ACTIVE Workgroup Meeting
October 27 – 28, 2022
Virtual Live Meeting

MINUTES

Participants:
Ray Anton, Medical University of South Carolina, Chair
Sarah Akerman, Alkermes
Arnie Aldridge, RTI
Henri Jean Aubin, Hôpitaux Universitaires Paris-Sud
Heather Davidson, Otsuka
Emmanuel de Rivoire, Kinnov Therapeutics
Dan Falk, NIAAA Advisor
Regina Grebla, Alkermes
John Hanrahan, Dicerna
Michaela Hoffman, Medical University of South Carolina
Raye Litten, NIAAA Advisor
Karl Mann, University of Heidelberg
Yuri Maricich, Pear Therapeutics
Stephanie O'Malley, Yale University School of Medicine
Alain Puech, Kinnov Therapeutics
Bernard Silverman
Mette Skalshoi Kjaer, Dicerna
Maria Sullivan, Pear Therapeutics
Celia Winchell, FDA
Katie Witkiewitz, University of New Mexico
Gary Zarkin, RTI
Maryam Afshar, FDA Guest
Bartholt Bloomfield-Clagett, FDA Guest
Laura Reynolds, Parthenon Management Group

Thursday, October 27, 2022

1. ***Welcome:*** New members and guests were welcomed to the meeting.

2. ***FDA Response Letter:*** In July 2022, the FDA sent a response letter to ACTIVE regarding the WHO RDL Qualification Plan which was submitted in 2018. R. Anton provided a summary of the letter, as well as provided an update on the progress that the ACTIVE Data Analysis Workgroup has made in answering additional questions raised.

3. ***Initial FDA Required Analyses of Horizant Study- Model for the COMBINE and Varenicline Studies:*** K. Witkiewitz has taken lead in creating the data analysis of the Horizant study, which will then be replicated for the Varenicline and COMBINE studies. These analyses will then be sent to the FDA along with other answers raised in the response letter. K. Witkiewitz shared with the group the details in building the analyses, as well as the results of the Horizant analyses once the variables were entered.

4. ***Discussion of FDA request regarding uniqueness/overlap of WHO RDL Categories as they relate to specific alcohol gram reductions:*** K. Witkiewitz and M. Hoffman discussed the WHO RDL categories as they relate to specific alcohol gram reductions.
    a. ***Comparison with the WHO Categorical Levels:*** There was concern that the same amount of alcohol use reduction might not result in a 2-level reduction due to the WHO categorical levels. The same amount of

alcohol reduction can result in false positive and false negative rates. For example, 30g daily alcohol consumption reduction can lead to no-change (e.g., reduce from 95g), 1-level reduction (e.g., reduce from 85g), 2-level reduction (e.g., reduce from 65g) for high-risk male AUD patients, depending on their actual average grams of daily alcohol consumption. The group discussed the best way to statistically address this in the revised qualification plan and agreed to explain that while it is rare, the binary variable explains more variance in AUD symptoms vs the grams per day predictability. The data presented were from the Horizant study, but it was suggested to address the FDA's concern using the COMBINE data.

b. ***Beyond WHO Very High Drinking:*** M. Hoffman discussed the lack of a ceiling for the very high drinking level category. Overall, the data show that extreme drinkers who do not drastically reduce their grams per day cannot be counted as a success for the outcome of the trial.

c. ***ACTION ITEM:*** It was suggested to prioritize the COMBINE trial when addressing the FDA's concern, by including both K. Witkiewitz's and M. Hoffman's results. By including both, it would provide a comprehensive look at the WHO risk levels good at predicting clinical benefit. The core workgroup will refine the plan on their next call.

5. ***Processes and Early Progress on the Development of a Patient Rated Outcome Measuring Craving in Substance Abuse and AUD Individuals:*** S. O'Malley provided an update on a study at Yale being conducted where they are developing patient rated outcome (PRO) to measure alcohol and drug craving. They were particularly interested in the idea of pursuing a craving measure that meets the standard of the FDA patient rated outcomes. They will be writing a grant to conduct the final phase of the process which is to field test the final item pool in a calibration sample in hopes of determining whether a single measure can be used to assess craving across the different substances or whether unique measures are needed for each substance.

Celia Winchell, Maryam Afshar, and Bartholt Bloomfield-Clagett recused themselves from the meeting before the Dicerna presentation.

6. ***A Novel Pharmacotherapeutic Approach to Drinking Reduction/Abstinence: What are the possible Target Populations and Drinking Outcome Measure(s)?*** J. Hanrahan began by explaining that DCR-AUD is an investigational RNA interference (RNAi) therapeutic designed to selectively knock down the expression of Aldehyde Dehydrogenase 2 (ALDH2) in the liver. ALDH2 is a viable target for AUD because ethanol ingestion leads to increased acetaldehyde levels, which leads to unpleasant physiological effects: peripheral vasodilation, facial flushing, headache, nausea—which could be leveraged as a stop-drinking-now signal. He noted that individuals carrying a mutant ALDH2 allele are protected against AUD. Additionally, he explained how DCR-AUD worked, as well as how the effect of ALDH2 knockdown was measured. **NOTE: It is noted that the FDA staff attending the meeting recused themselves from this presentation and discussion.**

<u>Friday, October 28, 2022</u>

7. ***Update on the Simulation Project:*** M. Hoffman and A. Aldridge provided an update on the clinical trial simulation project in which the core ACTIVE workgroup has been working on since late 2021.
M. Hoffman began by explaining the rationale for the project stating there is limited knowledge on the ideal conditions for AUD clinical trials, thus the ACTIVE workgroup have reexamined data from past trials and have published methodologies and tested new analytic ideas. A. Aldridge concluded the presentation by demonstrating how the simulation will work. It was noted that as more data is collected, the simulation model will be updated. The ultimate goal will be to make it publicly available and host on a website that companies and investigators can use.

8. ***Health Care Impact of Alcohol Use Disorder in Patients with Ambulatory Care Medical Conditions:*** R. Grebla presented a study conducted by Alkermes in which the purpose was to determine the association of alcohol dependence (AD), defined here as moderate-to-severe AUD, with healthcare utilization (HCRU) and costs for patients with selected chronic medical conditions.

9. ***Primary and Secondary Endpoints for AUD Trials: Clinical and Regulatory Considerations?*** M. Sullivan and Y. Maricich shared with the group work that is being planned by Pear Therapeutics in regard to AUD, as well as requested feedback on some of the questions that arise during the clinical trials as well as challenges regarding endpoints. They provided two different perspectives regarding the primary and secondary outcomes in AUD trials. M. Sullivan began by sharing the Clinical Perspective, followed by Y. Maricich sharing the Regulatory Perspective.

10. ***Future ACTIVE considerations:*** R. Anton shared with the group possible considerations for future ACTIVE work.

***Papers in Progress or to Be Considered*:**

- S. O'Malley might consider coordinating a publication on the PROMIS or Imbibe PRO measure.
- W. Dowd/A. Aldridge and G. Zarkin - paper on WHO and Employment/Labor outcomes

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

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