ACTIVE Workgroup Meeting
March 27 – 28, 2023
Courtyard by Marriott Rockville
2500 Research Blvd, Rockville, MD 20850
Meeting Room: Meeting Room 1

Participants:
Ray Anton
Arnie Aldridge
Henri-Jean Aubin
Michaela Hoffman
Raye Litten, Day Two
Karl Mann
Stephanie O'Malley
Bernie Silverman
Katie Witkiewitz
Maryam Afshar, FDA Guest
Laura Reynolds, staff

Minutes:

1. ***Introduction of Members, Status Update, and Agenda Overview:*** R. Anton welcomed the group and provided an overview of the program.

2. ***Update on WHO Risk Drinking Level (RDL) Metric Submission to the FDA:*** R. Anton provided an overview of the progress made with the WHO risk drinking qualification plan, stating that the NIAAA and ACTIVE workgroup submitted modifications requested by the FDA in the required format in early March 2023. R. Anton began by sharing the history of the process, as well as the major elements of the WHO-RDL. It is important to note, that the FDA wanted all of the code that went into the analysis in the event they needed to reanalyze some of the data; therefore, K. Witkiewitz included a nice feature where they can click on certain analyzes and it instantly shows data and the statistical structure making it easy to reproduce.
    a. ***Overview of the Qualification Plan:*** He concluded by sharing the following highlights from the qualification plan's executive summary:
        i. AUD is a ubiquitous and carries high morbidity and mortality.
        ii. AUD is undertreated with few medications approved for use.
        iii. AUD patients often want to reduce drinking rather than full abstinence.
        iv. The TLFB calendar method can validly quantify drinking in clinical trials and serve as the instrument from which WHO-RDL categories are derived.
        v. The WHO-RDL is related to how individuals feel and function across a range of physical and socio-behavioral measures.
        vi. A WHO-RDL reduction is related to patient improvement in RCT AUD clinical trials.
        vii. The WHO-RDL change is equal to, or more, sensitive to medication effects than traditional drinking outcome measures and it endures up to a year after treatment.
        viii. A "reduction in drinking" goal (as measured by the WHO-RDL change) should be more acceptable to patients and clinicians thereby encouraging more treatment seeking and success.
    b. ***Feedback:*** It was noted that this could be very impactful to many of early-stage companies who are seeking guidance from the FDA.

3. ***Reductions in WHO Risk Drinking Levels and DSM-5 AUD Remission: Analyses from the Horizant Trial:*** K. Witkiewitz shared that the focus of this presentation and future paper will be looking at AUD remission and Horizant Study, the only study that repeated a DSM-5 AUD criteria at the end of treatment.
    a. ***Background:*** She began by providing background for the paper, stating that work from NESARC found among very high-risk drinkers at Wave 1, each decrease in WHO drinking risk level was associated with significantly lower prevalence and adjusted odds of alcohol dependence diagnosis at Wave 2; however, no prior work has examined WHO risk levels and AUD criteria change during clinical trials.
    b. ***Summary of Findings:***
        i. It was noted that at least 1- and 2-level reductions are associated with greater odds of interim remission from DSM-5 AUD and greater reductions in AUD symptoms in a 6-month trial.
        ii. Additionally, it was found that the results align with epidemiological data from Hasin et al (2017), replicated in a clinical sample of individuals who all met criteria for DSM-5 AUD at baseline.
        iii. Baseline level of AUD does not appear to moderate associations, such that achieving at least 1- and 2-level reductions is associated with greater reductions in symptoms even among those with greater AUD severity at baseline.
    c. ACTION ITEM:
        i. K. Witkiewitz will look at the protocol for the Grace period for the DSM-5 window.
        ii. It was suggested to present the AUD symptoms at baseline and posttreatment for 1-level reduction versus referent differently by presenting the moderator coefficients a few different ways.
        iii. It was suggested to place the paper in the *Journal of Addiction Medicine.*
        iv. M. Hoffman will send K. Witkiewitz the method section of her sensitivity paper.

4. ***A Causal Analysis of WHO RDLs on Mental Health, Mental Health Functioning and Quality-adjusted Life-years:*** A. Aldridge presented on the effect of alcohol consumption on mental health-related quality of life and QALYs using mendelian instrumental variables methods in the NESARC III. He began by providing an overview of the design by discussing the endogeneity of alcohol consumption and mental health-related quality of life (MHrQoL). He then shared the data and measures of NESARC III, as well as discussed, the below methods. He concluded by sharing the results, stating the causal results were more substantial.
    a. ***Methods***
        i. Instrumental variables (IV)/Genetic Information
        ii. Conceptual issues
        iii. Ordinary least squares ignoring endogeneity
        iv. IV-Limited Information Maximum Likelihood
        v. XPO LASSO IV

5. ***Update on Simulation Study Application to Otsuka – Baseline Data Aggregation Results of NSIG AUD Trials:*** R. Anton shared the background of the simulation study application while M. Hoffman provided an update on the submission status, as well as next steps.
    a. Background of Submission: R. Anton provided an update on the status of the ISS stating that Otsuka decided not to fund the grant, so alternative options need to be discussed.
    b. Content of the Submission: M. Hoffman provided an overview of her current work with the harmonization of the five clinical trials that are part the ISS grant application. The goal is to build a database simulation by aggregating data from existing clinical trials to better understand the factors that impact the efficiency and efficacy of AUD multisite clinical trials . She began by

sharing the primary and secondary objectives, explained the data came from NIAAA funded AUD multisite trials: The COMBINE Study, Quetiapine, Levetiracetam, Varenicline, Horizant (gabapentin) showing the various study timelines, drinking data, sample size, demographics, and baseline drinking for each study. **ACTION ITEM:** It was suggested to add a column on the timeline slide showing if pre-treatment abstinence was required.

c. ***Next Steps:*** M. Hoffman shared that the next steps will include the following:

i. Determine how the trial factors impact the success of subjects (placebo subjects).
ii. Determine how the trial factors impact the effect sizes of the treatments.
iii. Use this information to model clinical trials varying salient the trial characteristics.

d. ***Funding Update:*** Since Otsuka decided not to fund this work, the group discussed alternative approaches which included:

i. Submit an R grant (R03, R21?).
ii. Partner with societies that are interested in trials.
iii. Submit a grant to Dr. Hoffman and Anton's Institution (MUSC), as they give small grants to young investigators for novel ideas.
iv. Consider an SBIR grant or partner with a company.
v. Consider adding cross-cultural comparisons. Germany has a very similar study to COMBINE, which would offer a nice comparison. Although it could not be used for the whole analysis because it does not include treatment, it could be compared with the baseline data. **ACTION ITEM:** Continued discussion with K. Mann is needed to determine the approval process.

e. ***Additional Suggestion:*** It was suggested to begin writing papers on the simulation model.

6. ***Associations between WHO Risk Drinking Levels and Alcohol Craving in Three Clinical Trials:*** K. Witkiewitz summarized the paper on *Craving by WHO Risk Drinking Level Change in COMBINE, Horizant, and Varenicline,* as well as shared the findings that were reported. She began by sharing an overview of the paper, stating that it focuses on whether or not drinking reductions support reductions and craving (e.g. OCDS, PACS, AUCS) or do people maybe experience even more craving if they're reducing their drinking versus total abstinence. The studies, measures, and analyses were all highlighted for each of the three studies. It was noted that generally, drinking reductions are significantly, positively associated with craving reductions for adults in treatment for alcohol use disorder (AUD). It was noted that it was null in Horizant when only abstainers are included in the sample. Additionally, the relationship is not specific to or driven by those who maintain abstinence. Generally, AUD severity is not a moderator of WHO risk drinking level reduction and end-of-treatment craving except for:

a. Whole-sample COMBINE at a 2+ level reduction
b. Only abstainers in COMBINE at a 2+ level reduction

ACTION ITEMS:

a. R. Anton will send K. Witkiewitz a paper he wrote on the measurement of OCDS Levels, as it could be a predictor or medication response.
b. Apply the same model that was used with the stress measurement to the craving data.
c. Include Treatment Effects as a control (esp. Naltroxene group vs placebo in the COMBINE Study) before the paper is submitted.
d. It was suggested to take out the responders versus those who achieved the WHO Risk level on Naltrexone and reevaluate craving reducing the heterogeneity.

7. ***Overview and Update on EMA's Guidelines On Drinking Outcomes For AUD Regulatory Trials – Recent Trial Applications/Findings:*** HJ Aubin presented an overview and update on the EMA's guidelines on drinking outcomes for AUD regulatory trials.

a. ***Proposals:*** He highlighted a few of the groundbreaking proposals listed below:

i. ***Inclusion Criteria:*** "Patients included in the main trials should […] have […] a high or very high level of total alcohol consumption at baseline (total consumption per month, presented on an average daily basis) in order to be clearly representative for moderate to severe alcohol dependent patients in the general population."

ii. ***Definition of Primary Endpoints:***

1. Full abstinence goal (relapse prevention after detoxification)
    a. Co-primary endpoints: continued abstinence rate at the end-of-active treatment period and at the end of the study
2. Intermediate harm reduction goal (significant moderation without prior detoxification)
    a. "it is necessary to aim at maintained abstinence as soon as the patient gets ready for it"
    b. Co-primary endpoints: change from baseline in TAC and HDD
    c. Key secondary endpoint efficacy should also be evaluated in terms of responders
        i. 50%, 70%, or 90% reduction in alcohol consumption, or abstinence
        ii. Another option : 2-level reduction in WHO RDL metric.
3. ***Therapeutic Confirmatory Studies:*** It was noted that this proposition was controversial as it includes extremely long harm reduction period.

b. ***Background:*** It was noted that the above propositions came from two European guidelines that had previously been published: 1.) Guidelines on an Evaluation of Treatment of Alcohol Dependence published by The Plinius Maior Society and 2.) ECNP Consensus Guidelines for the Investigation of Efficacy in Substance Use Disorder.

c. ***Submissions:*** Since the publication of the EMA Guidelines, the EMA has only received two submissions for the field of alcohol dependence:

i. Selincro, for alcohol consumption reduction, authorized
ii. Hopveus, for alcohol withdrawal and abstinence maintenance, refused

d. ***Updates:*** HJ Aubin concluded by stating that there was no update to the guidelines, nor any new submissions of an application for Marketing Autorisation for the indication "reduction of alcohol consumption in patients with alcohol dependence since Selincro, in 2013.

e. ***Group Discussion:***

i. It was noted that the EMA can give an authorization marketing for the whole EU but there's also the possibility to market a drug with an application in one country in which it will only be valid for that country, which is what happened with baclofen in France.
ii. Also, sodium oxybate is being assessed by some EU national agencies, based on previous marketing authorization in Italy and Austria, prior to the EMA ruling. Namely, it is currently submitted to the French agency.
iii. It was noted that the WHO RDL reduction was evaluated for the nalmefene approval as well but that it was not the only drinking variable considered.
iv. Dr. Anton reiterated that the EMA is very interested in the WHO RDL work as they have included it in their guidelines without much data to back up its utility. He also emphasized the desire to harmonize the AUD clinical trial guidelines as much as possibly between the FDA and EMA. This will be a focus of future discussions.

f. ***ACTION ITEMS:***

i. K. Witkiewitz will send HJ Aubin the 1995 article in which the Department of Human Services and Health in Australia references the EMA thresholds.

ii. HJ Aubin will send The Plinius Maior Society document once it has been scanned to the group.

iii. K. Mann will contact Michael Buehlen and share with him the information that was discussed during the 2023 Spring ACTIVE Meeting. If he is interested, ACTIVE might share its FDA dossier with EMA. Otherwise we wait for the FDA decision and then consider further steps to align with EMA.
iv. It was suggested to include an EMA Update on the ACTIVE meeting agendas each year.

8. ***Review of Clinical Trial Data and Real-World Evidence for Use of a PDT in Patients with AUD, Alone or in Combination with SUD:*** Maria Sullivan and Yuri Maricich shared with the group clinical trial data real, world evidence, as well as healthcare outcomes data on the use of a prescription digital therapeutic (PDT) in patients with AUD whether in combination with the substance use disorder or SUD alone. M. Sullivan began by sharing the role of PDTs in AUD treatment and reviewed secondary analysis of CTN 44. Y. Maricich shared real-word evidence and health economic and outcomes research (HEOR) data on clinical outcomes and healthcare resource utilization for SUB with and without alcohol use disorder.
    a. ***PDTs Role in AUD Treatment:*** Prescription Digital Therapeutics are software-based treatments evaluated for safety and efficacy in RCTs and authorized by the FDA to treat disease with approved indications for use. PDTs are 4th wave of therapeutics, after small molecules (1900s), biologics (1980s), gene therapies (early 2000s) and now prescription digital therapeutics (ca. 2020). They are designed to target serious psychiatric disorders that can be modified by behavior and are challenging to manage with existing therapeutics. PDTs increase outpatient access to standardized, validated treatments (CRA, CBT, and CM) that can effect neurobehavioral change either as monotherapy or in combination with medication (e.g. buprenorphine) to improve clinical outcomes.
    b. ***Secondary Analysis Results of CTN 44:*** The study conducted was an NIDA-funded RCT to evaluate effectiveness of an interactive, web-based version of Community Reinforcement Approach (CRA) intervention.
    c. ***Real World Evidence:*** The real word data comes from the use of reSET, Pear's PDT. The results are listed below:
        i. Rates of primary substances used among patients in this large, geographically diverse real-world sample (33%, 30%, 22%, and 7% for patients with disorders related to alcohol, opioids, stimulants/cocaine, and cannabis, respectively) closely mirror most frequently reported primary substances in 2019 Treatment Episode Data Set (alcohol, 31%; opioids, 30%; stimulants/cocaine, 18%; and cannabis, 11%)
            1. Findings reported here indicate that the reach of this PDT across SUD subtypes was proportional to what has been observed in treatment-seeking populations more generally.
        ii. Findings demonstrate a high level of engagement with the PDT irrespective of primary SUD diagnosis
            1. Patients across different SUD diagnoses show broadly similar benefits in terms of retention in treatment and abstinence in last 4 weeks of a PDT prescription
        iii. Retention rates observed after 12 weeks of treatment with a PDT are substantially higher (69%, 69%, 72%, and 68% for patients with disorders related to alcohol, opioids, stimulants/cocaine, and cannabis, respectively) than national rates of treatment completion for conventional clinician-delivered services (15.5%-29.8%) [SAMHSA TEDS-D: https://www.datafiles.samhsa.gov/dataset/teds-d-2019-ds0001-teds-d-2019-ds0001]
        iv. Taken together, these data support the use of PDTs as an accessible and effective treatment option for a broad range of SUDs

9. ***Discussion, Plans for Further Analyses, and Possible Addition of Other Academic Members:*** The group concluded the meeting by summarizing the overall meeting, plans for further analyses and possible new academic members to invite to join ACTIVE.
    a. ***Potential New Members:*** The below individuals were mentioned as potential new members:
        i. Jeffrey Samet
        ii. Josh Lee
        iii. Lara Ray
        iv. Laura Clark – **ACTION ITEM:** R. Litten will speak to her about joining.
    b. ***Insurance Industry Representative:*** Additionally, the group discussed the need to have a representative from the insurance industry participate in the meeting so the ACTIVE group was familiar with their needs. The below individuals were mentioned to potentially invite:
        i. Keith Isenberg
        ii. Connie Weisner
    c. ***Health Services Researcher:*** The group also discussed the possibility of inviting a health services researcher to attend the meetings.
    d. **ACTION ITEM**:
        i. The ACTIVE sub-group will generate a list of potential members and share the full group for approval. Consideration will be taken to include mid-level alcohol researchers that have experience with clinical trials.

ACTIVE Published/In-Press/Submitted Papers*:*

- Aldridge AP, Zarkin GA, Dowd WN, Witkiewitz K, Hasin DS, O'Malley SS, Isenberg K, Anton RF. The Relationship Between Reductions in WHO Risk Drinking Levels During Treatment and Subsequent Healthcare Costs for the ACTIVE Workgroup. J Addict Med. 2021 Dec 3. doi: 10.1097/ADM.0000000000000925. Epub ahead of print. PMID: 34864785.
- Witkiewitz K, Kranzler H, Hallgren K, Hasin D, Aldridge A, Zarkin G, Mann K, O'Malley S, and Anton RF. Stability of Drinking Reductions and Long-term Functioning Among Patients with Alcohol Use Disorder. Journal of General Internal Medicine. 2021 Feb; 36(2):404-412. PubMed PMID: 33180306; PubMed Central PMCID: PMC7878601.
- Shmulewitz D, Aharonovich E,Witkiewitz K, Raymond RF, Kranzler HR, Scodes J, Mann KF, Wall MM, Hasin D. The World Health Organization Risk Drinking Levels Measure of Alcohol Consumption: Prevalence and Health Correlates in US Adult Nationally Representative Surveys, 2001-2002 and 2012-2013. American Journal of Psychiatry. 2021 Jan 21. PubMed PMID: 33472388.
- Witkiewitz K, Heather N, Falk DE, Litten RZ, Hasin DS, Kranzler HR, Mann KF, O'Malley SS, Anton RF. World Health Organization risk drinking level reductions are associated with improved functioning and are sustained among patients with mild, moderate and severe alcohol dependence in clinical trials in the United States and United Kingdom. Addiction. 2020 Sep;115(9):1668-1680. doi: 10.1111/add.15011. Epub 2020 Mar 10. PMID: 32056311; PMCID: PMC7841874.
- Knox J, Scodes J, Witkiewitz K, Kranzler H, Mann K, O'Malley S, Wall M, Anton R, Hasin D, ACTIVE Group. Reduction in World Health Organization (WHO) Risk Drinking Levels and Cardiovascular Disease. Alcohol Clinical and Experimental Research. 2020 Aug; 44(8):1625-1635. PubMed PMID: 32619058; PubMed Central PMCID: PMC7484295.
- Anton RF, Witkiewitz K, Falk D, Litten R, Hasin D, Mann K, O'Malley SS., Response to Dr. Mark Litt Commentary. Alcohol Clinical and Experimental Research. 2019 Aug 5. PubMed PMID: 31381170.
- Witkiewitz K, Falk DE, Litten RZ, Hasin DS, Kranzler HR, Mann KF, O'Malley SS, Anton RF. Maintenance of World Health Organization Risk Drinking Level Reductions and Posttreatment Functioning Following a Large Alcohol Use Disorder Clinical Trial. Alcoholism: Clinical and Experimental Research. 2019 May; 43(5): 979-987. PubMed PMID: 30951210; PubMed Central PMCID: PMC6502682.
- Knox J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten R, Mann K, O'Malley SS, Scodes J, Anton R, Hasin DS. Reduction in Non-abstinent World Health Organization (WHO) Drinking risk Levels and Drug Use Disorders: 3-year Follow-up Results in the US General Population. Drug Alcohol Depend. 2019 Apr 1; 197: 228-235. PubMed PMID: 30852375; PubMed Central PMCID: PMC440807.

- Falk DE, O'Malley SS, Witkiewitz K, Anton RF, Litten RZ, Slater M, Kranzler HR, Mann KF, Hasin DF, Johnson B, Meulien D, Ryan M, & Fertig J. Evaluation of Drinking Risk Levels as Outcomes in Alcohol Pharmacotherapy Trials: A Secondary Analysis of 3 Randomized Clinical Trials. JAMA Psychiatry. 2019 March 13. PubMed PMID: 30865232l; PubMed PMCID: PMC6450273.
- Knox J, Scodes J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten RZ, Mann KF, O'Malley SS, Anton RF, Hasin DS; Alcohol Clinical Trials (ACTIVE) Workgroup. Reduction in non-abstinent WHO drinking risk levels and depression/anxiety disorders: 3-year follow-up results in the US general population. Drug Alcohol Depend. 2019 Feb 14; 197:228-235. PubMed PMID: 30852375.
- Witkiewitz K, Kranzler HR, Hallgren KA, Hasin DE, Mann KF, Falk DE, Litten RZ, O'Malley SS, & Anton RF. Drinking Risk Level Reductions Associated with Improvements in Physical Health and Quality of Life Among Individuals with Alcohol Use Disorder. Alcoholism: Clinical and Experimental Research. 2018 Dec; 42(12):2453-2465. PubMed PMID: 30395350; PubMed Central PMCID: PMC6286196.
- Knox J, Wall M, Witkiewitz K, Kranzler HR, Falk DE, Litten RZ, Mann KF, O'Malley SS, Scodes J, Anton RF, & Hasin DS. Reduction in Non-Abstinent WHO Drinking Risk Levels and Change in Risk for Liver Disease and Positive AUDIT-C Scores: Prospective 3-Year Follow-Up Results in the US General Population. Alcoholism: Clinical and Experimental Research. 2018 Nov; 42(11)2256-2265. PubMed PMID: 30204248; PubMed Central PMCID: PMC6263142.
- Mann K, Aubin HJ, Charlet K, & Witkiewitz K. Can Reduced Drinking be a Viable Goal for Alcohol Dependent Patients? World Psychiatry. 2017 Oct; 16(3):325-326. PubMed PMID: 28941117; PubMed Central PMCID: PMC5608854.
- Mann K, Aubin HJ, & Witkiewitz K. Reduced Drinking in Alcohol Dependence Treatment, What is the Evidence? European Addiction Research. 2017 Sep 22;23(5):219-230. PubMed PMID: 28934736.
- Litten RZ, Falk DE, O'Malley SS, Witkiewitz K, Mann KF, Anton RF. Letter to Editor in Response to Johnson's Commentary (2017) on the Witkiewitz et al. (2017) Article. Alcoholism: Clinical and Experimental Research. 2017 May 4. PubMed PMID: 28471501.
- Witkiewitz K, Wilson AD, Pearson MR, Hallgren KA, Falk DE, Litten RZ, Kranzler HR, Mann KR, Hasin DS, O'Malley SS, & Anton RF. Temporal Stability of Heavy Drinking Days and Drinking Reductions Among Heavy Drinkers in the COMBINE Study. Alcoholism: Clinical and Experimental Research. 2017 May;41(5):1054-1062. PubMed PMID: 28295414; PubMed Central PMCID: PMC5404970.
- Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten RZ, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton RF. Change in Non-Abstinent World Health Organization Risk Drinking Levels and Alcohol Dependence: A 3-Year Follow-Up Study in the United States General Population. Lancet Psychiatry. 2017 Jun; 4(6):469-476. PubMed PMID: 28456501.
- Witkiewitz K, Hallgren KA, Kranzler HR, Mann KR, Hasin DS, Falk DE, Litten RZ, O'Malley SS, & Anton RF. Clinical Validation of Reduced Alcohol Consumption after Treatment for Alcohol Dependence using the World Health Organization Risk Drinking Levels. Alcoholism: Clinical and Experimental Research. 2017 Jan;41(1):179-186. PubMed PMID: 28019652; PubMed Central PMCID: PMC5205540.
- Witkiewitz, K, Falk, DE, Kranzler HR, Litten RZ, Hallgren KA, O'Malley SS, & Anton RF. Missing Data in Alcohol Clinical Trials with Binary Outcomes. Alcoholism: Clinical and Experimental Research. 2016 Jul;40(7):1548-57. PubMed PMID: 27254113.
- Witkiewitz K, Falk DE, Kranzler HR, Litten RZ, Hallgren KA, O'Malley SS, & Anton RF. Methods to analyze treatment effects in the presence of missing data for a continuous heavy drinking outcome measure when participants drop out from treatment in alcohol clinical trials. Alcoholism: Clinical and Experimental Research. 2014 Nov;38(11):2826-34. PubMed PMID: 25421518; PubMed Central PMCID: PMC4244651.
- Stout RL, Braciszewski JM, Subbaraman MS, Kranzler HR, O'Malley SS, Falk D and ACTIVE group. What happens when people discontinue taking medications? Lessons from COMBINE. Addiction. 2014 Dec; 109(12):2044-52. PubMed PMID: 25098969 PubMed Central PMCID: PMC4254710.
- Falk DE, Litten RZ, Anton RF, Kranzler HR, Johnson BA, Active Workgroup. Cumulative proportion of responders analysis (CPRA) as a tool to assess treatment outcome in alcohol clinical trials. J Stud Alcohol Drugs. 2014 Mar;75(2):335-46. PubMed PMID: 24650828; PubMed Central PMCID: PMC3965687.
- Greenfield TK, Ye Y, Bond J, Kerr WC, Nayak MB, Kaskutas LA, Anton RF, Litten RZ, Kranzler HR. Risks of alcohol use disorders related to drinking patterns in the US general population. J Stud Alcohol Drugs. 2014 Mar;75(2):319-27. PubMed PMID: 24650826; PubMed Central PMCID: PMC3965685.

- Anton RF, Litten RZ, Falk DE, Palumbo JM, Bartus RT, Robinson RL, Kranzler HR, Kosten TR, Meyer RE, O'Brien CP, Mann K, Meulien D. The Alcohol Clinical Trials Initiative (ACTIVE): purpose and goals for assessing important and salient issues for medications development in alcohol use disorders. Neuropsychopharmacology. 2012 Jan;37(2):402-11. PubMed PMID: 21900883; PubMed Central PMCID: PMC3242301.

ACTIVE Posters:

- Knox J. (2019, June). WHO Findings from the NESARC. Poster presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.
- O'Malley SS. (2018, June). Response to Pharmacotherapy: A Comparison of Endpoints Based on Abstinence, No Heavy Drinking and Reductions in WHO Drinking Levels in Three Trials. Poster presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Hasin D. (2018, June). WHO-Defined Risk Drinking Levels and Drinking Consequences: Prospective Findings From the NESARC Waves 1 & 2 (2001-2005). Poster presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Falk DE. (2017, December). Novel Efficacy Endpoints Based on Shifts in the World Health Organization (WHO) Risk Levels of Drinking: Treatment Effects in Alcohol Pharmacotherapy Trials. Poster presented at the American College of Neuropsychopharmacology 56th Annual Meeting, Palm Springs, CA.

ACTIVE Data Presentations:

- O'Malley S. (2021, June). WHO Risk Drinking Reduction A New Endpoint for Clinical Trials. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Anton, R. (2021, June). WHO Risk Drinking Level: A Harm Reduction Outcome For Clinical Trials For Alcohol Use Disorder. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Knox J. (presenter), Scodes J., Witkiewitz K., Kranzler H., Mann K., O'Malley S., Wall M., Anton R., Hasin D. (2021, June). Reduction in WHO Risk Drinking Levels and Cardiovascular Disease: 3-year Follow-up Results in the US General Population. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Virtual.
- Schacht J., Anton R. (2019, June). Prediction Of Alcohol Harm Reduction (Who RDL) Outcomes From Cue-Elicited Brain Activation In A Randomized Trial Of Naltrexone. Symposium presented at the Research Society on Alcoholism Scientific Meeting, Minneapolis, Minnesota.
- Witkiewitz K. (2019, June). Beyond Abstinence: Reductions in Drinking as an Endpoint for Alcohol Clinical Trials. Symposium presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.
- Hasin D. (2019, June). Validation of a Measure of Opioid Use Disorder Among Chronic Pain Patients Treated With Opioids. Workshop presented at the College on Problems of Drug Dependence 81st Annual Scientific Meeting, San Antonio, Texas.
- Anton RF. (2018, December) Harm Reduction as a Goal in AUD Pharmacotherapy– Role For the WHO Risk Drinking Category Change. Symposium presented at the AAAP Annual Meeting and Scientific Symposium, Bonita Springs, FL.
- O'Malley SS. (2018, June) 2018 RSA Distinguished Researcher Awardee: Beyond Abstinence: An Evolving Perspective on Naltrexone and Pharmacotherapy for Alcohol Use Disorder. Plenary presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- Anton RF. (2018, June) Insights From The Design and Implementation of Medications Development Trials for Alcohol Use Disorder. Panel presented at the Research Society on Alcoholism Scientific Meeting, San Diego, CA.
- O'Malley SS. (2018, May) ACTIVE Update: Reduction in World Health Organization (WHO) Drinking Risks Level as a Primary Endpoint for Alcohol Treatment Trials. Panel presented at the ASCP Annual Meeting, Miami Beach, Florida.
- Witkiewitz K. (2017, August). Reduction in World Health Organization (WHO) Drinking Risk Level as an Endpoint for Alcohol Clinical Trials. Symposium presented at the APA Annual Meeting, Washington D.C.

- O'Malley SS. (2017, May). The Development and Selected Performance of Patient Reported Outcomes (PRO) in Psychopharmacotherapy Trials – is the Juice Worth the Squeeze? A Review of Initiatives by the FDA, NIH, and the Alcohol Clinical Trials Initiative (ACTIVE). Panel presented at the ASCP Annual Meeting, Miami Beach, Florida.

ACTIVE Press Coverage:

- O'Connor, A. (2021, July 12). Alcohol Abuse Is on the Rise, but Doctors Too Often Fail to Treat It. *The New York Times*, Retrieved from https://www.nytimes.com/2021/07/12/well/live/alcohol-abuse-drinking-treatment.html?referringSource=articleShare

Financial Disclosure:

The ACTIVE Workgroup has been supported previously, but not in the past 36 months, by Abbott/Abbvie, Amygdala Neurosciences, Arbor Pharmaceuticals, GSK, Indivior, Janssen, Lilly, Mitsubishi, Pfizer, and Schering Plough, but in the past 36 months its activities were supported by Alkermes, Dicerna, Ethypharm, Kinnov Therapeutics, Lundbeck, Otsuka, and Pear Therapeutics.