

The following is a list of questions/issues that were identified by ACTIVE participants in regards to gaps in knowledge or need for clarification in conducting clinical trials of alcohol dependence. The questions /issues were rated on a scale of 1 (most important/highest priority to address) to 3 (least important/lowest priority to address) by the ACTIVE group members. In addition, the members also expressed whether each particular question could be addressed by potentially available data and only by consensus opinion. The top seven questions/issues were ones that the group decided to focus on initially. These seven are addressed in the main body of the paper.

TALLY - QUESTIONS ON STUDY DESIGN/OUTCOME MEASUREMENT				
	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
A. POPULATION:				
QUESTION: A1. Some published clinical trials have required abstinence (usually voluntary abstinence lasting a minimum of 3-4 days) prior to randomization and some have required active drinking prior to randomization. What is the effect of selecting subjects who are drinking daily up until day of randomization versus those that are abstinent for some days prior to randomization on drinking outcome endpoints?				
TALLY: A1	Y= 8	Y= 2	1=5	
	N=1	N=5	2=3	
			3=1	1.6
QUESTION: A2. Does a longer duration of pre-randomization abstinence have a different moderating effect on the response to specific treatments?				
TALLY: A2	Y= 8	Y= 2	1=4	
	N=1	N=3	2=5	
			3=0	1.6
QUESTION: A3. Should we include subjects in trials who do not have a goal of abstinence and, if so, how does this affect the primary outcome drinking variable(s)?				
TALLY: A3	Y= 6	Y= 3	1=2	
	N=2	N=3	2=7	
			3=0	1.8
QUESTION: A4. What are the advantages and disadvantages of including subjects who a) had past medical detoxes or b) need to be medically detoxified currently?				
TALLY: A4	Y= 3	Y= 4	1=1	
	N=3	N=2	2=4	
			3=3	2.3
QUESTION: A5. What liver and concomitant medications are allowable/preferable in a clinical trial? Should this be done in a separate safety study?				
TALLY: A5	Y= 1	Y= 7	1=3	
	N=4	N=2	2=3	
			3=4	2.1
QUESTION: A6. What are the advantages and disadvantages of including subjects with psychiatric comorbidities in clinical trials?				
TALLY: A6	Y= 2	Y= 5	1=5	
	N=3	N=1	2=3	
			3=0	1.4

	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
B. STUDY DURATION:				
QUESTION: B1. Is there data to show that a longer period of observation is needed to document a stable response, or that a shorter period will give sufficient information to predict longer-term results? Might different trial durations be suitable depending on the behavioral outcome sought (e.g. complete abstinence vs. non-risk drinking)?				
TALLY: B1	Y= 7	Y= 6	1=8	
	N=1	N=3	2=2	
			3=0	1.2
QUESTION: B2. Should this be based on the ability of the observed drinking behavior to predict longer-term outcome? Or should short-term outcome endpoints be viewed more along the line of a circumscribed intervention model with long-term outcomes ONLY evaluated to predict how long the benefits of the treatment might last?				
TALLY: B2	Y= 3	Y= 7	1=4	
	N=5	N=2	2=6	
			3=0	1.6
QUESTION: B3. What are the practical limitations (sample size, statistical power estimates, retention rates) and cost implications (companies willing to pay for a new indication) for longer term versus shorter time trials?				
TALLY: B3	Y= 7	Y= 8	1=5	
	N=1	N=1	2=4	
			3=1	1.6

	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
C. DATA TO BE COLLECTED:				
QUESTION: C1. Is this level of detail necessary when the outcome measure is a binary (drank heavily/did not drink heavily) analysis? Could a simpler data collection measure be used?				
TALLY: C1	Y= 5 N=2	Y= 7 N=2	1=4 2=3 3=3	1.9
QUESTION: C2. Are other analyses important enough to require that we continue to collect data at this granular a level?				
TALLY: C2	Y= 2 N=3	Y= 8 N=1	1=4 2=4 3=2	1.8
QUESTION: C3. If self-reported abstinence that is contradicted by biological markers (including breath analysis) should the subject still be rated as being abstinent. How should this be recorded in the TLFB daily drinking calendar? Should composite measures of drinking and biomarkers be used?				
TALLY: C3	Y= 5 N=2	Y= 4 N=3	1=5 2=5 3=0	1.5
QUESTION: C4. Should dimensional scales of alcohol severity, consequences, and quality of life be obtained in clinical trials? When collected (baseline and end?) and how should they be used (alone, in combination with drinking data and/or biological markers?). Can significant change in severity, alcohol consequences, or QOL be a satisfactory end-point?				
TALLY: C4	Y= 5 N=2	Y= 7 N=1	1=5 2=5 3=0	1.5
QUESTION: C5. What is the appropriate "grace period" (period in which drinking or other outcome data will not be heavily weighed in efficacy analysis) when evaluating a response to treatment? This should be examined by MOA and across studies, if possible.				
TALLY: C5	Y= 5 N=1	Y= 3 N=5	1=5 2=2 3=2	1.7

	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
D. ANALYSIS:				
QUESTION: D1. Are there other patterns of drinking that could be considered as end-points? How do different patterns of drinking behavior relate to alcohol dependence severity, consequences, and QOL?				
TALLY: D1	Y= 7 N=0	Y= 6 N=2	1=4 2=6 3=0	1.6
QUESTION: D2. Are there other acceptable medical or social endpoints such as reduction in blood pressure, days worked, or medication (for other conditions) compliance, that can be used as surrogates of success?				
TALLY: D2	Y= 4 N=2	Y= 3 N=5	1=1 2=6 3=3	2.2
QUESTION: D3. Can a composite measure such as drinking and consequences capture how many individuals are doing well (better) versus poorly (same or worse)?				
TALLY: D3	Y= 5 N=2	Y= 3 N=5	1=3 2=3 3=4	2.1
QUESTION: D4. How appropriate is average (parametric or continuous data) versus categorical (number of individuals) type of end point data.				
TALLY: D4	Y= 6 N=1	Y= 6 N=2	1=4 2=6 3=0	1.6
QUESTION: D5. How should missing data be handled as a result of study dropout? Should a data substitution/imputation method be used to "fill in" the missing values? If so, which one? This is particularly relevant when the missing data includes daily alcohol consumption during treatment and follow-up (critical to the computation of drinking outcome measures).				
TALLY: D5	Y= 6 N=0	Y= 5 N=2	1=8 2=1 3=0	1.1

	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
E. DURATION OF USE:				
QUESTION: E1. Is this a reasonable assumption given the natural history of the disorder? This assumption could also relate to treatment length and safety issues.				
TALLY: E1	Y= 3	Y= 6	1=3	
	N=4	N=3	2=5	
			3=2	1.9
	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
F. TYPICAL RESPONSE RATES:				
QUESTION: F1. For the purpose of calculating sample size, what are typical treatment results in placebo-treated patients or those treated with behavioral interventions alone? What is known about spontaneous, unassisted, or self-help remission?				
TALLY: F1	Y= 8	Y= 3	1=3	
	N=0	N=5	2=5	
			3=2	1.9
QUESTION: F2. How important is it to match drinking outcome endpoints to both mechanisms of action of the drug and also to the motivation of the subjects (abstinence versus cut-down)?				
TALLY: F2	Y= 3	Y= 4	1=3	
	N=4	N=2	2=3	
			3=3	2.0

	A. Can question be addressed with available data?	B. Should question be addressed by consensus of opinion?	C. Rate importance/priority 1=High 3=Low	Average Score of Respondents
G. GENERAL QUESTIONS:				
QUESTION: G1. What is a "clinically significant" change from pre-randomization drinking if "reduction " in drinking might be considered as a primary endpoint in clinical trials?				
TALLY: G1	Y= 4 N=2	Y= 4 N=3	1=5 2=3 3=0	1.4
QUESTION: G2. What type of phase 1 and alcohol interaction studies are appropriate prior to initiating a phase 2 trial?				
TALLY: G2	Y= 2 N=3	Y= 7 N=2	1=3 2=2 3=5	2.2
QUESTION: G3: What kind of a signal in a phase 2 trial justifies going into phase 3?				
TALLY: G3	Y= 3 N=3	Y= 6 N=2	1=3 2=3 3=3	2.0
QUESTION: G4. What are the appropriate qualifications for investigators conducting alcohol clinical trials in order to reduce heterogeneity or variability in results?				
TALLY: G4	Y= 3 N=3	Y= 6 N=2	1=1 2=7 3=2	2.1
TOTAL RESPONDENTS = 10				