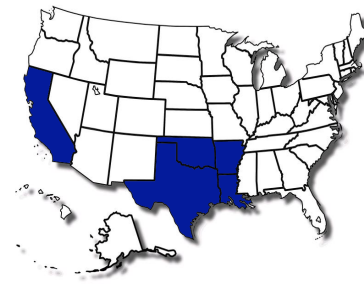
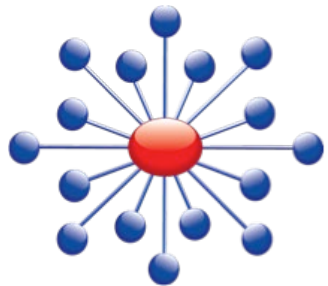


Outcomes From a Randomized, Double-Blind, Placebo-Controlled Trial of Monthly Injectable Buprenorphine for Methamphetamine Use Disorder: CTN0110

Steve Shoptaw, Udi Ghitza, Steven Nieto, Erik Anderson, Tara Chowdhury, Julie Croff, Timothy Hall, Judith Tsui, Thomas Carmody, Sidarth Wakhlu, Manish Jha, Mariah Kalmin, Madhukar Trivedi

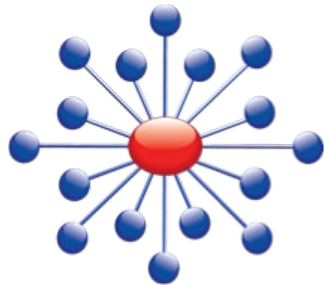
Big South West Node, NIDA CTN

June 18, 2024



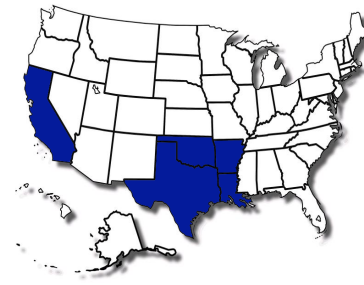
Disclosure

Investigators in this trial received clinical supplies from Indivior, Inc



Acknowledgement

- Research reported in this presentation was supported by Helping to End Addiction Long-term[®] Initiative, or NIH HEAL Initiative[®] under award number **UG1DA020024**
- The views and opinions expressed in this presentation are those of the authors only and do not necessarily represent the views, official policy, or position of the US Department of Health and Human Services or any of its affiliated institutions or agencies.
- Dr Ghitza was substantially involved in UG1DA020024, consistent with his role as NIDA Scientific Officer



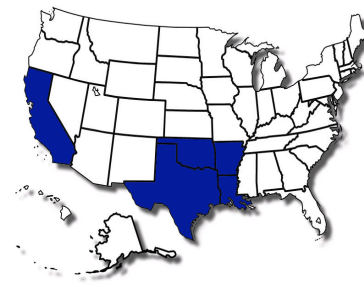
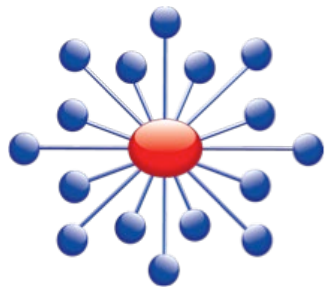
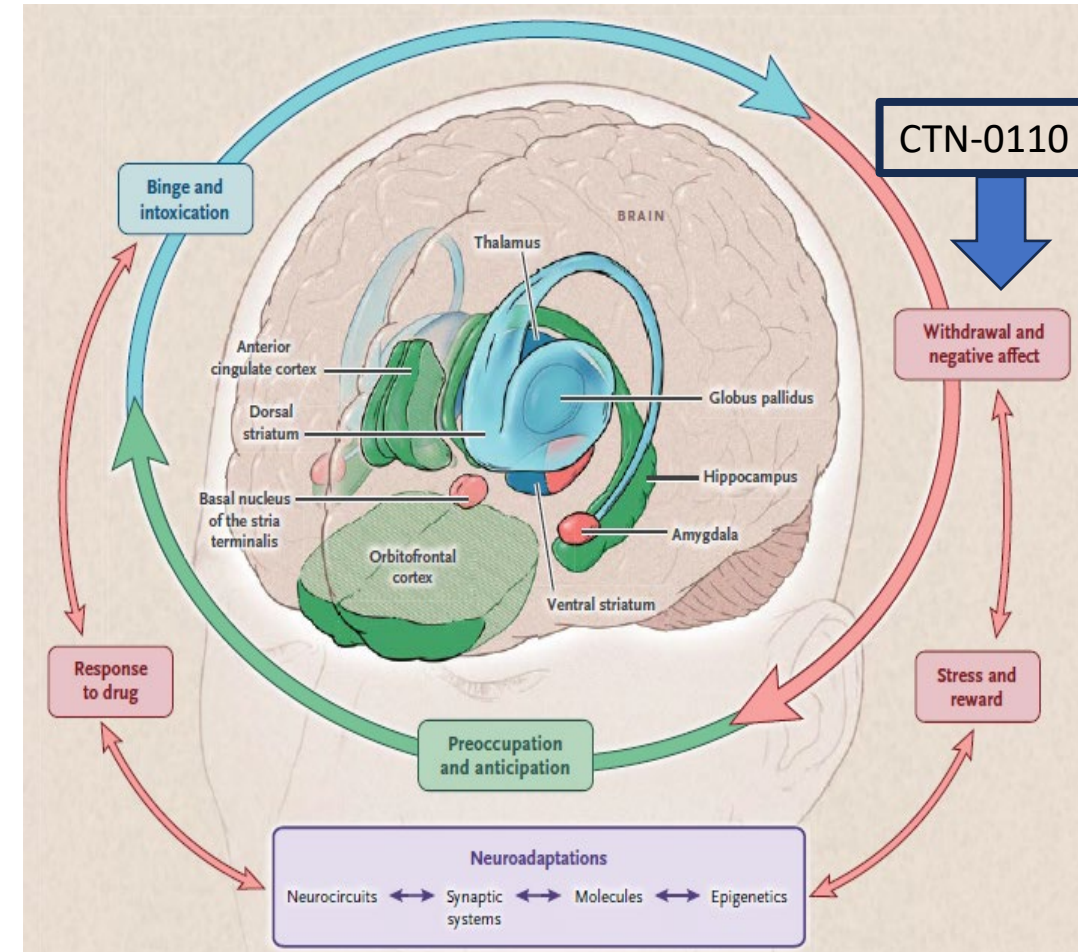
Rationale: Kappa Opioid Receptor Antagonist

Stimulants are the drivers of the fourth wave of the United States drug overdose epidemic

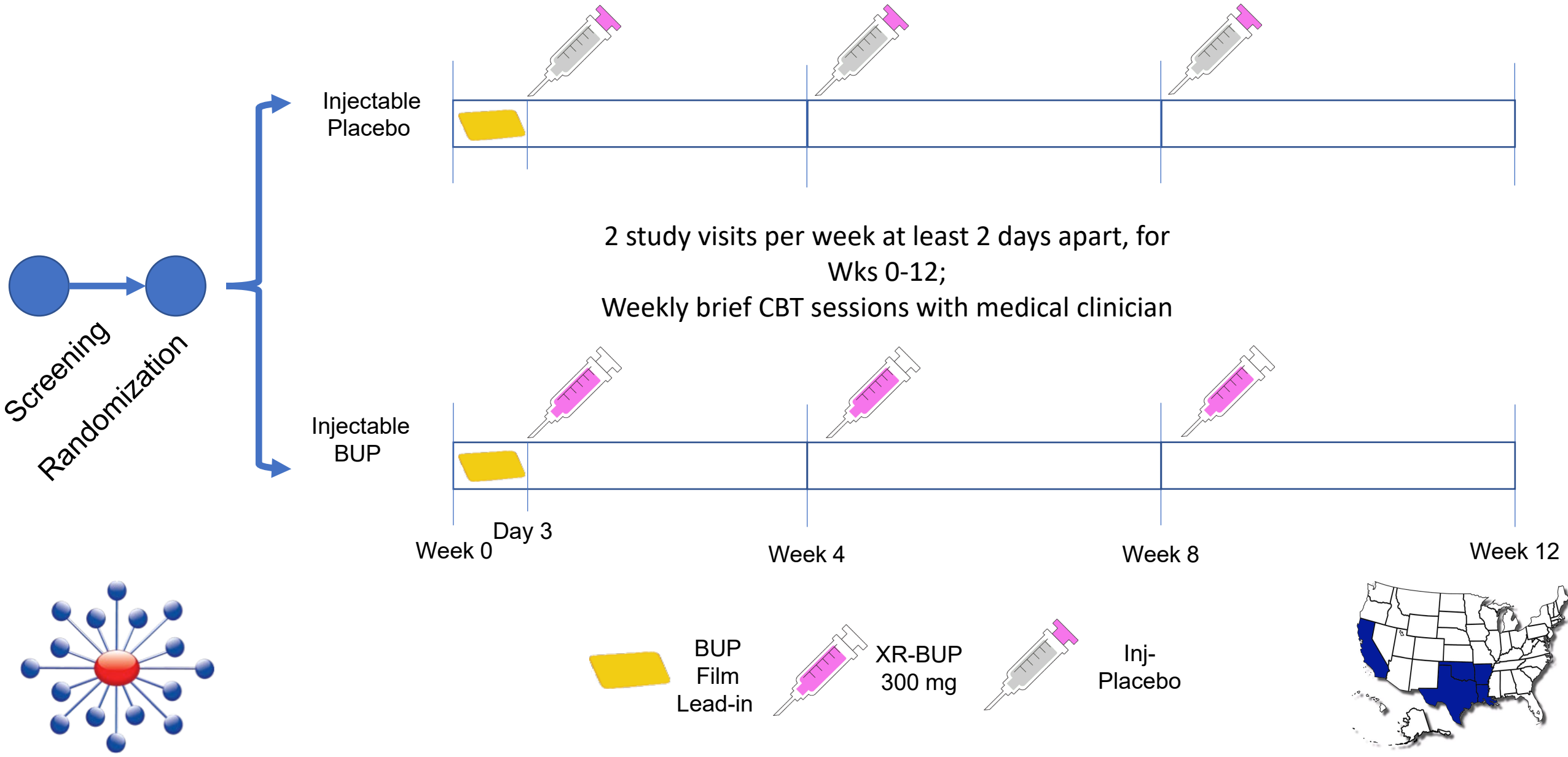
Kappa opioid receptor antagonists promote feelings of wellbeing and represent a medication addressing the “dark side” (e.g., Falcon E et al., *Neuropsychopharmacology*, 41:2344-51)

Pilot findings: extended-release Naltrexone (XR-NTX) plus oral BUP (4mg and 16 mg), produced modest, though statistically significant, reductions in cocaine use (urine-verified) among those adherent to oral BUP compared to placebo (verified with BUP blood levels; Ling, W., et al., *Addiction*, 2016. 111:1416-1427)

This study was designed to test monotherapy for Buprenorphine as the medication is used for treatment refractory depression in persons with no OUD

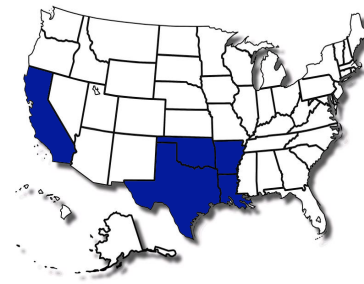
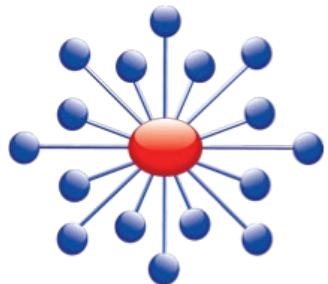


CTN-0110 Study Design



Inclusion Criteria

- 18 to 65 years of age, inclusive;
- **MA Criteria**
 - Interested in reducing or stopping methamphetamine (MA) use;
 - DSM-5 criteria for moderate or severe methamphetamine use disorder (≥ 4 criteria; MINI);
 - Self-report MA use on ≥ 18 days in 30-days prior to consent (Time-Line Follow-Back);
- **Opioid Criteria**
 - DSM-5 criteria for mild Opioid Use Disorder (≤ 2 criteria) or opioid misuse;
 - > 2 urine drug screens (UDS) positive for MA out of a possible 3 tests within 10-days;
 - > 1 UDS positive for opioids during the screening phase to document recent opioid use;
 - UDS negative for opioids on the day of randomization to indicate control over opioid use;
- Agree to use acceptable birth control methods;
- Willing and able to comply with all study procedures and medication instructions.



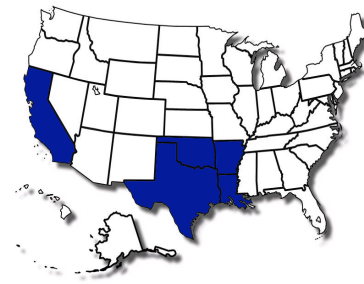
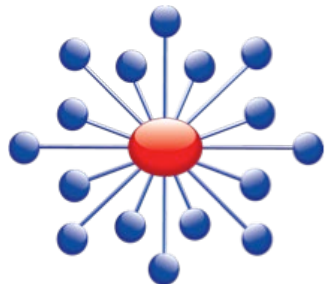
Outcomes

Primary Outcome:

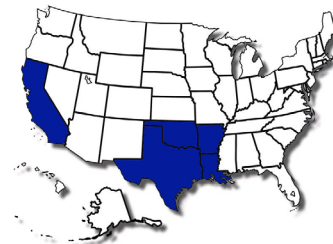
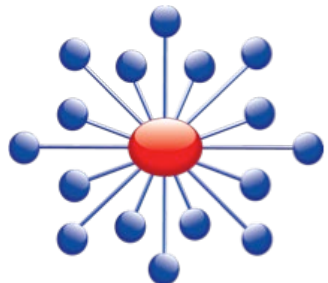
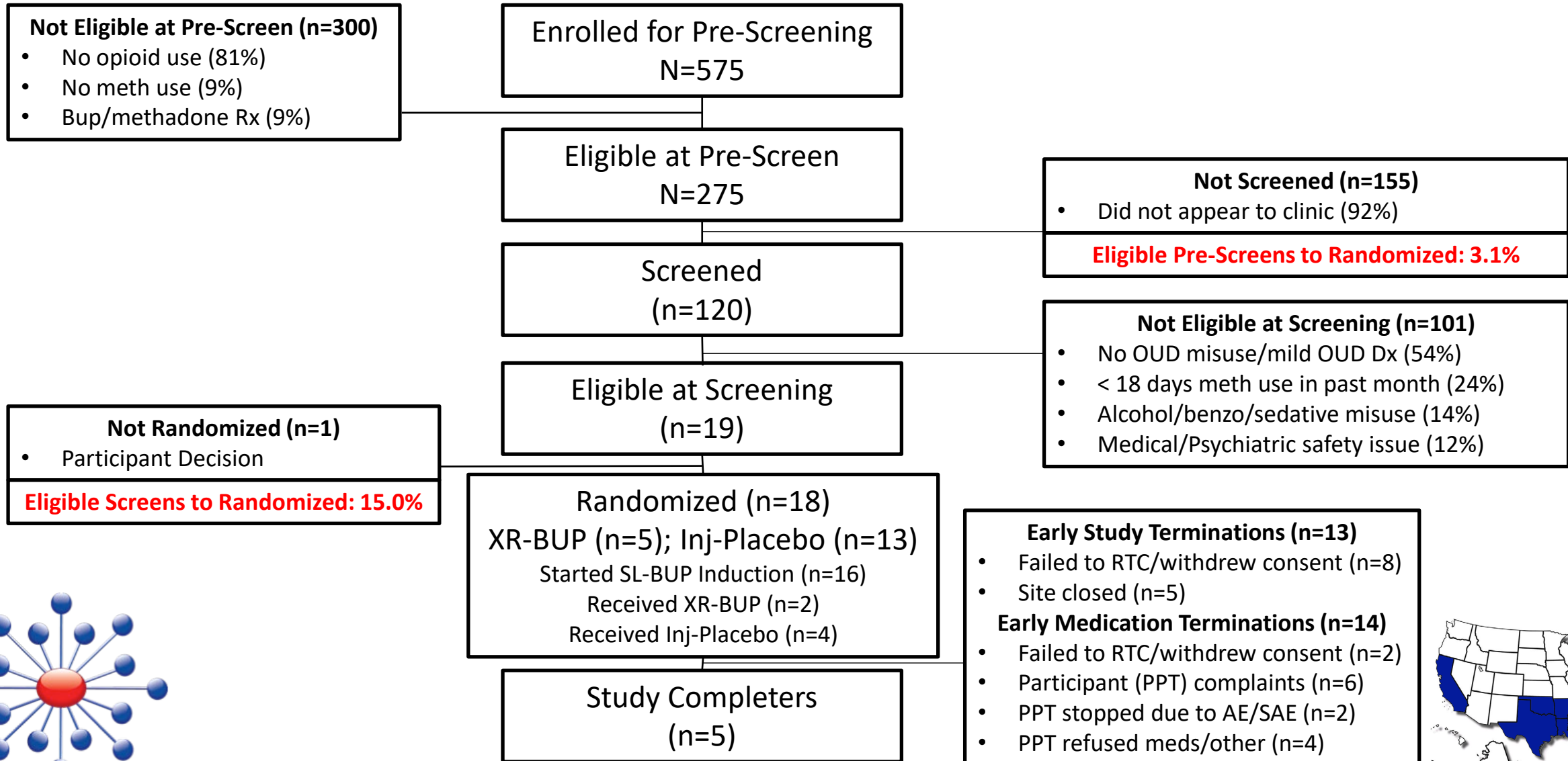
- Number of MA-negative UDS results obtained during weeks 9 through 12 for the XR-BUP and Inj-Placebo conditions

Secondary Outcomes:

- Alternate measures/composites of methamphetamine use (TES, TLFB)
- Measures of Opioid Use – Opioid TES, TLFB opioid use;
- Measures of MA and opioid co-use (TES, TLFB)



STROBE FLOW DIAGRAM



Demographics of Randomized Participants (n=18)

Characteristic	N (%) or M (SD)
Sex at Birth	
Male	13 (72.2%)
Female	5 (27.8%)
Age	44.1 (8.5)
Latino/Hispanic Ethnicity	4 (22.2%)
Race	
Black/Afr Amer	4 (22.2%)
White	10 (55.6%)
Other/Multirace	4 (22.2%)
Education*	
HS or less	4 (22.2%)
Some College	8 (44.4%)
Post HS Degree	4 (22.2%)
Marital Status	
Never Married	7 (38.9%)
Partner/ed	11 (61.1%)
Housing Status*	
Alone/with Family	10 (55.6%)
Unstably Housed	8 (44.4%)

Evaluable Participants (n=6)

Inj-Placebo = 4

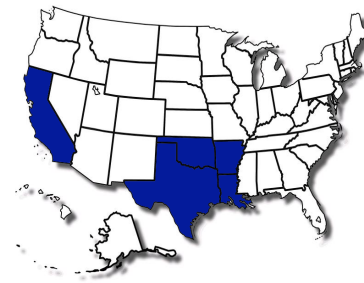
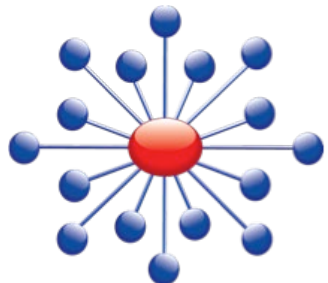
XR-BUP = 2

* Completers (n=5)

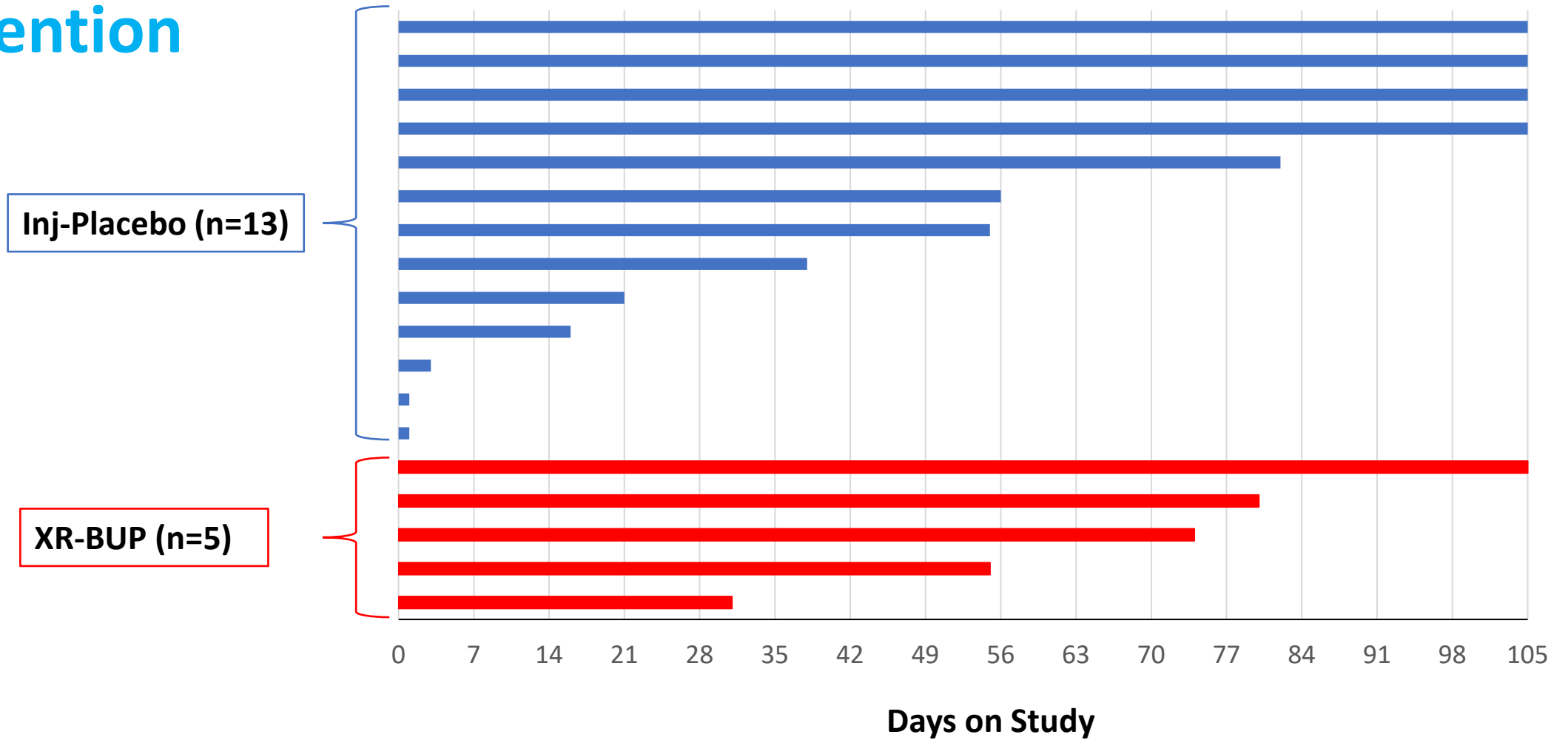
Inj-Placebo = 4

XR-BUP = 1

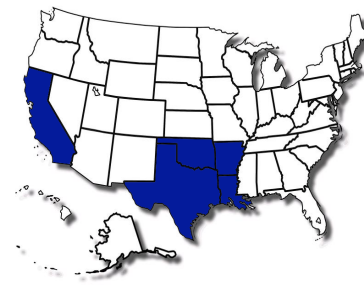
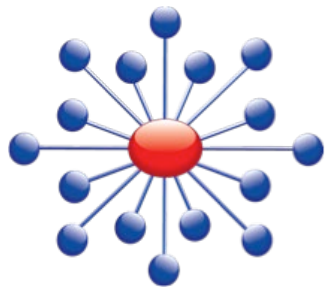
- 4 had post HS school education
- 2 were unhoused



Retention

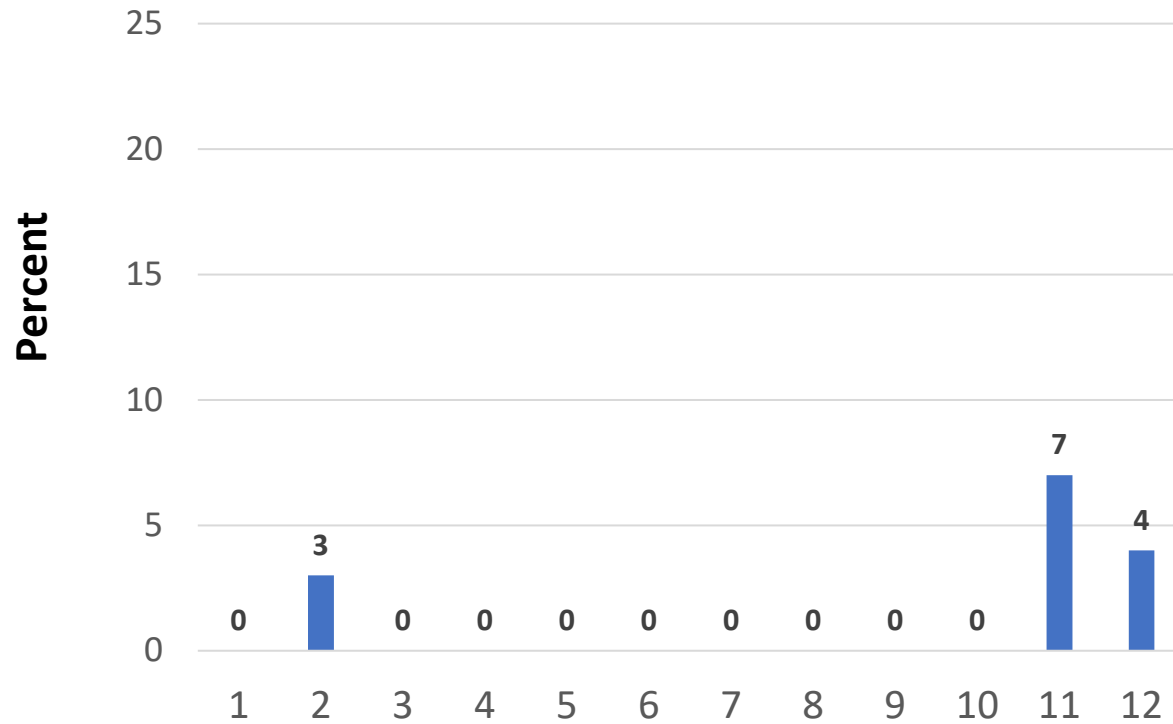


- Protocol Approved June 2022
- Six sites activated March 2023 to June 2023
- 6 months of energetic, multi-pronged recruitment strategies implemented
- DSMB recommended closing enrollment September 28, 2023

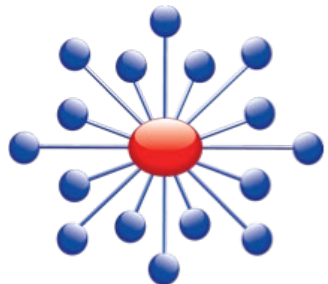
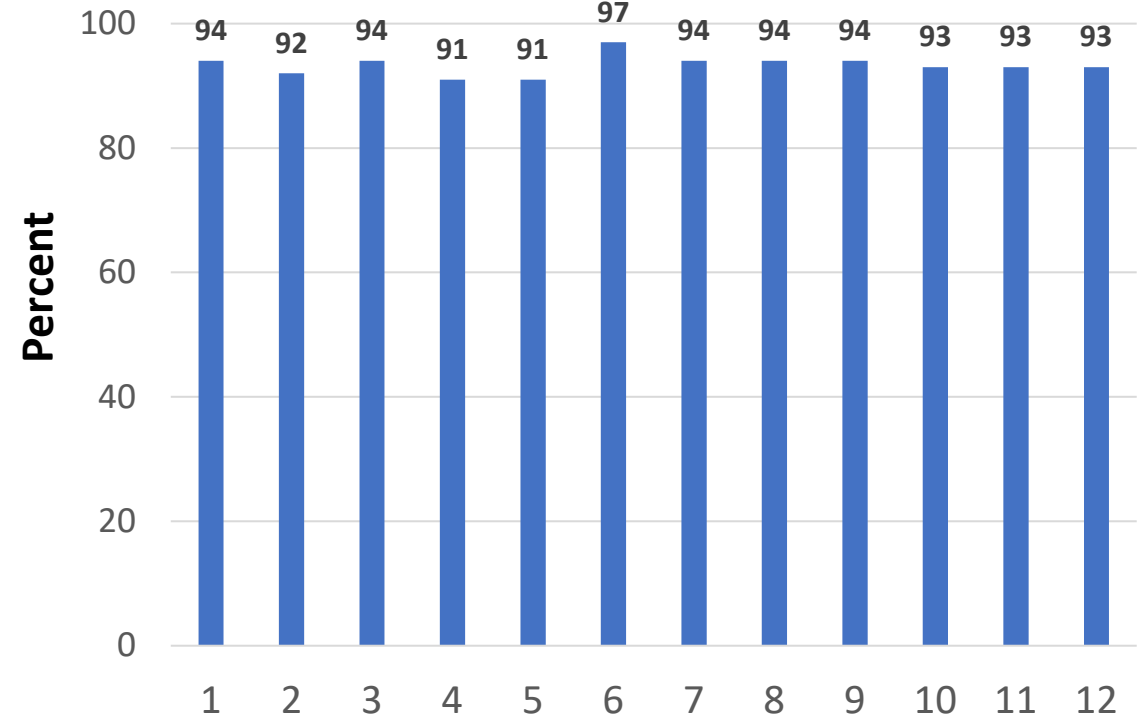


Urine Drug Screen Results Across 12 Weeks: Full Sample (n=18)*

Methamphetamine Negative Samples¹

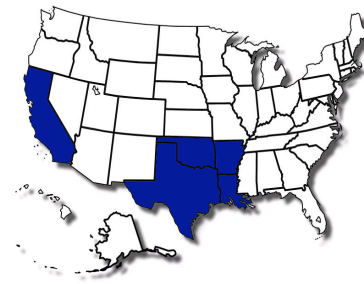


Opioid Negative Samples^{1,2}



Study Week

Study Week



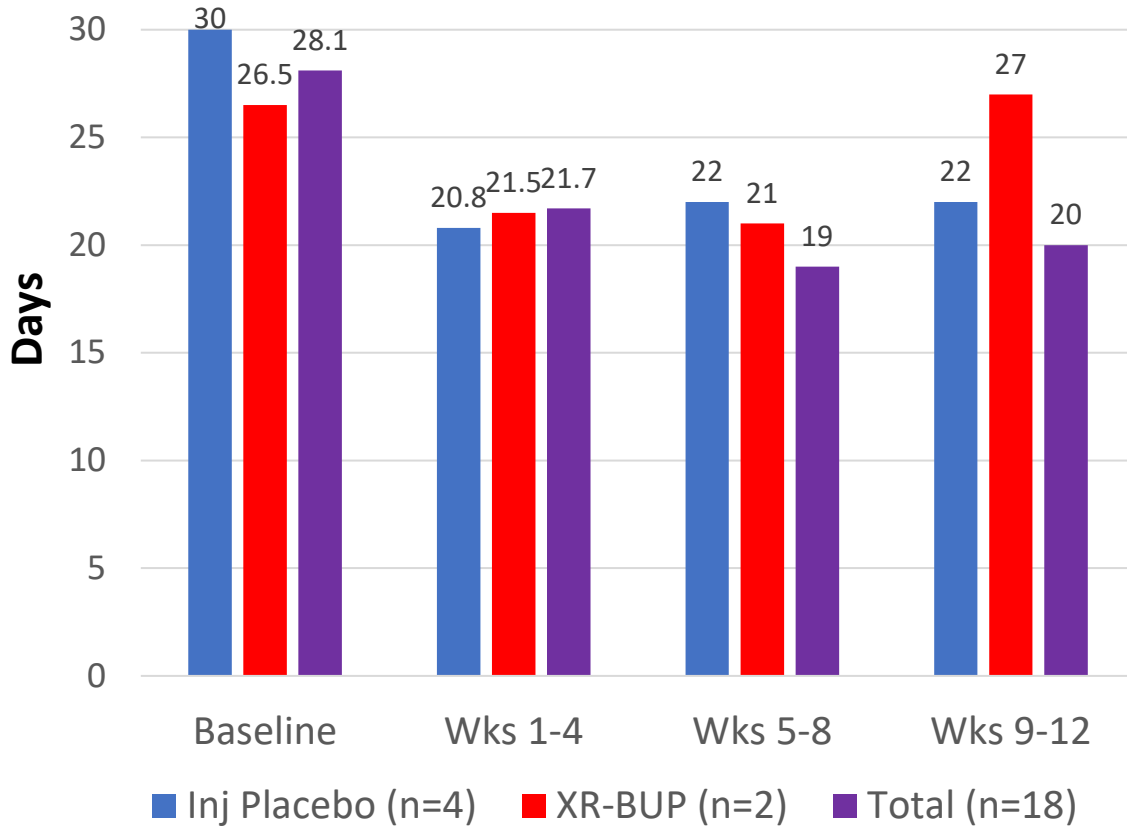
¹ Evaluable Participants analysis (n=6): 0% meth negative and 100% opioid negative samples

² Opioid urine samples not tested for buprenorphine; were tested for fentanyl

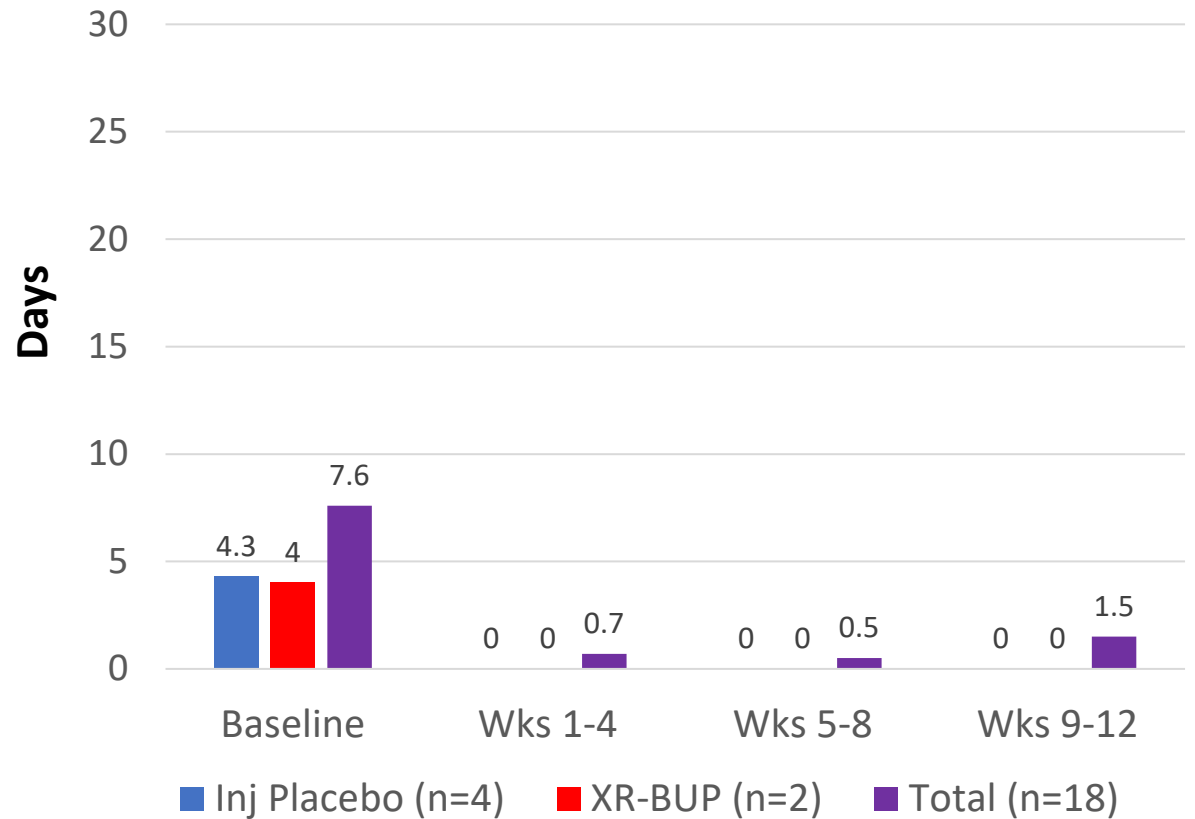
* Missing UDS problem is severe; denominator of 18, numerator # negative samples

Self-Reported Methamphetamine and Opioid Use, Past 30 Days

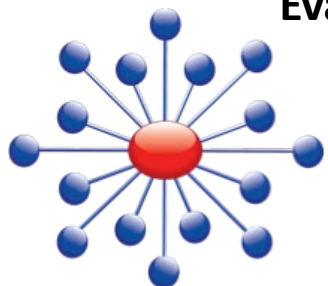
Methamphetamine



Opioids²



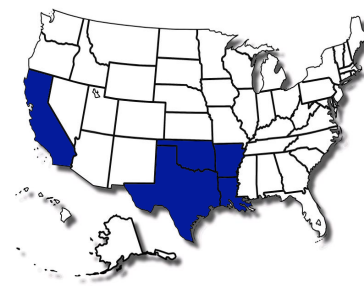
Evaluable Participants¹



¹ There were 6 evaluable participants in this analysis (blue and red bars)

² None of the 16 participants who received at least one dose of SL-BUP, nor either of the 2 participants on > 1 dose of SL-BUP reported iatrogenic opioid use disorder

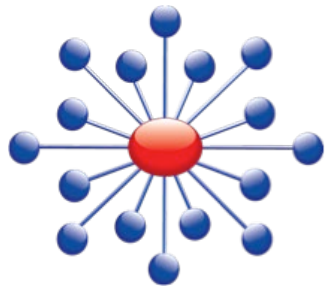
Evaluable Participants¹



Study Treatment Emergent Adverse Events

SAE

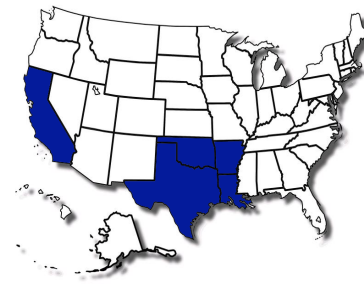
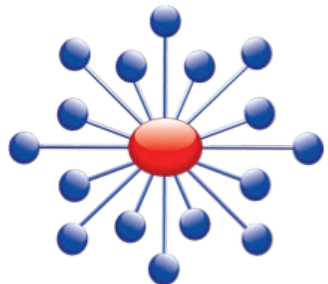
- XR-BUP Condition during induction after 4mg SL/BUP - Acute hypoxic and hypercapnic respiratory failure
 - No study injection administered



AE Description	XR-BUP	Grade	Inj-Placebo	Grade
Aches/Pains			1	Mild
Acute Allergic Reaction			1	Moderate
Bite Wound			1	Mild
R/L Lower Leg Cellulitis			1	Mild
Constipation	1	Mild	2	Mild
Intermittent Dizziness			1	Mild
Intermittent Drowsiness			1	Mild
Headache			1	Mild
Nausea	1	Mild	1	Mild
Navel Candidiasis			1	Mild
Non-specific ST elevation			1	Mild
Rash/Pruritis	2	Mild		
Increased Sweating	1	Mild		
Toothache			1	Mild

Summary/Discussion

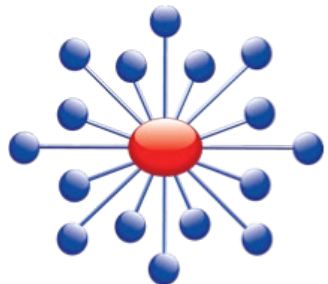
- Unusually challenging to recruit sample of persons with moderate-to-severe methamphetamine use disorder with mild opioid use disorder/opioid misuse
 - Data from pre-screening to screening to randomized participants document the low number of individuals with this poly-substance use profile
- Buprenorphine without mu antagonist leads people with primary identity as a person who uses stimulants to refuse further treatment with the medication
 - Opposing mu using XR-NTX prior to XR-BUP *is tolerable* to participants with cocaine use disorder; CURB-2 (CTN-0109) has 217 randomized participants as of 5/31/2024



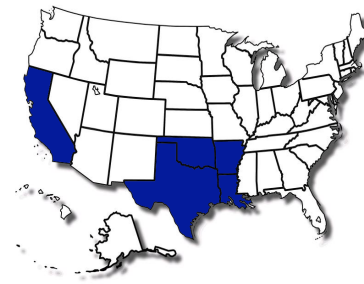
Discussion Continued

Issues of Identities When Conducting Stimulant Medication Research

- Epi documents increasing prevalence of poly-substance use at all points of addiction career – from incident use, through treatment settings, through overdose and deaths
- Even though many are using poly-substances, often combining stimulants with opioid use, everyone has preferences for which drug is the trunk and which is the branch
 - Qualitative data is in analysis phase to understand experiences and perceptions regarding meth use when treated with at least one dose of buprenorphine
 - Buprenorphine without mu antagonist is the standard of care for persons with moderate-to-severe opioid use disorder and stimulant co-use
 - Clinical reports of benefits to some aspects of MOUD outcomes, especially retention, for such individuals who co-use methamphetamine (Tsui et al., 2020, JoSAT, 80-85)
- Consulted with Dr. Mark Greenwald regarding ways anxiety levels correspond with poor outcomes when inducing patients onto buprenorphine
 - Evaluation of the correlates of anxiety levels in SL-BUP induction in poster W149 (Steven Nieto et al), Weds 2:15-3:45



What's next for medication development for methamphetamine use disorder?



THANK YOU

