duration for Phase 3 trials. Overall, the work supports evaluating trial length further with qualitative data, examination of retention, risk, safety, and functioning, examination of long-term outcomes, and use of individual patient data meta-analysis tools.

6. **Baseline Drinking Goals and Study Length Related to Drinking Outcomes:** This presentation by M. Hoffman analyzed combined data from multiple AUD clinical trials which shows that baseline drinking goals (e.g. abstinence vs reduced drinking) are one of the strongest predictors of better outcomes (i.e. abstinence, no heavy drinking days, and WHO risk reduction). Pre-study abstinence goals are predictive of abstinence during the study but at a low base rate while reduced-drinking goals are associated with poorer abstinence outcomes but predict success in reduced drinking. Her analyses also demonstrated that "percent heavy drinking days (PHDD)" aligns closely with WHO risk level reductions and can serve as a meaningful continuous endpoint (repeated measurement over time), with specific thresholds (e.g., 50% reduction in PHDD) linked to clinically meaningful WHO-RDL reductions. Overall, the work emphasizes that patient goals and baseline characteristics are critical for designing AUD trial subject selection, interpreting, and selecting appropriate drinking outcome measures, and may be a key factor in trial design along with shorter trial length.

7. **Does AUD Trial Length Matter? Using Shorter Trial Drinking-Outcomes to Estimate Effect Sizes in Longer Duration Trials:** Dr. Arnie Aldridge presented data in which simulation of longer trial length from actual shorter trials was examined for stability of medication effect sizes, and variation around drinking estimates that might affect the ability to detect medication over placebo effects (effect size estimates). His first attempt at simulations used data from a 6-month study on which he projected effects observed in shorter periods of the trial and compared them to the actual observed 6-month data. For the most part, there was good correspondence.

Wednesday, March 25, 2026, 9:00 AM – 2:30 PM

8. **Overview of Previous Day Discussions & Today's Agenda:** S. O'Malley thanked those who presented yesterday and reviewed the previous day's discussions. The agenda for day two was presented.

9. **Discussion of Possible Further Regulatory Interface Needs/Clarifications/Enhancements of AUD Clinical Trials:** The discussion focused on FDA requirements for Phase 2 trials and their impact on the overall drug development process. While the FDA does not specify a particular time requirement for Phase 2 trials, negative results would require discussion with the FDA to justify proceeding to Phase 3, with the sponsor needing to provide a clear rationale and potentially modify the Phase 3 program to address concerns. The conversation also touched on NIAAA funding limitations, noting that most NSIG (NIAAA contracts for AUD clinical trials) are typically 3-month studies due to "cost constraints". The group discussed the challenges and considerations in designing Phase 2 clinical trials for alcohol use disorder treatments, emphasizing the importance of carefully selecting patient populations, considering study duration, and being mindful of site selection to improve trial efficiency and outcomes.

   It was suggested that ACTIVE could create a primer on designing Phase 2 trials, highlighting the need for standardized approaches and timelines. Areas for standardization were discussed including a standard duration of at least 3 months, consistent measurement instruments across studies, guidance on participant selection, and the importance of incorporating biomarkers, such as PETH, CDT, and ETG, to enhance data validity and address issues with self-reported drinking. The benefits of using biomarkers in Phase 2 trials, particularly for baseline assessments and stratifying participants (e.g., based on recency of drinking), was noted and an example was given demonstrating that using biomarkers to correct/confirm self-reports (e.g., a person who reports total abstinence, but has a positive bio-marker of drinking) could detect a positive drug effect, whereas the analyses were negative when based exclusively on self-reports. The conversation continued with discussion of craving as a potential endpoint for substance use studies, highlighting its value as a patient-reported outcome and suggesting future work on validating and potentially qualifying it with regulatory bodies like the FDA.

10. **What is needed for better translational outcomes in medication development for AUD:** C. Wong described his background in pharmaceutical development and regulatory affairs at Lilly but has since retired. The focus of the discussion was on FDA-accepted primary endpoints for establishing substantial evidence of effectiveness in alcohol use disorder, including abstinence, no heavy drinking days, and the WHO 2-level reduction in risky drinking severity. The requirements for primary endpoints in clinical trials were discussed, emphasizing the need for high experimental and statistical control, typically demonstrated through low p-values. While single pivotal studies can support drug approval, they require thorough investigation of all data and endpoints. Drug labeling processes were discussed, using an example to illustrate how clinical study information is incorporated into the USPI. The structure of the label, including sections on warnings, adverse events, and clinical studies, and detailed the approval process for both migraine and episodic cluster headache indications were explained. Also mentioned was

the use of a patient-reported outcome measure, the MSQ role function restrictive domain score, which was qualified through the COA process. The importance of key secondary endpoints in drug labels, emphasizing their relevance for communicating clinical benefits to prescribers and patients, was discussed. Additional endpoints could be explored through consulting the scientific literature, including NIAAA research, to identify important constructs. It was highlighted that while clinicians may focus on blood pressure and liver disease, patients often prioritize being able to drink while managing without problems making endpoints like RDL important for patient care.

11. **NIAAA initiatives on drinking biomarkers and interactions with the FDA and other entities:** C. Seneviratne presented NIAAA's biomarker research priorities, highlighting advances in consumption biomarkers, biosensors, and pathology-based markers. The discussion addressed challenges in clinical translation, the need for context-specific biomarkers, and the role of biomarkers in precision medicine (especially genetic type differences). Key questions were raised about FDA regulatory pathways for biomarker qualification and the potential for including additional drinking endpoints in clinical trials beyond the current WHO criteria. The group discussed prioritizing different types of biomarkers in development, specifically focusing on consumption biomarkers that are further along in the pipeline versus pathology-based biomarkers still in the discovery phase. They explored questions about who should conduct the research and how to move biomarkers from discovery to clinical practice or phase 3 trials. FDA clarified that biomarkers already in clinical use with adequate justification could be included in regulatory submissions, similar to how HbA1c is used to monitor diabetes treatment.

12. **Extension/Education of clinicians regarding drinking reduction goals. What is needed and collaborations/publications:** P. O'Connor provided an overview of alcohol use disorder treatment in primary care, focusing on screening, intervention strategies, and pharmacotherapy options. Data comparing the effectiveness of medications used for alcohol use disorder to other common treatments in primary care, highlighting their favorable effectiveness was presented. Challenges and opportunities for improving treatment in primary care settings, including addressing stigma, improving training, and enhancing support systems, were also discussed. The presentation included insights from a survey of expert primary care physicians on key challenges and opportunities in treating alcohol use disorders in primary care. The panel identified several strengths of the drinking reduction metric, including its harm reduction approach, clinical relevance, and ability to document benefits, while also noting weaknesses such as self-reporting challenges and questions about cutoff levels. The discussion highlighted the potential for this metric to serve as a global standard for alcohol use disorder measurement and treatment outcomes in primary care. The group expressed interest in the metric's patient-centered approach and harm reduction outcomes but raised concerns about the need for more evidence, physician training, and biomarker validation. The discussion concluded with recommendations for next steps, including investing in education for healthcare providers, developing infographics, integrating metrics into EHR systems, potentially linking metric use to financial incentives, publishing in high-profile journals, and potential funding opportunities for further research in primary care settings.

13. **Providers Clinical Support System – Medications for Alcohol Use Disorder – Collaboration Possibilities:** This presentation from M. Weimer described the PCSS-MAUD program, a SAMHSA-funded national initiative aimed at improving the use of medications for alcohol use disorder (AUD) through education and training of healthcare professionals. It highlighted that MAUD is significantly underutilized due to barriers like lack of training, stigma, and limited resources, and emphasized the need for better education, integrated care models, and broader awareness. The program has exceeded its goals, training over 26,000 professionals and delivering extensive educational resources, demonstrating strong engagement and impact in expanding access to evidence-based AUD treatment. The possibility of creating an educational module on the WHO drinking risk reduction endpoint was discussed.

14. **Summary:** S. O'Malley summarized the discussion and potential next steps for further consideration by ACTIVE including: 1) efforts to reengage the EMA in discussions of trial design and endpoints; 2) a primer for Phase 2 studies; 3) identification of additional clinical trial data sets to be incorporated into the simulation studies, including data on drinking biomarkers; 4) research mapping clinic based drinking data (e.g., AUDIT-C) onto the WHO drinking risk levels; 5) the development of a computer based WHO-RDL algorithm for use in the EMR; and 6) publications and slide decks on the WHO-shift outcomes tailored to a primary care audience and highlighting a) physical and social function, b) biomarkers, c) medication response (JAMA Psych article data), d) health cost reductions (A. Aldridge Paper) and e) d) how to calculate WHO Risk Factor Levels.

    She thanked attendees for their participation and for traveling to the in-person meeting. She especially thanked the presenters for producing targeted, thoughtful presentations that led to questions, discussions, and ideas for future ACTIVE meetings and efforts.