An Update on Long-acting Buprenorphine: Implications for Reducing Rural Disparities

Michelle Lofwall MD

Professor of Behavioral Science and Psychiatry

University of Kentucky College of Medicine

Center on Drug and Alcohol Research

Disclosure

- Camurus: Consultant in 2019

Outline for today's discussion

- Potential benefits of long-acting buprenorphine (bup) medications in rural populations
  - How can they help us move forwards to improve opioid use disorder (OUD) treatment access and retention?
- Three different products
- Four new large multi-site trials
- Conclusions

Moving forwards: Who may benefit?

- Patients with difficult transitions – e.g., leaving a hospital, emergency room, jail.

JAMA. 2015 Apr 28;313(16):1636-44. doi: 10.1001/jama.2015.3474.

Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial.

D'Onofrio G[1], O'Connor PG[2], Pantalon MV[1], Chawarski MC[3], Busch SH[4], Owens PH[1], Bernstein SL[1], Fiellin DA[5].

  - 2-fold increase in attending the first outpatient appointment if started SL BUP in the ER (78% vs. 37%). But many providers hesitant to prescribe because of concerns about diversion and misuse of SL BUP– what if they could just give a shot? Sometimes can't get in soon enough to a local provider – what if don't need to see a doc for a week or more?

- Pregnant women and newborns – might there be better outcomes from steady medication levels?
- Patients at risk for non-adherence and misuse
  - Unstable living situations, transportation problems, addicted to injection

- Patient preference (e.g., no need for pharmacy visits, supervised dosing)

Moving forwards: Where to deliver long-acting treatments?

- Willie Sutton: infamous bank robber from the 1930s. “Why do you rob banks?”…“Because that’s *where* the money is.”

- Where are our potential patients?
  - Criminal justice
  - Emergency rooms, hospitals and primary care
- These venues exist in rural areas

Overview of long-acting buprenorphine products

	6-month implants (Sixmo®/Probuphine®)	Monthly injection (Sublocade®)	Weekly and monthly injection (Buvidal®/Brixadi®)
Approval	EMA & USA	Australia & USA	Australia, EMA, USA*
Indications	Clinically stable adults with OUD, already on SL bup 8mg/day or less and already receiving medical, psychological and social support	Adults with moderate-severe OUD, tolerating SL bup at 8-24 mg/day for at least 7 days. Counseling and psychological support should be part of treatment plan.	Treatment OUD (age 16yrs +) within framework of medical, psychological and social treatment
Mean bup concentration at steady state (ng/mL)	~0.82	100 mg injection: 3.21 300 mg injection: 6.54	Variable depending on dose but >1
Minor surgical procedure required	Yes	No	No
Medication administration site	Upper arm - subdermal	Abdomen – subcutaneous (SC)	Abdomen, arm, leg, buttock (SC)
Refrigeration required?	No	Yes	No

Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med Volume 13, Number 2, March/April 2019. *Not on US market due to Sublocade having exclusivity until 2020.

JAMA. 2016 July 19; 316(3): 282–290. doi:10.1001/jama.2016.9382.

Effect of Buprenorphine Implants on Illicit Opioid Use Among Abstinent Adults With Opioid Dependence Treated With Sublingual Buprenorphine: A Randomized Clinical Trial.

Richard N. Rosenthal, MD.; Michelle R. Lofwall, MD; Sonnie Kim, PharmD; Michael Chen, PhD; Katherine L. Beebe, PhD.; Frank J. Vocci, PhD.; PRO-814 Study Group

26 mm long, 2.5 mm diameter, 4 rods/6 months

- 177 randomized; 166 completed (93.8% retention!!)

Responder rate	Implant	SL Bup/naloxone	P value	NNT
Primary Analysis				
- At least 4 of 6 months without illicit opioid use	81/84 (96.4%)	78/89 (87.6%)	<0.001[a]	11.4
Secondary Analysis				
- All 6 months without illicit opioid use	72/84 (85.7%)	64/89 (71.9%)	0.03[b]	7.3

[a] Non-inferiority. [b] Superiority

- Case reports of patients with positive outcomes after 3-7 rounds of implants (Campbell MC. Recurrent use of implantable buprenorphine. Prim Care Companion CNS Disord. 2019;21(6):19l02434; Lofwall unpublished data).

RBP-6000: Monthly subcutaneous buprenorphine vs. monthly naltrexone in CJ-involved adults

FDA Indivior AdCom, 10/31/2018

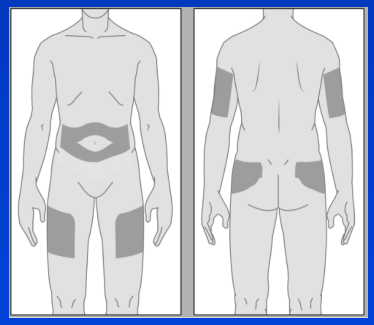
5 site open-label, non-inferiority trial recruiting incarcerated adults age 18-65 with moderate- severe opioid use disorder willing to be on either medication and expected to be released within next 6 months.

Randomized prior to release and receive 24-weeks of mediation treatment

Primary outcome: # of injections during the 24-week post-release treatment phase, range 0-6.

ClinicalTrials.gov Identifier: NCT04219540, Sponsor: NIDA, PI Joshua Lee MD

Subcutaneous weekly and monthly CAM2038



BUP-Sublingual	CAM2038 weekly	CAM2038 monthly
≤6 mg	8 mg (0.16 mL)	--
8-10 mg	16 mg (0.32 mL)	64 mg (0.18 mL)
12-16 mg	24 mg (0.48 mL)	96 mg (0.27 mL)
18-24 mg	32 mg (0.64 mL)	128 mg (0.36 mL)

BUP-SL dose and approximate equivalent weekly and monthly BUP-XR injections
NOTE: BUP-SL doses are in Subutex® equivalents

1. Albayaty et al. Advances in Therapy (2017)

Three new multi-site NIDA CTN RCTs comparing this long-acting Injection to SL – one in hospitals, one in emergency rooms and one In pregnant women

Hospital care for OUD

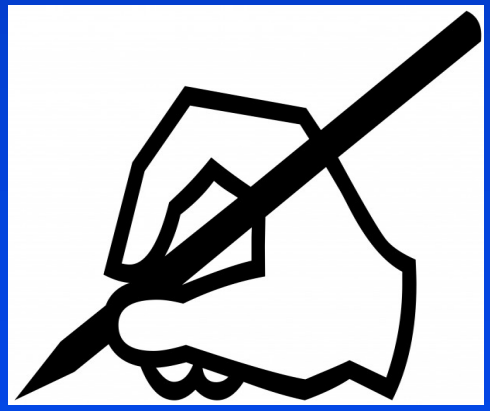
- Rarely includes medication for OUD
- Often ignored even if underlying cause for admission
- Patients with OUD more likely to be readmitted
- Yet such a reachable time ---
- Opioid withdrawal (w/d) + referral vs MOUD + linkage
  - 12% of w/d group on MOUD by 6 months
  - 72% MOUD+linkage group on MOUD by 6 months
  - Less illicit opioid use in MOUD+linkage vs w/d group

Fanucchi et al. 2016, Gupta et al. 2018; Walley et al. 2012; Liebschutz et al. 2014

CTN-0098A: Protocol development team

- Gavin Bart, MD PhD –NorthStar
- JoAn Laes, MD - NorthStar
- James Hodges, PhD - NorthStar
- Hildi Hagedorn, PhD – NorthStar
- Eva Enns, PhD – NorthStar
- Dave Gustafson, PhD- NorthStar
- Todd Korthuis, MD MPH – Western States
- Honora Englander, MD - Western States
- Rich Saitz, MD MPH – New England
- Alex Walley, MD MSc – New England
- Zoe Weinstein, MD MS – New England
- Sarah Wakeman, MD – New England
- Kelly Barth, DO - Southern
- Susan Sonne, PharmD BCPP - Southern
- Jennifer McNeely, MD MS - Greater New York
- Jane Liebschutz, MD MPH – New England

- Project Manager: Paulette Baukol
- Project Manager: Lynn Kunkel, MS CCRP
- CCTN Scientific officer: Udi Ghitza, PhD
- CCC: Eve Jelstrom, CRNA MBA
- DSC



CTN-0098A EXHIT ENTRE: COMPARATIVE EFFECTIVENESS TRIAL OF XR-BUP VERSUS TAU FOR HOSPITALIZED PATIENTS WITH OUD

314 Hospitalized Patients with OUD

Consent, Eligibility Determination, Enrollment

Participant is Randomized to XR-BUP or TAU

XR-BUP (N = 157)

TAU (N = 157)

OUTCOME MEASURES

DAY 34

DAY 90

DAY 180

PRIMARY OUTCOME MEASURE:OUD Treatment Engagement 34 Days Following Hospital Discharge

A Randomized Trial of ED-Initiated Interventions for Opioid Dependence

Research

Original Investigation

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD

JAMA Report Vide
Author Video Inte
jama.com

CME Quiz at
jamanetworkcr
CME Questior

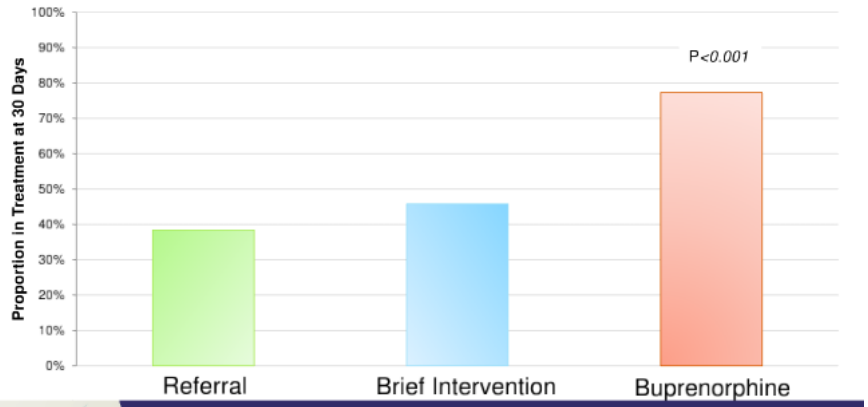
IMPORTANCE Opioid-dependent patients often use the emergency department (ED) for medical care.

OBJECTIVE To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).

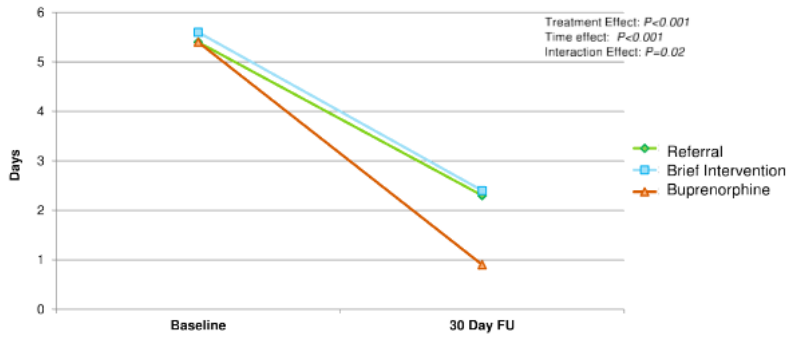
DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.

INTERVENTIONS After screening, 104 patients were randomized to the referral group, 111 to

Engaged in Treatment 30-Days



Past 7 Day illicit Opioid Use

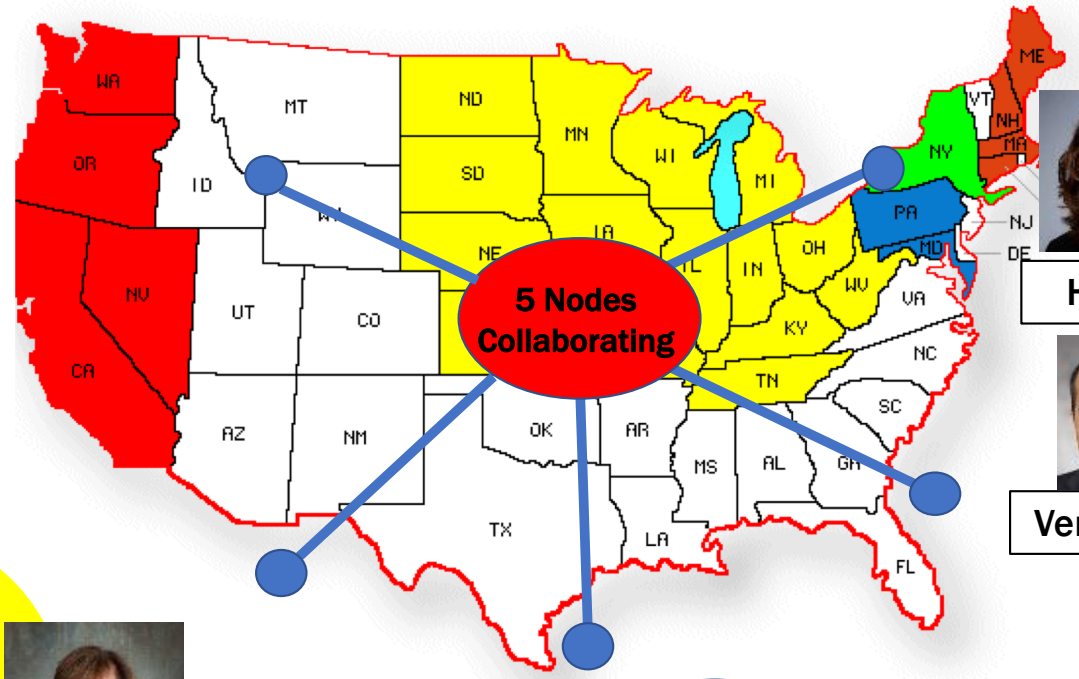


ED-INNOVATION

Emergency **D**epartment-**IN**itiated
Bupre**NO**rphine **VA**lida**TIO**N
Network Trial

CTN 0099

Lead Team



PNW

Herring

D'Onofrio

Fiellin

Hawk

Dziura

NE

Edelman

Venkatesh

Taylor

Pantalon

Lofwall

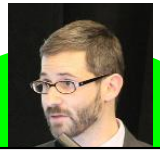
KY

Walsh

Expert Consultants

Perrone

Mid Atlantic



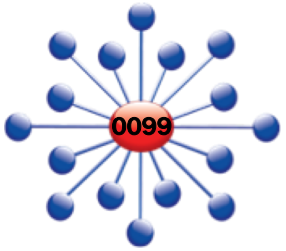
Cowan

NY

McCormack

Murphy

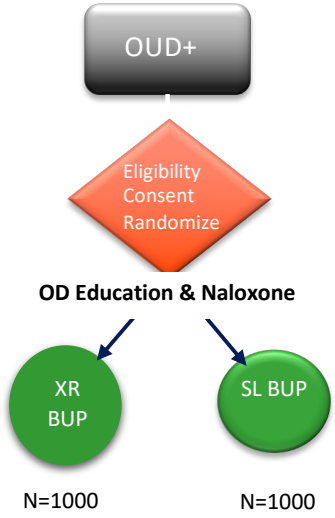
Randomized Clinical Trial



Comparing the effectiveness of XR-BUP injection and SL-BUP in 2000 patients across approximately 30 diverse EDs

Primary Outcome

Engagement in formal addiction treatment at 7 days



Patient Eligibility: Inclusion

All patients enrolled into the study must be:

- 18 years or older
- Treated in the ED during study screening hours
- Meet DSM-5 diagnostic criteria for moderate to severe OUD
- Have a COWS score of $\geq$ 8
- Have a urine toxicology test that is positive for opioids (opiates, oxycodone, buprenorphine).
  - Patients with urines that are only positive for fentanyl will be eligible if their clinical history and physical exam are consistent with opioid use and they meet DSM-5 criteria for moderate to severe OUD.
- Able to speak English sufficiently to understand the study the study procedures and provide written informed consent to participate in the study.

Pregnant women with OUD

- US opioid-use epidemic associated with a significant increase in the prevalence of:
  - pregnant women with opioid use disorder (OUD)
  - infants with neonatal opioid withdrawal syndrome (NOWS)
- NOWS is associated with adverse health effects for the infant and with costly hospitalizations
- Methadone- or buprenorphine (BUP)-maintenance treatment recommended for pregnant women with OUD

CTN-0080 MOMs

Winhusen T, Lofwall M, Jones HE, et al. Medication treatment for opioid use disorder in expectant mothers (MOMs): Design considerations for a pragmatic randomized trial comparing extended-release and daily buprenorphine formulations. *Contemp Clin Trials*. 2020;93:106014.

CTN-0080: Medication treatment for Opioid use disorder in expectant Mothers (MOMs): A pragmatic randomized trial comparing extended-release and daily buprenorphine formulations

Executive Team

Theresa Winhusen, PhD (Lead Investigator)
Michelle Lofwall, MD (Sub-Investigator)
Frankie Kropp, MS (Protocol Manager)
Elizabeth Krans, MD, MSc (Co-Investigator)
Scott Wexelblatt, MD (Co-Investigator)
Christine Wilder, MD (Co-Investigator)
Carmen Rosa, MS (NIDA CCTN Scientific Officer)

Emmes

Dikla Blumberg, PhD
Eve Jelstrom, MBA
Mitra Lewis, MS
Robert Lindblad, MD
Abigail G Matthews, PhD
Casey Nelson, MPH
Lauren Yesko

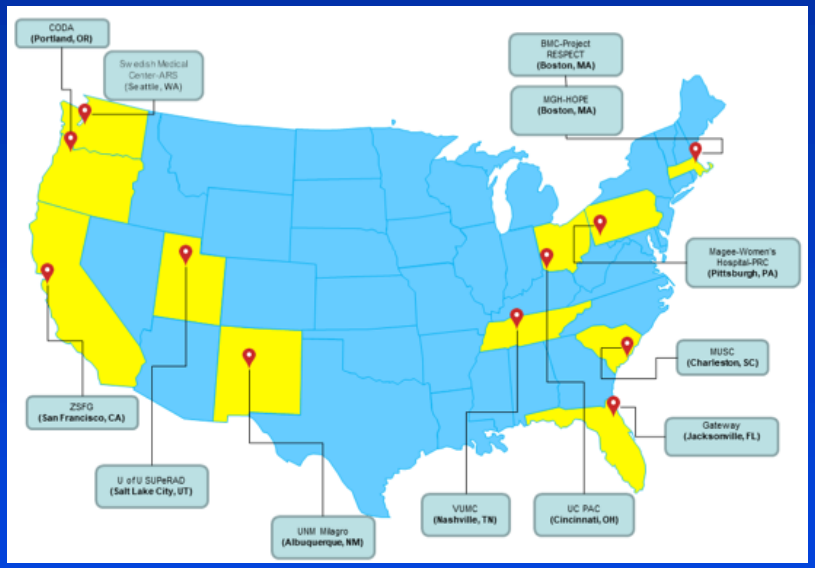
Protocol Development Team

Shelly Greenfield, MD, MPH (Harvard University)
Connie Guille, MD (Medical University of South Carolina)
Hendree Jones, PhD (University of North Carolina)
Michelle Lofwall, MD (University of Kentucky)
Stephanie Merhar, MD, MS (Cincinnati Children's Hospital)
Sean M. Murphy, PhD (Weill Cornell Medicine)
Edward Nunes, MD (Columbia University)
John Rotrosen, MD (New York University)
Davida M. Schiff, MD (Massachusetts General Hospital)
Michael Silverstein, MD, MPH (Boston University)
Mishka Terplan, MD, MPH (Virginia Commonwealth University)
Elisha M Wachman, MD (Boston Medical Center)
Scott Wexelblatt, MD (Cincinnati Children's Hospital)
Christine Wilder, MD (University of Cincinnati)

Celebrating 20 Years of
Research-Practice Partnerships

Study Design

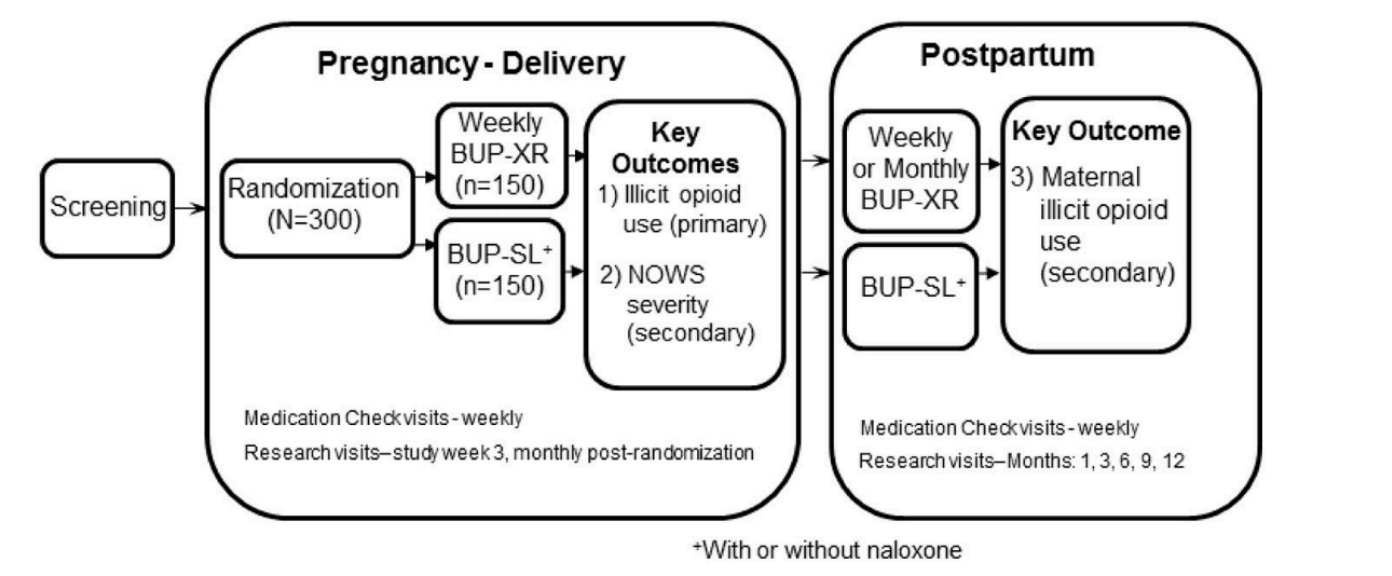
- Two-arm, open-label, non-inferiority, outpatient pragmatic randomized controlled trial
- N=300 (150 per treatment arm); 12 Sites
- BUP-XR (CAM2038) vs. BUP-SL
- Randomization 1:1, stratified by Site, Estimated Gestational Age (EGA; 6-18 vs. 19-30 weeks), taking BUP-SL at randomization
- BUP provided through 12 months postpartum
- Two optional sub-studies:
  - Conceptual Model Assessment (CMA)
  - Infant Neurodevelopmental Outcomes (INO)



CTN-0080 MOMs

Celebrating 20 Years of
Research-Practice Partnerships

Study Schema



CTN-0080 MOMs

Celebrating 20 Years of Research-Practice Partnerships

Outcomes: Main Study

- Primary and key secondary outcomes for mom and infant
  - Proportion of illicit opioid negative urine samples during pregnancy (primary)
  - NOWS severity assessed by total days of infant opioid treatment (secondary)
  - Mother postpartum illicit opioid abstinence assessed by weekly UDSs (secondary)
- Multitude of Safety Outcomes

CTN-0080 MOMs

Celebrating 20 Years of Research-Practice Partnerships

Outcomes: Health Economics and Sub-studies

- Health Economics
  - Incremental cost-effectiveness ratios (ICERs) of effectiveness will be calculated over two periods, during pregnancy through delivery and the entire study
- Conceptual Model Assessment Sub-study
  - Maternal peak and trough BUP/metabolite levels
  - Fetal heart rate variability, maternal BUP peak at ~36 weeks EGA
  - Cord and maternal plasma BUP/metabolite levels at delivery
- Infant Neurodevelopmental Outcomes Sub-study
  - Main outcome: Cognitive subscale of the Bayley Scales of Infant Development when the child is approximately 24 months of age

CTN-0080 MOMs

Celebrating 20 Years of Research-Practice Partnerships

Conclusions

- Long-acting medications for OUD hold much promise for improving treatment entry, retention and patient outcomes in rural areas

- Look forward to results from many ongoing studies and learning about real world clinical implementation and effectiveness

Questions