

ACTIVE Workgroup Meeting #18
March 29 – 30, 2017
Hilton Washington D.C./Rockville Hotel & Executive Meeting Center
Location: Potomac

Participants:

Ray Anton, Medical University of South Carolina, Chair
Anne Andorn, Indivior
Henri-Jean Aubin, Hôpitaux Universitaires Paris-Sud
Maeva Deniaud, MDSTAT Consulting
Dan Falk, NIAAA
Jay Graham, Indivior
Deborah Hasin, Columbia University, Thursday only by phone
Henry Kranzler, University of Connecticut Health Center
Raye Litten, NIAAA
Roger Meyer, Penn State Hershey College of Medicine
Meghan Morean, Oberlin College
Martin Mumenthaler, Amygdala Neurosciences
Charles O'Brien, University of Pennsylvania
Stephanie O'Malley, Yale University
Tom Permutt, FDA
Tanya Ramey, NIDA
Evan Scullin, Arbor Pharmaceuticals
Bernie Silverman, Alkermes
Peter Strumph, Amygdala Neurosciences
Celia Winchell, FDA
Katie Witkiewitz, University of New Mexico, Wednesday only by phone
Gary Zarkin, RTI, Wednesday only by phone
Benjamin Zakine, Ethypharm
Lindsay Snyder, Parthenon Management Group

Summary of the Meeting:

- New members and guests were welcomed to the meeting.
- FDA-CEDA Approval for participation in the meeting was discussed and reviewed. The group agreed to actuate public disclosure as outlined in the action plan of that approval.
- A discussion in how the Surgeon General's Report on Addiction and the American Psychiatric Association's draft guidelines on the Treatment of Alcohol Use Disorder converged on reduced drinking and harm reduction as an acceptable and useful goal of treatment that could affect patient care and public health. The group acknowledged that this was consistent with the workgroups direction of finding drinking outcome variables that were short of full abstinence, but would be indicative meaningful clinical improvement, while be acceptable to a wide range of AUD patients.

- The group agreed that reaching out to Primary Care Health Providers would be a good point at this point in the progress and evolution of its work. Names will be solicited from members and perhaps societies. A person familiar with the issues but also capable and willing to communicate important issues from the ACTIVE workgroup to the wider Primary Care audience would be desirable.
- Discussion of a workgroup paper, first authored by Dr. Dan Falk of the NIAAA, showing how the World Health Organization (WHO) drinking risk level reduction could be used in clinical trials of AUD was conducted. Dr. Falk presented data from 4 separate AUD clinical trials:
 - NIAAA's Varenicline Study (Litten et al., 2013):
 - COMBINE (Anton et al., 2006)
 - Multi-site Topiramate Study (Johnson et al., 2007)
 - Lundbeck's Nalmefene Study (Aubin et al., 2015):

The retrospective data analysis showed that the WHO risk level shift from higher risk to lower risk was equal to or better in all of these trials when compared to traditional drinking outcome measures. This information combined with past ACTIVE workgroup papers (see published manuscripts) that showed a meaningful diagnostic and/or clinical change with these risk level shifts, strongly supports the consideration of the WHO drinking risk level reduction as a goal/endpoint in AUD clinical trials. How to handle missing data still needs resolution. A paper is being prepared and will likely be submitted to a high impact journal.
- Preliminary data was presented on how the WHO risk level reduction measure related to some health consequence markers. There is some evidence from the COMBINE Study that a reduction in WHO risk level drinking has effects on blood pressure (reduced), GGT and CDT (reduced), and ER visits (reduced). More detailed work on these measures are needed.
- The workgroup agreed to contract with Gary Zarkin of RTI in North Carolina to replicate and extend the economic impact work that they did on the COMBINE Study and published many years ago but this time using the WHO drinking risk level change as the marker/outcome of improvement. Phase one would focus on health care costs. Phase two would focus on social costs (e.g. criminal justice and automobile accidents etc.). The importance of this work to provide high quality data that might be needed by insurance companies to support coverage for AUD medications if the WHO drinking risk reduction was the primary endpoint.
- As a corollary to the above work continued analysis of the NESARC data (large epidemiological data base capturing change in drinking and AUD diagnosis over a 2-3 year period) focusing on change in WHO drinking risk level as that relates 1) to change in AUDIT scores and 2) change in health and utilization measures will be undertaken by the Columbia group (Hasin et. al.). This would be an extension of the data presented in a paper in Lancet Psychiatry (In press).

- The workgroup engaged in a discussion led by Dan Falk of NIAAA that overviewed adaptive design in clinical trials with the goal of evaluating whether any of these designs might be applied to AUD registration trials. Early stage discussion led to interest in pursuing these discussions more thoroughly at future meetings.
- The need and desirability of a Patient Reported Outcome measure was reintroduced with data presented on the IMBIBE drinking consequence measure suggesting that it was not metrically ideal. The potential of the NIH sponsored PROMISE questionnaire for clinical trials was overviewed. It appears more metrically sound but might lack items germane to alcohol health effects focusing more on psychosocial behaviors. More analysis and consideration of the PROMISE is deemed warranted.
- Future directions of ACTIVE inquiry and consensus occurred. A short list included more work on: appropriate clinical trial length, potential use of wearable measures of alcohol use/level, lab tests indicating recent and/or sustained heavy alcohol use, translational paradigms to guide medication development (e.g. brain imaging, lab drinking experiments) and pharmacogenetics.
- Discussed available data sets to evaluate the stability of the WHO risk drinking measure over time. A formal request to obtain the 6 month Vivitrol clinical trial data set - focusing on placebo treated subjects only was endorsed.
- The group was reminded about an NIAAA/ACTIVE symposium at the ASCP meeting in May.