REAGAN-UDALL FOUNDATION FOR THE FDA

A Practical Research Agenda for Treatment Development for Stimulant Use Disorder:

A Virtual Public Workshop

The broadcast will begin shortly

October 18, 2021
12 – 5 p.m. Eastern Time

This activity is one part of a multi-part Foundation project related to substance use disorder. The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $173,835 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome

Susan C. Winckler, RPh, Esq.
Reagan-Udall Foundation for the FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome and Thank You

Agenda

REAGAN-UDALL FOUNDATION FOR THE FDA

12pm	**Welcome and Introduction**
12:05pm	**Session 1: Efforts to Promote Treatment Development for Stimulant Use Disorder**
12:45pm	**Session 2: Optimizing Clinical Trial Design for Stimulant Use Disorder**
2:15 p.m.	**Break**
2:30pm	**Session 3: Identifying Clinically Meaningful and Patient-Centric Endpoints**
4:00pm	**Session 4: Future Directions for Stimulant Use Disorder Research**
5:00pm	**Adjourn**

Session 1: Efforts to Promote Treatment Development for Stimulant Use Disorder

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters:

Janet Woodcock, MD, *U.S. Food and Drug Administration*

Nora Volkow, MD, *National Institute on Drug Abuse*

REAGAN-UDALL FOUNDATION FOR THE FDA

Janet Woodcock, MD

Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration

REAGAN-UDALL FOUNDATION FOR THE FDA

Nora Volkow, MD

Director

National Institute on Drug Abuse

Stimulant Use Disorder Treatment Development

Nora D. Volkow, M.D.

Director

National Institute on Drug Abuse

NIH National Institute on Drug Abuse

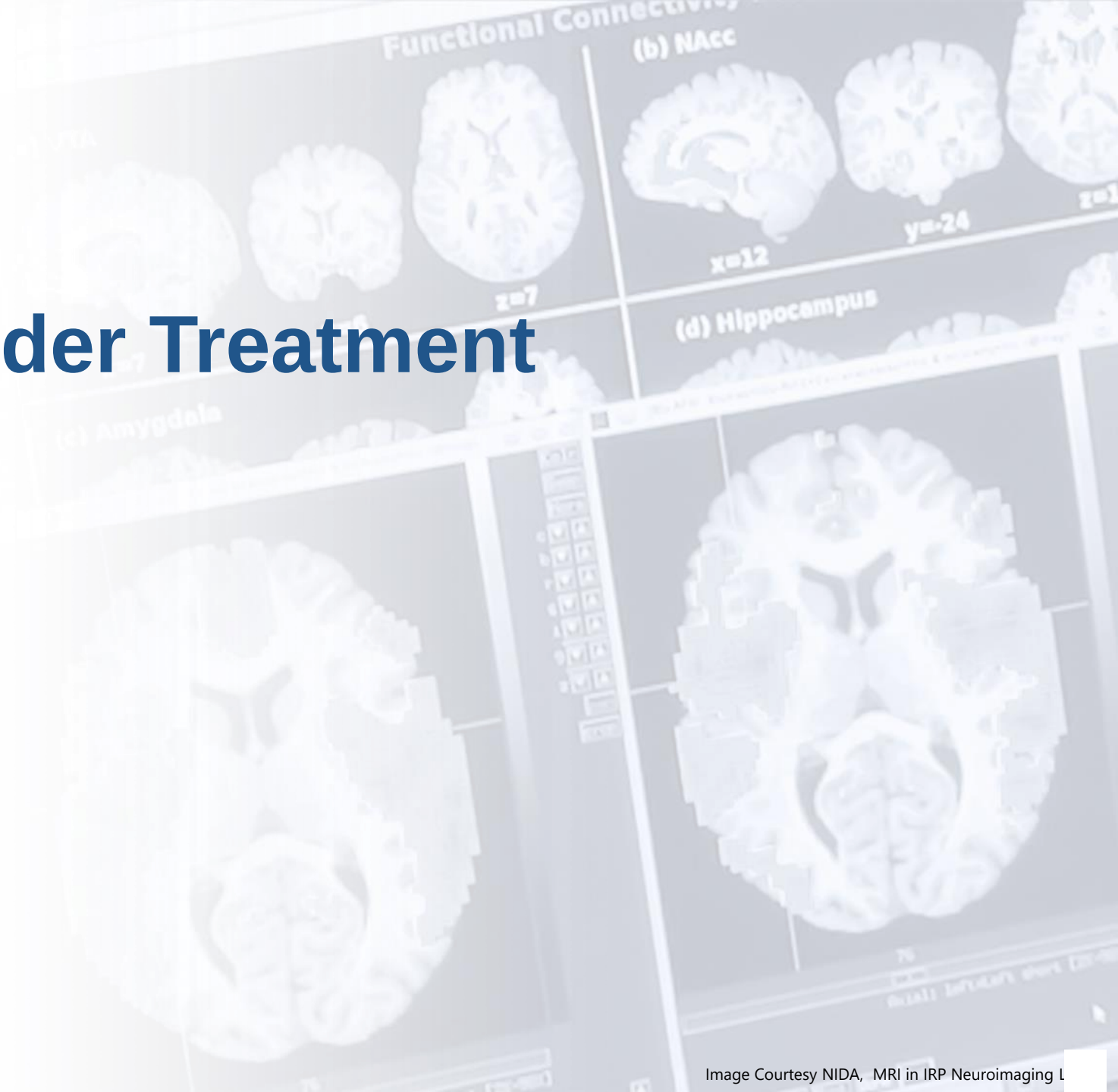
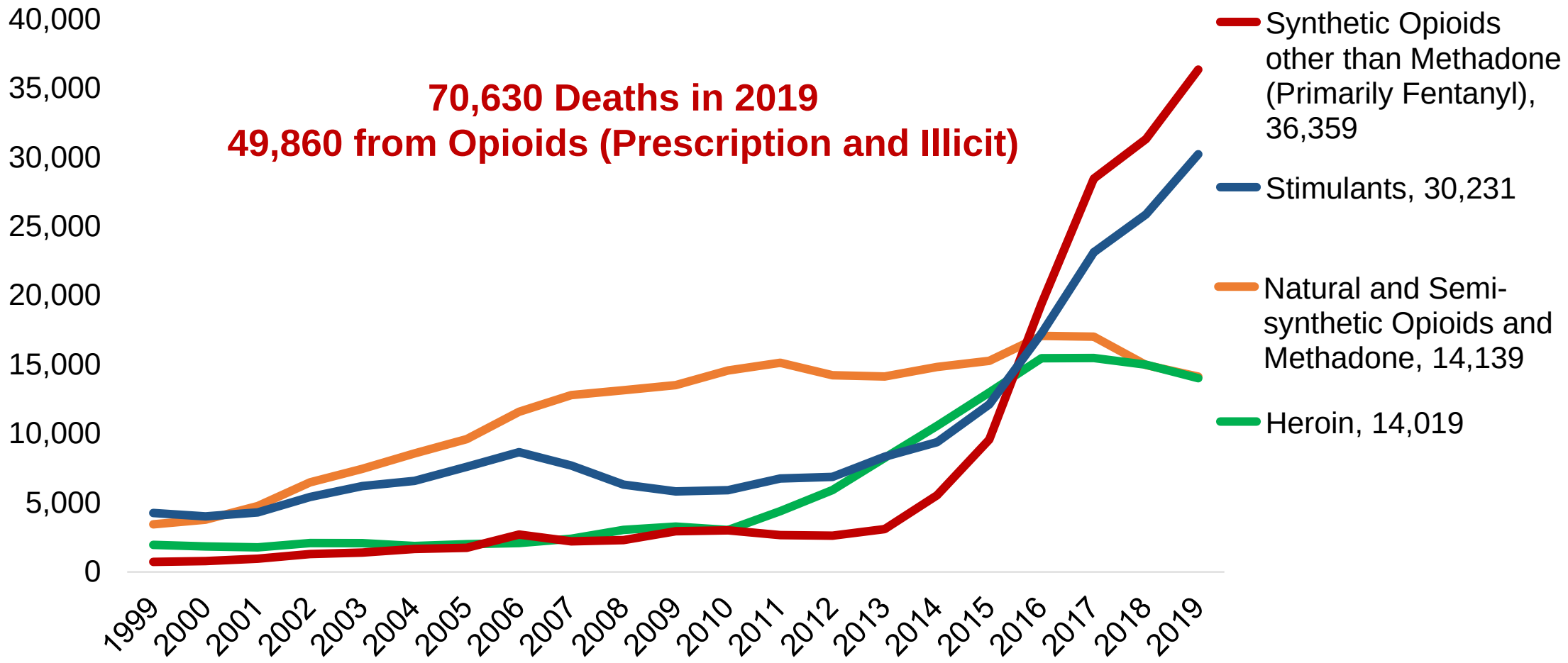


Image Courtesy NIDA, MRI in IRP Neuroimaging L

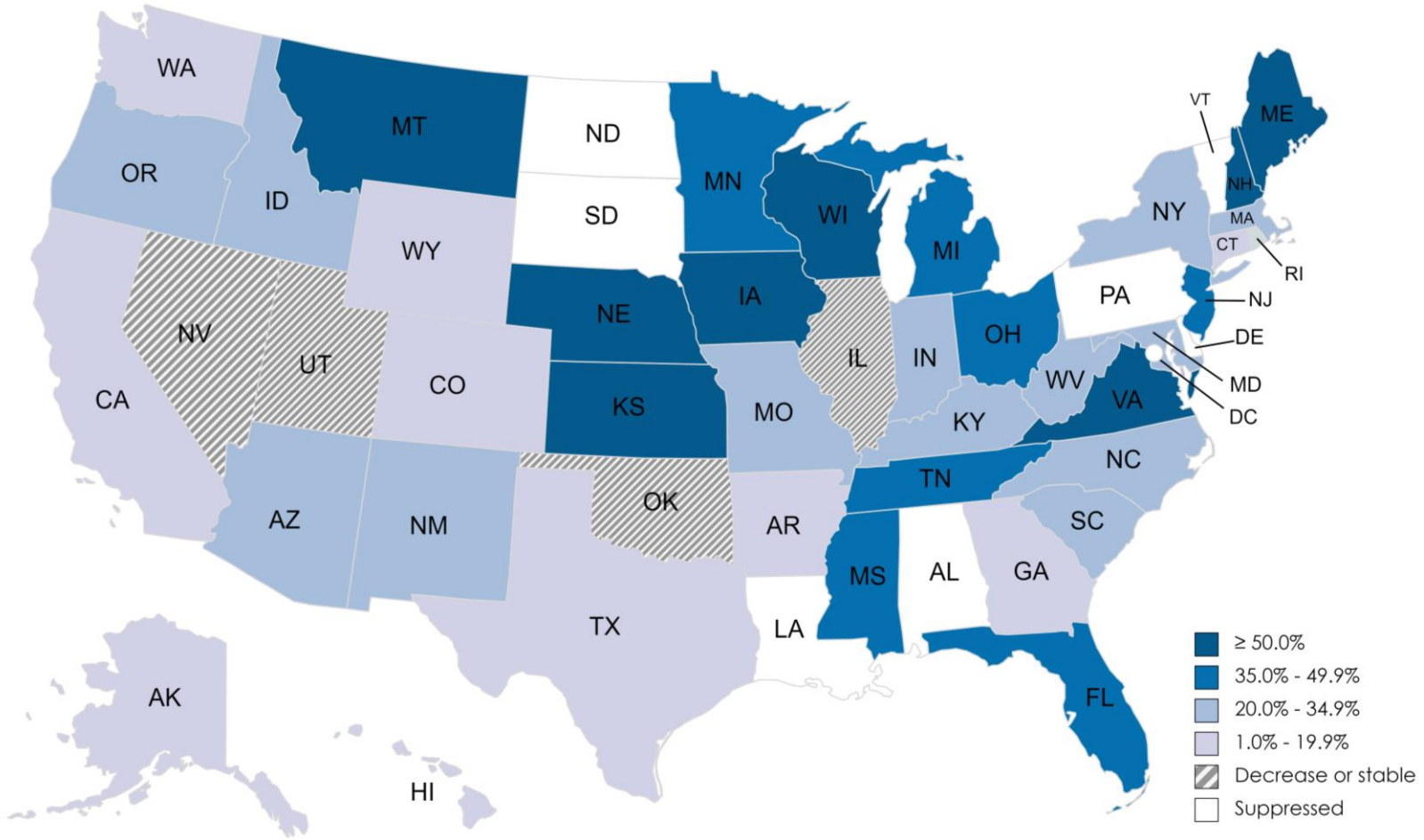
Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants



Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

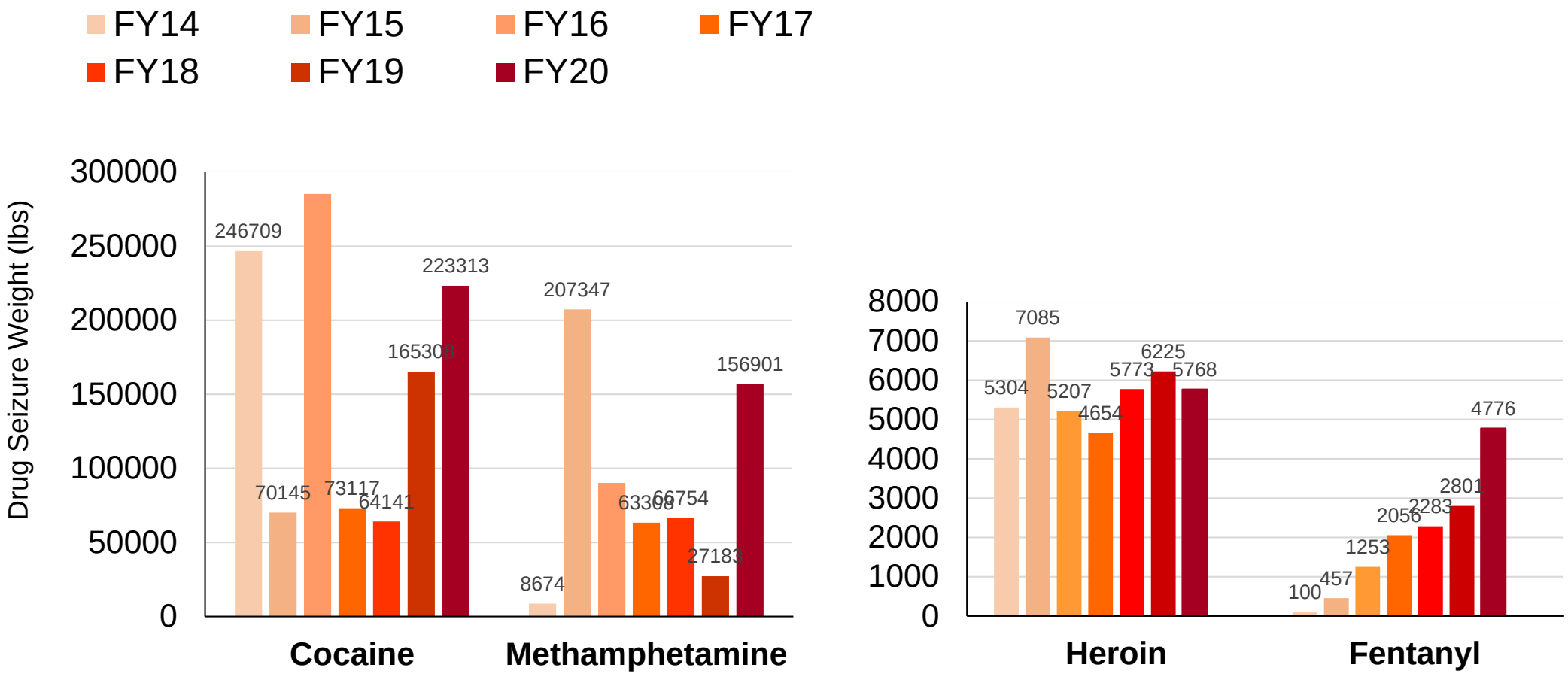
Relative Change in Age-Adjusted Rates of Overdose Deaths from 2018 to 2019 Involving Psychostimulants with Abuse Potential



Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and Geographic Patterns in Drug and Synthetic Opioid Overdose Deaths — United States, 2013–2019. MMWR Morb Mortal Wkly Rep 2021;70:202–207. DOI: http://dx.doi.org/10.15585/mmwr.mm7006a4external icon

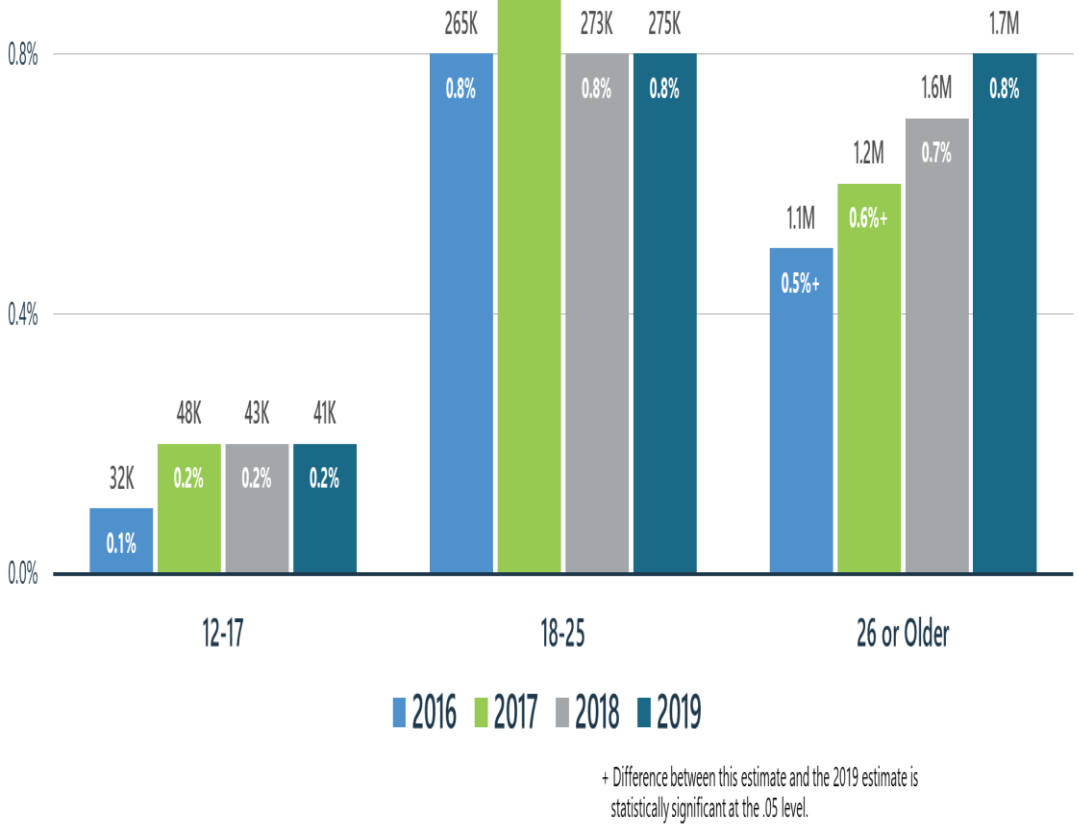
TOTAL DRUG SEIZURES NATIONWIDE

Office of Field Operations (FY14 to FY20) + US Border Patrol (FY14 to FY20) + Air and Marine Operations (FY17 to FY 20)



Methamphetamine Use

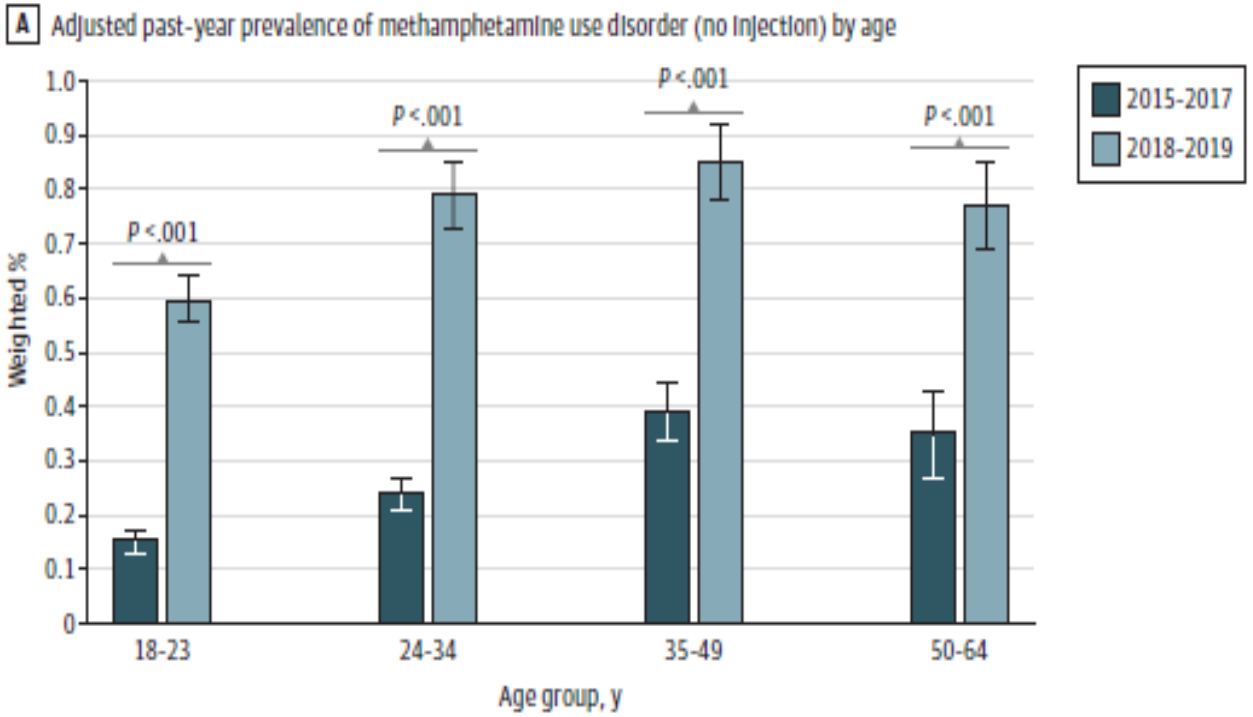
PAST YEAR, 2018-2019, NSDUH, 12+



+ Difference between this estimate and the 2019 estimate is statistically significant at the .05 level.

Source: SAMHSA, 2019 NSDUH, 2020.

Methamphetamine Use Disorder



Han B et al., JAMA Psychiatry. 2021.

Treating Methamphetamine Use Disorder & Overdoses

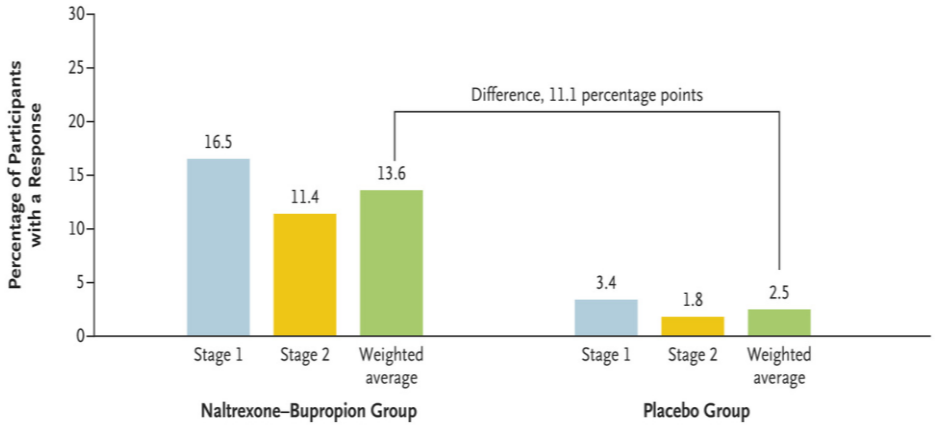
- No FDA approved medications
- Behavioral therapies: contingency management combined with a community reinforcement approach (De Crescenzo et al., 2018).
- No overdoses reversal medications available

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bupropion and Naltrexone in Methamphetamine Use Disorder

M.H. Trivedi, R. Walker, W. Ling, A. dela Cruz, G. Sharma, T. Carmody, U.E. Ghitza, A. Wahle, M. Kim, K. Shores-Wilson, S. Sparenborg, P. Coffin, J. Schmitz, K. Wiest, G. Bart, S.C. Sonne, S. Wakhlu, A.J. Rush, E.V. Nunes, and S. Shoptaw



NIDA-Supported Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

KEY: **Black:** New Molecular Entity **Red**: New Indication **Blue**: Biologic **Green**: Gene Therapy [C] cocaine [M] meth

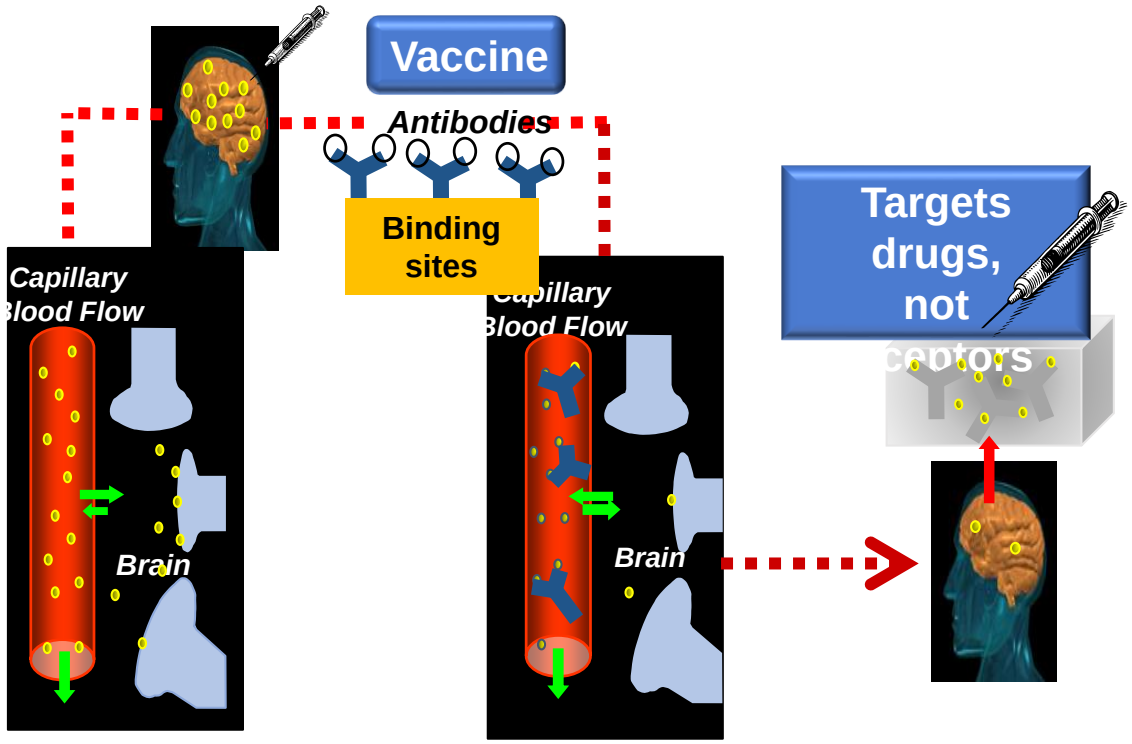
Drug Discovery/Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
cocaine hydrolase [C]	IXT-m200 [M]	Cocaine hydrolase gene therapy [C]	Cariprazine [C]	Bupropion [C]	
GLT-1 up-regulator [C]	Methamphetamine conjugate vaccine [M]	dAdGNE [C]	Clavulanic acid [C]	EMB-001[C]	
Peptidic KOR agonists [C]		h2E2[C]	Duloxetine & Methylphenidate [M]	Guanfacine [C]	
PTPRD ligands [C M]		IXT-m200 [M]	Mirtazapine [M]	Ketamine [C]	
VMAT-2 inhibitor [M]		Methamphetamine conjugate vaccine [M]	Pomaglumetad methionil [M]	IXT-m200 [M]	
CS-1103 [M]				Pioglitazone [C]	

National Institute on Drug Abuse

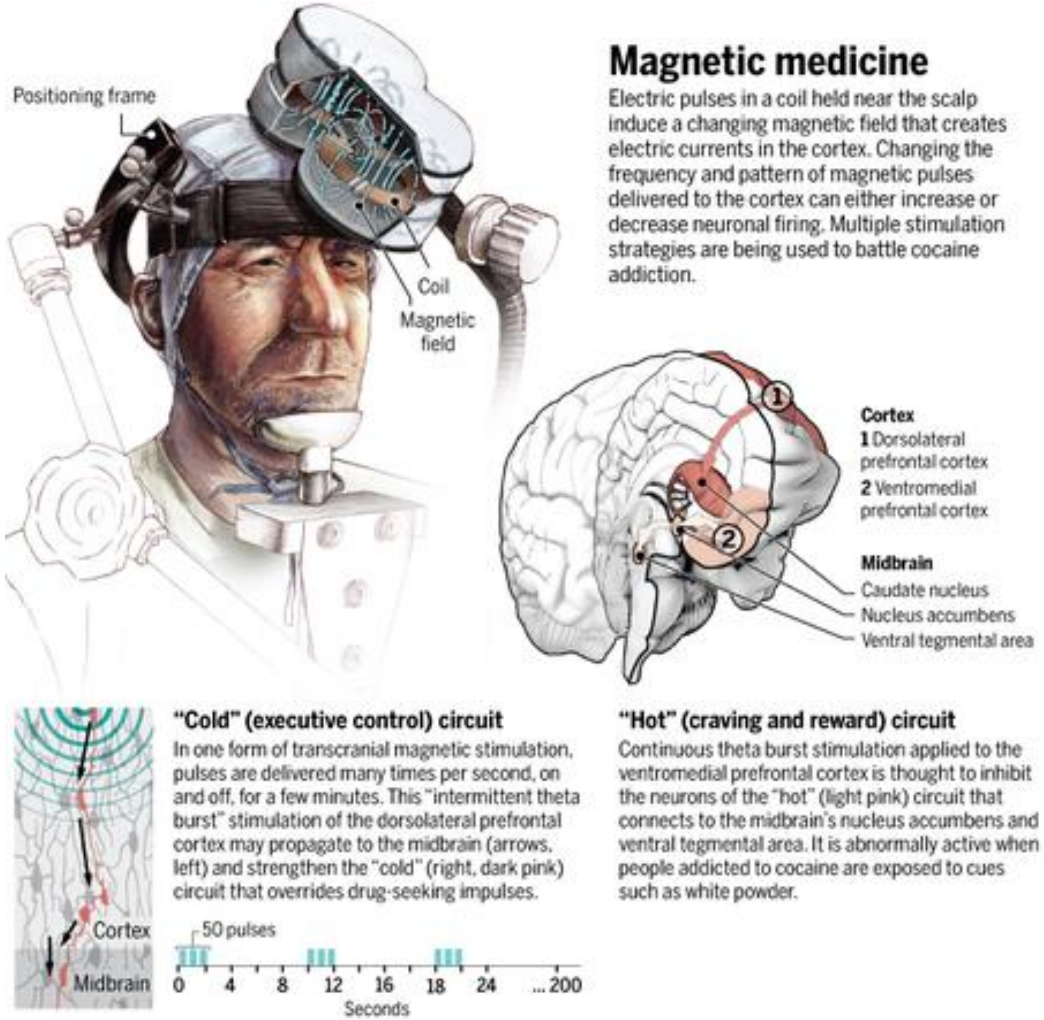
Updated 10/13/2021

Treating Psychostimulant Addiction: **Vaccines and mAB**

Antibodies reduce amount of drug in the brain



Treating Psychostimulant Addiction: **Transcranial Magnetic Stimulation**



Wadman, Science 2017.

Alternative Endpoints for Stimulant Use Disorder Treatment Trials

- Clinically meaningful, patient-centric endpoints beyond abstinence are needed to define success in clinical trials
    - Reduced use?
    - Controlled use?
    - Decreased craving?
    - Improved cognitive function?
    - Improved sleep?
    - Others?
- Methods for measuring alternative endpoints are needed

THANK YOU!

Session 2: Optimizing Clinical Trial Design for Stimulant Use Disorder

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters:

David McCann, PhD, *National Institute on Drug Abuse*
Madhukar Trivedi, MD, *UT Southwestern*

Panelists:

Sarah Akerman, MD, *Alkermes*
Maria Sullivan, MD, PhD, *Pear Therapeutics*
Jessica Hulsey, *Addiction Policy Forum*
Frances Levin, MD, *Columbia University*
Robert Walsh, RAC, *National Institute on Drug Abuse*
Maryam Afshar, MD, *U.S. Food and Drug Administration*

Optimizing Clinical Trial Design to Address Medication Nonadherence

David J. McCann, Ph.D.
Associate Director, NIDA Division of Therapeutics and Medical Consequences

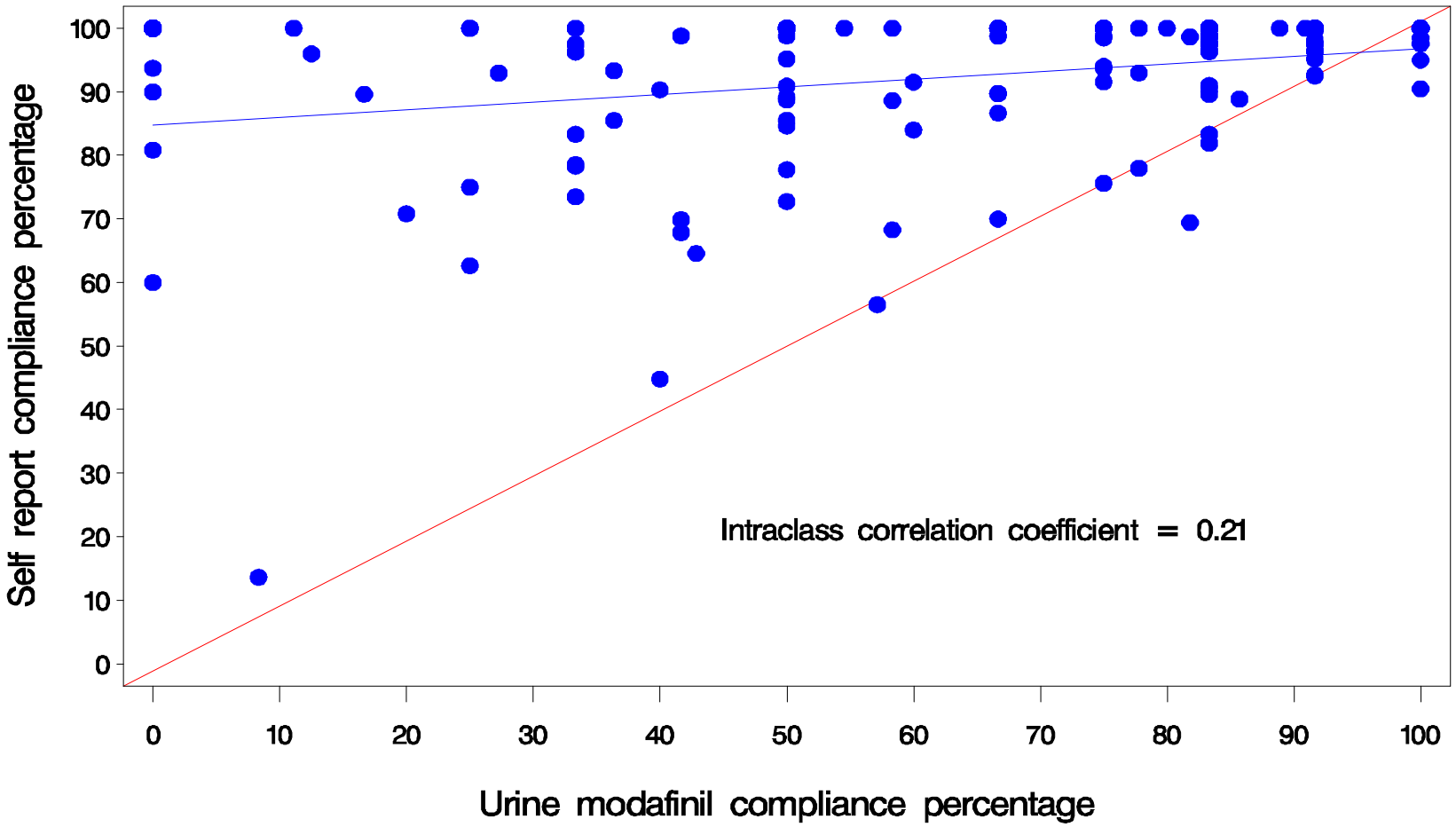
October 18, 2021

During workshop planning, clinical trial endpoints were the initial focus; however, study design details also deserve careful consideration.

Efficacy endpoints may be irrelevant if study participants don’t take their medication.

If no significant efficacy is observed, did the medication fail or did the study fail?

VA/NIDA Study #1026: Modafinil for Methamphetamine Dependence



Anderson *et al.*, 2012

Analysis 2: Agreement Analysis of self report compliance with urine modafinil compliance

Doc Path: H:\p1026\reports\docs\Agreement.doc; Prgm Path: H:\p1026\reports\MEDCOMP–v2.sas; Date run: 09/03/2010; Data last updated: 03/10/2010

Compliance Based on Urine Modafinil
(% compliance = % urines containing any detectable modafinil)

≥ 90% Compliance:	34/142 (24%)
≥ 80% Compliance:	61/142 (43%)
≥ 70% Compliance:	73/142 (51%)
0% Compliance:	14/142 (10%)

Compliance Based on Urine Modafinil
(% compliance = % urines containing any detectable modafinil)

≥ 90% Compliance:	34/142 (24%)
≥ 80% Compliance:	61/142 (43%)
≥ 70% Compliance:	73/142 (51%)
0% Compliance:	14/142 (10%)

Why do some subjects enroll with no apparent intention of taking study medication?

(Professional Subjects)

“Professional Subjects”

We know they exist because they have been caught or confessed.

[ORIGINAL RESEARCH]

CNS Sites Cooperate to Detect Duplicate Subjects with a Clinical Trial Subject Registry

FUNDING: There was no funding for the development and writing of this article.

FINANCIAL DISCLOSURES: Dr. Shiovitz is president of CTSdatabase, LLC, the database used in this study. Dr. Wilcox, Ms. Gevorgyan, and Mr. Shawkat have no conflicts of interest relevant to the content of this article.

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KEYWORDS: Duplicate subjects, professional subjects, professional patients, site cooperation, investigator collaboration, subject database, subject registry

by THOMAS M. SHIOVITZ, MD; CHARLES S. WILCOX, PhD, MPA, MBA; LILIT GEVORGYAN, BS; and ADNAN SHAWKAT, BA

Dr. Shiovitz is from CTSdatabase, LLC, in Beverly Hills, California and California Neuroscience Research Medical Group, Inc., Sherman Oaks, California; Dr. Wilcox is from Pharmacology Research Institute, Los Alamitos, California; Ms. Gevorgyan is from California Neuroscience Research Medical Group, Inc., Sherman Oaks, and Mr. Shawkat is from CTSdatabase, LLC, in Beverly Hills, California.

Innov Clin Neurosci. 2013;10(2):17–21

ABSTRACT

Objective: To report the results of the first 1,132 subjects in a pilot project where local central nervous system trial sites collaborated in the use of a subject database to identify potential duplicate subjects.

Method: Central nervous system sites in Los Angeles and Orange County, California, were contacted by the lead author to seek participation in the project. CTSdatabase, a central nervous system-focused trial subject registry, was utilized to track potential subjects at pre-screen. Subjects signed an institutional review board-approved authorization prior to participation, and site staff entered their identifiers by accessing a website. Sites were prompted to communicate with each other or with the database administrator when a match occurred between a newly entered subject and a subject already in the database.

Results: Between October 30, 2011, and August 31, 2012, 1,132 subjects were entered at nine central nervous system sites. Subjects continue to be entered, and more sites are anticipated to begin participation by the time of publication. Initially, there were concerns at a few sites over patient acceptance, financial implications, and/or legal and privacy issues, but these were eventually overcome. Patient acceptance was estimated to be above 95 percent.

Duplicate Subjects (those that matched several key identifiers with subjects at different sites) made up 7.78 percent of the sample and Certain Duplicates (matching identifiers with a greater than 1 in 10 million likelihood of occurring by chance in the general population) accounted for 3.45 percent of pre-screens entered into the database. Many of these certain duplicates were not consented for studies because of the information provided by the registry.

Conclusion: The use of a clinical trial subject registry and cooperation between central nervous system trial sites can reduce the number of duplicate and professional subjects entering clinical trials. To be fully effective, a trial subject database could be integrated into protocols across pharmaceutical companies,

Shiovitz et al., 2013

CLINICAL TRIALS *ETHICS*

Clinical Trials 2013; **10**: 935–948

Concealment and fabrication by experienced research subjects

Eric G Devine[a], Megan E Waters[a], Megan Putnam[b], Caitlin Surprise[a], Katie O'Malley[a], Courtney Richambault[a], Rachel L Fishman[a], Clifford M Knapp[a], Elissa H Patterson[a], Ofra Sarid-Segal[a], Chris Streeter[a], Laurie Colanari[a] and Domenic A Ciraulo[a]

Background Subjects who enroll in multiple studies have been found to use deception at times to overcome restrictive screening criteria. Deception undermines subject safety as well as study integrity. Little is known about the extent to which experienced research subjects use deception and what type of information is concealed, withheld, or distorted.

Purpose This study examined the prevalence of deception and types of deception used by subjects enrolling in multiple studies.

Methods Self-report of deceptive behavior used to gain entry into clinical trials was measured among a sample of 100 subjects who had participated in at least two studies in the past year.

Results Three quarters of subjects reported concealing some health information from researchers in their lifetime to avoid exclusion from enrollment in a study. Health problems were concealed by 32% of the sample, use of prescribed medications by 28%, and recreational drug use by 20% of the sample. One quarter of subjects reported exaggerating symptoms in order to qualify for a study and 14% reported pretending to have a health condition in order to qualify.

Limitations Although this study finds high rates of lifetime deceptive behavior, the frequency and context of this behavior is unknown. Understanding the context and frequency of deception will inform the extent to which it jeopardizes study integrity and safety.

Conclusion The use of deception threatens both participant safety and the integrity of research findings. Deception may be fueled in part by undue inducements, overly restrictive criteria for entry, and increased demand for healthy controls. Screening measures designed to detect deception among study subjects would aid in both protecting subjects and ensuring the quality of research findings. *Clinical Trials* 2013; **10**: 935–948. http://ctj.sagepub.com

Introduction

The use of human subjects in clinical trials is a necessary component of drug and device development. These areas of research expose subjects to potential risks. The ethical issues related to balancing the risk and benefit to human subjects in research have been the subject of intense media coverage following high-profile studies in which healthy volunteers died during phase 1 medication

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[b]Department of Psychology, Fairleigh Dickenson University, Florham, NJ, USA
Author for correspondence: Eric G Devine, Department of Psychiatry, Boston University School of Medicine, Suite 1150, Doctors Office Building, 720 Harrison Avenue, Boston, MA 02118, USA.
Email: edevine@bu.edu

Devine et al., 2013

Survey for experienced research subjects

- Have you enrolled in more than one study in the past year?
- Have you been in more than three studies in the past three years?

If you answered yes to either of these questions you qualify for the Experienced subject survey.

- **Participation involves a one-time interview lasting 60 minutes**
- **Qualified subjects reimbursed for their time**

Call 888-552-5264 and ask for "The experienced subjects study"

Devine et al., 2013

N = 100

75% reported concealing health information to avoid exclusion.

43% reported concealing their participation in another study.

25% reported exaggerating symptoms in order to qualify for a study.

14% reported pretending to have a health condition in order to qualify.

For "deceivers:" Avg. # studies during the prior year = 12.8

Avg. earnings per study during the prior year = $133

Typical Compensation in a Stimulant Use Disorder Efficacy Trial: **Trivedi et al., 2021**

Visit/Assessment	Amount	# of Payments	Total
Screening Assessments	$50	1	$50
Eligibility Phase Clinic Visits	$10	4	$40
Injection Visits	$25	4	$100
Clinic Visits (12-week Medication Phase)	$10	23	$230
In-clinic dosing/med return (2x/wk)	$5	24	$120
Mid-Treatment Visit (visit 602) and End-of-Treatment Visit (visit 1202)	$40	2	$80
Dosing video (5x/wk+4 taper days)	$5	64	$320
Attendance Bonus (attending all expected visits in each 2-week block)	$20	6	$120
Follow-up Visits (Weeks 13 and 16)	$30	2	$60
Additional data service for dosing app on personal device OR smartphone device return	$40	1	$40
Maximum Compensation Possible			**$ 1,160**

How can we Adapt to the Reality of Medication Nonadherence & Professional Subjects?

- **Always use a subject registry to reduce enrollment of "professional subjects" and prevent dual enrollment (same subject at multiple sites within a trial).**

CTSdatabase

Verified Clinical Trials (VCT)

SubectRegistry.com
(joint platform created by CTSdatabase and VCT)

clinicalRSVP

Others?

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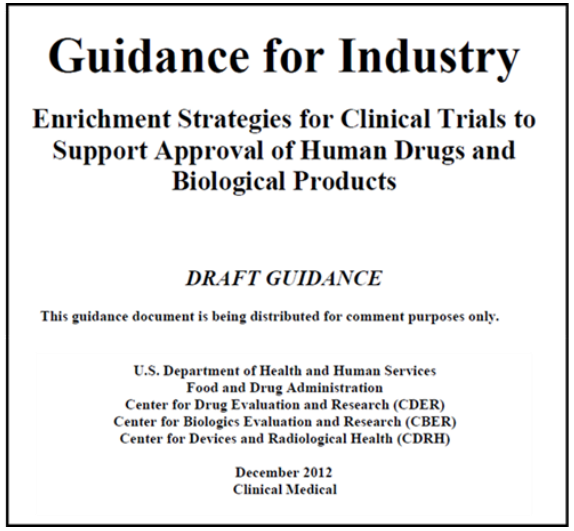
- **Prior to randomization, try to detect subjects who are likely to be medication nonadherent and exclude them from randomization…or exclude their data from analysis for the primary efficacy endpoint.**



Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2012
Clinical Medical

Examples cited in guidance:

VA Cooperative Study on Hypertension (1967/1970)

Physicians Health Study (1989)

How can we Adapt to the Reality of Medication Nonadherence & Professional Subjects?

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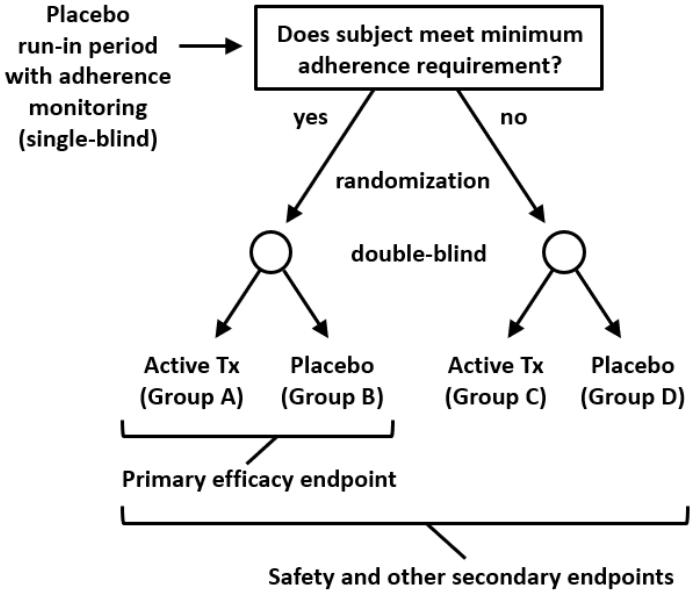


Current approach in NIDA-directed trials:

RAMPUP Study Design

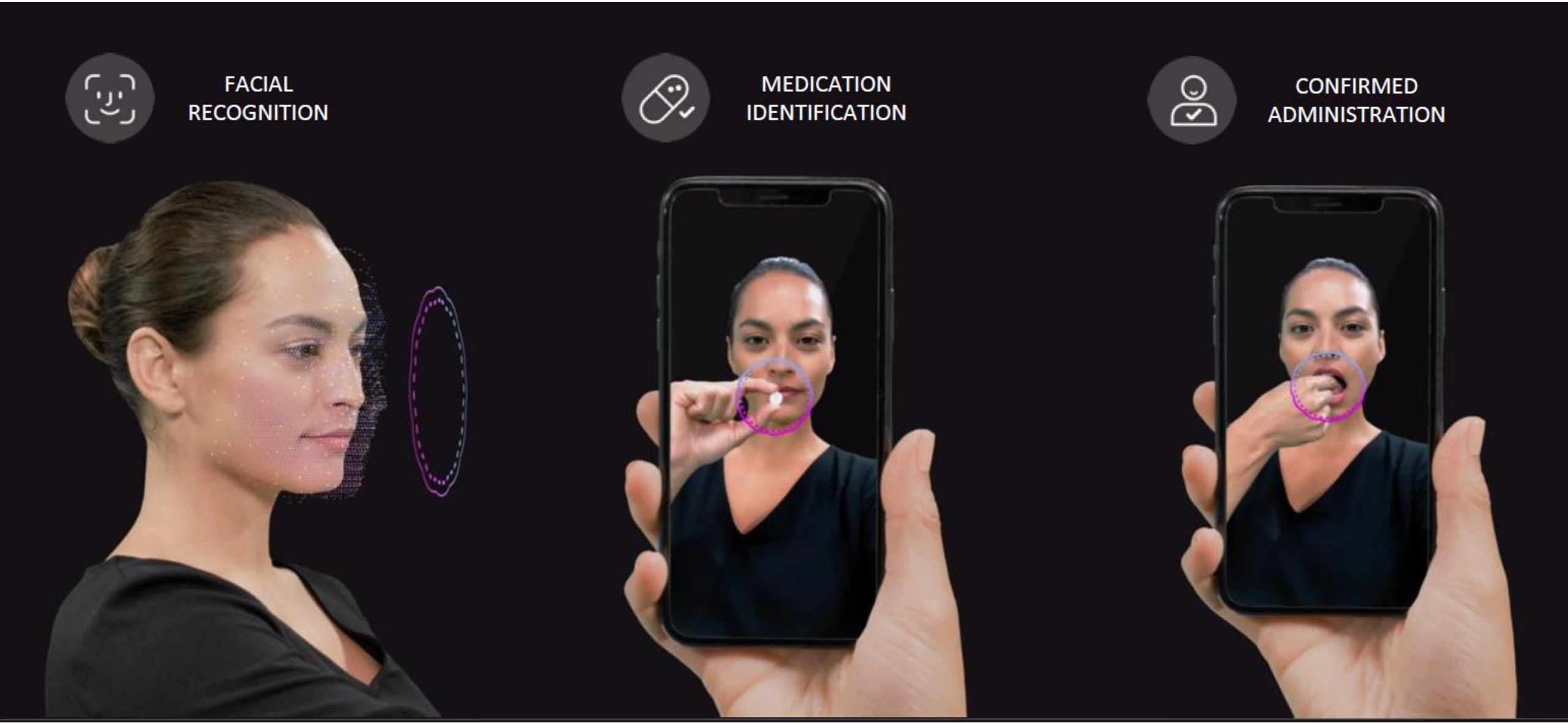
"Run-In with Adherence Monitoring for Prequalification but Undiminished Participation"

McCann et al., 2015
J Clin Psychopharm 35: 556

AiCure software

3 Key Steps:

The app can also be used for collection of self-report data (e.g., daily cocaine or methamphetamine use)



NIDA Experience using AiCure in a Recent Cocaine Use Disorder Trial (lorcaserin)

- **Overall medication adherence was determined to be 75.5%, and this level of adherence resulted in a significant treatment effect (weight loss).**
- **Adherence during the first week of use was generally predictive of adherence throughout the study, with a decrease over time (e.g., overall adherence during the first week of use was 83.0%, decreasing to 75.5% for the entire study)**
- **16% of study participants (39/242) were *intentionally* non-adherent during the first week of device use! For example:**
  - **Removed capsule from mouth before drinking water**
  - **Pretended to swallow capsule (still apparent when showing "empty mouth")**
  - **Spit capsule into glass of water**

Use of AiCure during a one-week placebo run-in period may reduce the impact of intentionally nonadherent “profession subjects” in efficacy trials.

Subjects found to be intentionally nonadherent (based on pre-randomization data) can be excluded from efficacy analyses.

How can we Adapt to the Reality of Medication Nonadherence & Professional Subjects?

- **Always use a subject registry to reduce enrollment of "professional subjects" and prevent dual enrollment (same subject at multiple sites within a trial).**
- **Prior to randomization, try to detect subjects who are likely to be medication nonadherent and exclude them from randomization…or exclude their data from analysis for the primary efficacy endpoint.**
- **After randomization, actively promote medication adherence.**
    - **counseling**
    - **dosing reminders**
    - **observed, in-clinic dosing**
    - **observed, at-home dosing**

DMCCANN@NIH.GOV

Lessons Learned from the CTN-0068 "Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder (ADAPT-2)" Study

funded by NIDA UG1DA020024 Trivedi MH PI

Madhukar H. Trivedi, M.D.
Professor of Psychiatry
Julie K Hersh Chair in Depression Research and Clinical Care
Betty Jo Hay Distinguished Chair in Psychiatry
PI, Big South/West Node of the NIDA Funded CTN
Founding Director, Center for Depression Research and Clinical Care
Peter O'Donnell Jr. Brain Institute
University of Texas Southwestern Medical Center
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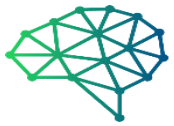


CDRC
Solving Depression, Saving Tomorrows

UT Southwestern
Medical Center

Objectives

- Review the background and rationale for study design innovation for Stimulant Use Disorders
- Review Design options including SPCD
- Examine outcomes using one adaptive design study
- Review challenges and lessons learned

Background and Rationale

- No FDA approved medication for methamphetamine (MA) use disorder
- Promising candidates showing preliminary clinical utility include naltrexone and bupropion
- Combination of bupropion + naltrexone predicated on potentially complementary effects as shown in clinical research[1]

1. Hanson, 2004; Newton et al., 2006; Ornellas & Chavez, 2011

Tradition of Placebo in Addiction Medicine: Methamphetamine Studies

Study	Intervention	Population	Results
Shoptaw et al., 2013	Bupropion, 12 weeks	MA-dependent (n=73; n=36 b vs. n=37 placebo)	No effect overall, positive effect in reducing MA use in lighter users. Reduced cigarette smoking.
Elkashef et al., 2008	Bupropion, 12 weeks	MA-dependent (n=151; n=79 b vs. n=72 placebo)	No effect overall, but lowered MA use in men with lower MA use.
Newton et al., 2006	Bupropion	MA abusers or dependent (n= B vs. n=10 placebo)	Reduced some positive subjective effects and cue-induced craving.
Heinserling, et al., 2015	Bupropion, 12 weeks	MA-dependent with high MA use (n=41 bup vs. n=43 placebo)	No difference in end of treatment abstinence between groups but those with high adherence to bup had significantly higher abstinence.
Santos et al., 2017	Naltrexone, 8 weeks	MA users and binge drinking MSM (n=30; n=15 N vs. n=15 placebo)	Some reduction in MA use in frequent users, some reduction in binge drinking in frequent study med users and reductions in sexual risk taking.
Coffin et al., 2018	Naltrexone-XR, 12 weeks	MA-dependent MSM (n=100; n=50 N; n=50 placebo)	No effects.
Jayaram-Lindstrom et al., 2008	Naltrexone, 12 weeks	AMP-dependence (n=80; n=40 N vs. n=40 placebo)	Reduced AMP use, measured by % + UDS.
Kohno et al., 2018	Naltrexone-XR, 1 x 4 week dose	MUD (n=37; n=19 N vs. n=18 placebo)	Reduced MA use, no changes in craving. Effects on brain connectivity.
Grant et al., 2010	N-acetyl cysteine + Naltrexone, 8 weeks	MA-dependent (n=31; n=14 N +N, n=17 placebo)	No effects.
McElhiney et al., 2018	Modafinil, 12 weeks + CBT, 16 weeks	MA in HIV+ men (n=13)	60% of completers reduced MA use by >50%.
Laboratory Based Studies			
De La Garza II, et al., 2010	Modafinil, 3 days, cross-over	MA-dependent (n=13)	Some reduction of positive subjective effects of MA but not statistically significant.
Ray et al., 2015	Naltrexone, 4 days, cross-over	MA abusers or dependence (n=30)	Blunted MA cue-induced craving and attenuated some subjective effects.
Marks et al., 2017	Naltrexone, alprazolam, Naltrexone + alprazolam, cross-over with challenge	Non-treatment seeking inpatients with recent stimulant use (n=8)	Combination was able to reduce some subject-rated drug effects of d-amphetamine.

Tradition of Placebo in Addiction Medicine: Cocaine Studies

Study	Intervention	Population	Results
Pettinati et al. 2014	XR-NTX vs. PBO for 8 weeks	Cocaine & Alcohol dependent (N=80; PBO=41)	No group differences % abstinent for cocaine at least 3 weeks w/o heavy drinking (XR-NTX=12.8% and PBO=14.6%)
Ling et al. 2016	BUP+XR-NTX vs. PBO for 12 weeks [BUP: 4mg (BUP4, n=100 & 16mg(BUP16, n=100)	Cocaine dependent (N=302; PBO: n=102)	No group differences for the primary outcome Secondary outcomes (% cocaine negative urine BUP16=50.9%; PBO=45.8%)
Pettinati et al. 2008	Mixed Amphetamine Salts and Topiramate vs. PBO for 11 weeks	Cocaine & Alcohol dependent (N= 208; PBO: n=54)	% cocaine abstinence (Combination=34.7%; monotherapy=17%; PBO=15%)
Jayaram-Lindstrom et al., 2008	Oral NTX for 12 weeks	Methamphetamine dependent (N=55; PBO: n=26)	% methamphetamine negative urine (NTX=79.7; PBO=64.1)
Mariani et al., 2012	BUP+XR-NTX vs. PBO for 12 weeks	Cocaine dependent (N=81; PBO: n=42	% cocaine abstinent 3 consecutive weeks (MAS-ER + Topiramate = 33.3%; PBO=16.7%
Winhusen et al., 2014	Buspirone vs. PBO for 11 weeks	Cocaine dependent (N=62; PBO: n=27)	Probability of maintaining abstinence (Buspirone = 20%; PBO=22%)
Kahn et al., 2009	Baclofen vs. PBO for 8 weeks	Cocaine dependent (N=160; PBO: n=80)	% Cocaine reduction days to 50% or less (Baclofen=15.6; PBO=19.2)
Schmitz et al., 2001	Fluoxetine vs. PBO for 12 weeks	Cocaine dependent (N=68; PBO: n=34)	No group differences in primary outcomes inpatients with cocaine and MDD
Johnson et al., 2013	Topiramate vs. PBO for 12 weeks	Cocaine dependent (N=142; PBO: n=71)	Negative urine weeks 6-12 was 16.6% Topiramate compared to 5.8% placebo

*Litten et al., (2013) evaluated 55 studies evaluating naltrexone (25) and acamprosate (17) for AUD suggested placebo response (naltrexone trials: median [range] = **77.5%** [46.7% – 93.5%]; acamprosate trials: **39.1%** [20.8% – 76.1%])

Rationale for Adaptive Designs

Failed vs. Negative Trials

Failed Trial

- A trial in which the new drug and the active control were not distinguished from placebo.

Negative Trial

- A trial in which the new drug was not superior to placebo, but an active control was
- A trial in which the new drug was not superior to placebo and there was no active control

Mosholder, NCDEU 2001

The Problem…

In the best case

Placebo response forces the use of a larger "*n*", thereby lengthening "time-to-market" and increasing cost

In the worst case

Placebo response causes failure of a trial, and potentially termination of product development

Why Use Adaptive Designs?

Benefits to Investigators/Sponsors

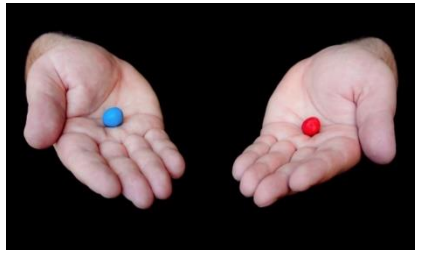
- Reduced sample size
- Refining allocation ratio of patients to trial arms
- Highlighting patients most likely to benefit and prioritize recruitment efforts
- Earlier completion or termination of trial

Benefits to Participants

- Opportunity for active treatment, even if initially randomized to control
- End unnecessary treatment arms
- Decrease likelihood of randomization to a less promising treatment/dose

ADAPT-2 Study Designs Considered

1. Fixed Placebo Run-In (Fava et al., 2003)
    - (+) Reduce PLB response
        - (-)No support from MDD studies (Trivedi and Rush, 1994; Walsh et al, 2002).
2. Variable Length Placebo Run-In
    - (+) Identify likely adherent participants
        - (-) Offset large effect size because of inclusion of subjects that will not be used in the efficacy analysis (Fava e al., 2003)
3. RAMPUP (McCann et al., 2015)
    - (+) PLB responders not included in analyses
    - (+) Accounts for “professional participants”
        - (-)Only theoretical at this point
        - (-) Number of subjects excluded from the primary analysis would be even greater that variable length placebo run-in.



ADAPT-2 Study Designs Considered

4. Two-way Enriched (Ivanova and Tamura, 2015)

(+) Similar to SPCD, but Stage 2 re-randomizes both placebo non-responders and treatment group responders.

(-) More complex than the SPCD design, not used

*Sequential Parallel Comparison Design

(SPCD; Fava et al., 2003)

(+) Helps reduce placebo (PLB) response

(+) Improves PLB-drug difference where it exists

(+) Smaller N than traditional Phase 3 trials

Previous MUD Studies

Retention

- Only 7 (31.8%) had retention rates >60%. Less than 1 out of 4 studies had retention rates above 80%.
- Nine studies (40.9%) had retention rates <50%

Efficacy

- 4 studies showed an improvement in the active intervention
  - Dextroamphetamine (Galloway et al., 2011)
  - Mirtazapine (Colfax et al., 2011; Coffin et al., 2020)
  - Contingency management (Roll et al., 2006)
  - Open label NTX+Bupropion (Mooney et al 2016)

Sequential Parallel Comparison Design (SPCD)

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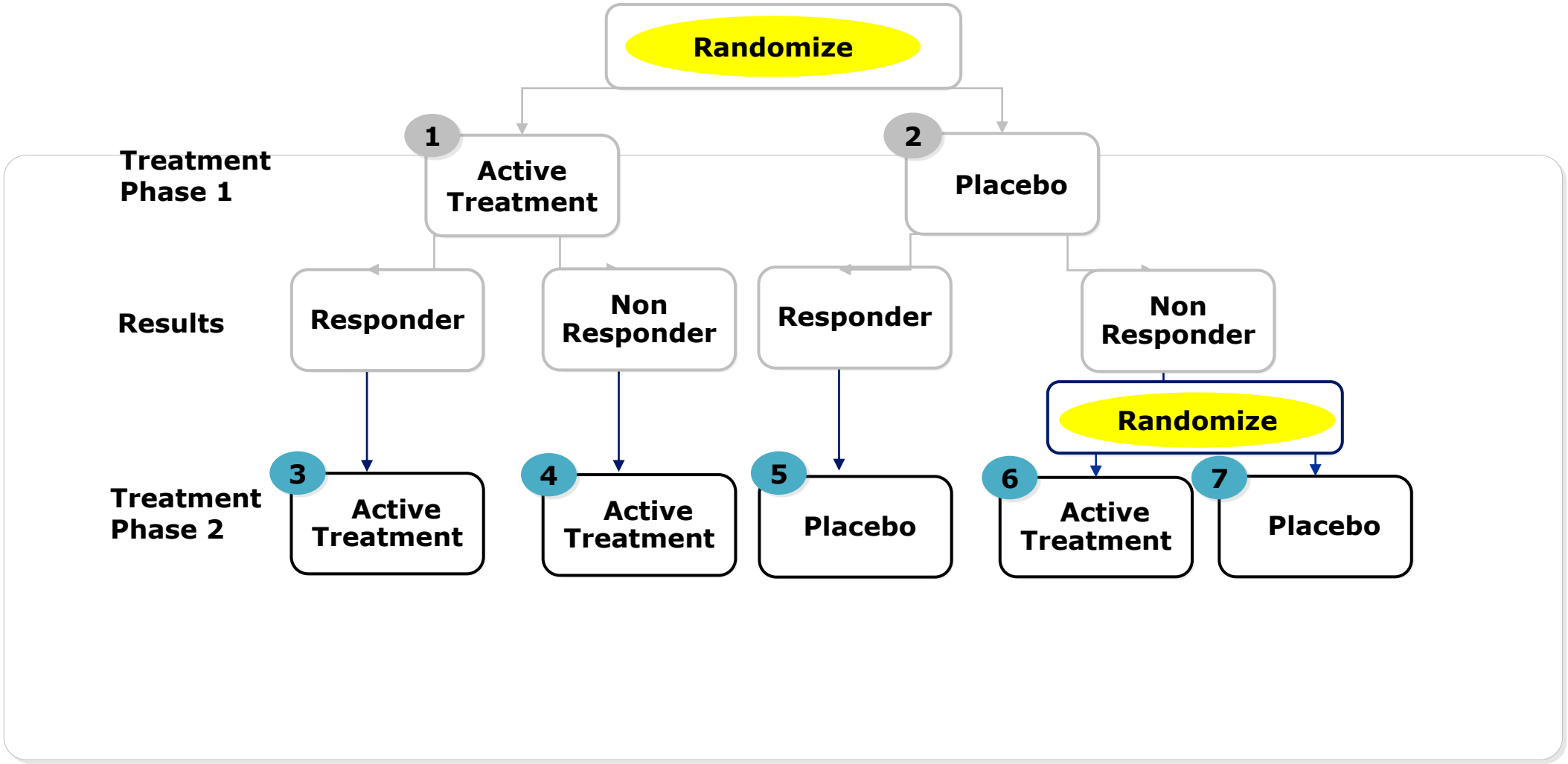
Sequential Parallel Comparison Design (SPCD)

A Highly Cost-Efficient Approach to Placebo Response!

- Characteristics of a Typical SPCD Trial with a Placebo Cohort:
  - Two phases of treatment and two randomizations (i.e., re-randomization before the second phase)
    - Some authors have referred to SPCD with this format as “SPD-ReR” or as being “Doubly Randomized”
  - Data from both phases are utilized for the efficacy analysis:
    - All subjects are utilized at least once
    - Some subjects are utilized twice

SPCD Sample Design



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Results from an SPCD Study: ADAPT-2

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ADAPT-2 Study Design Priorities

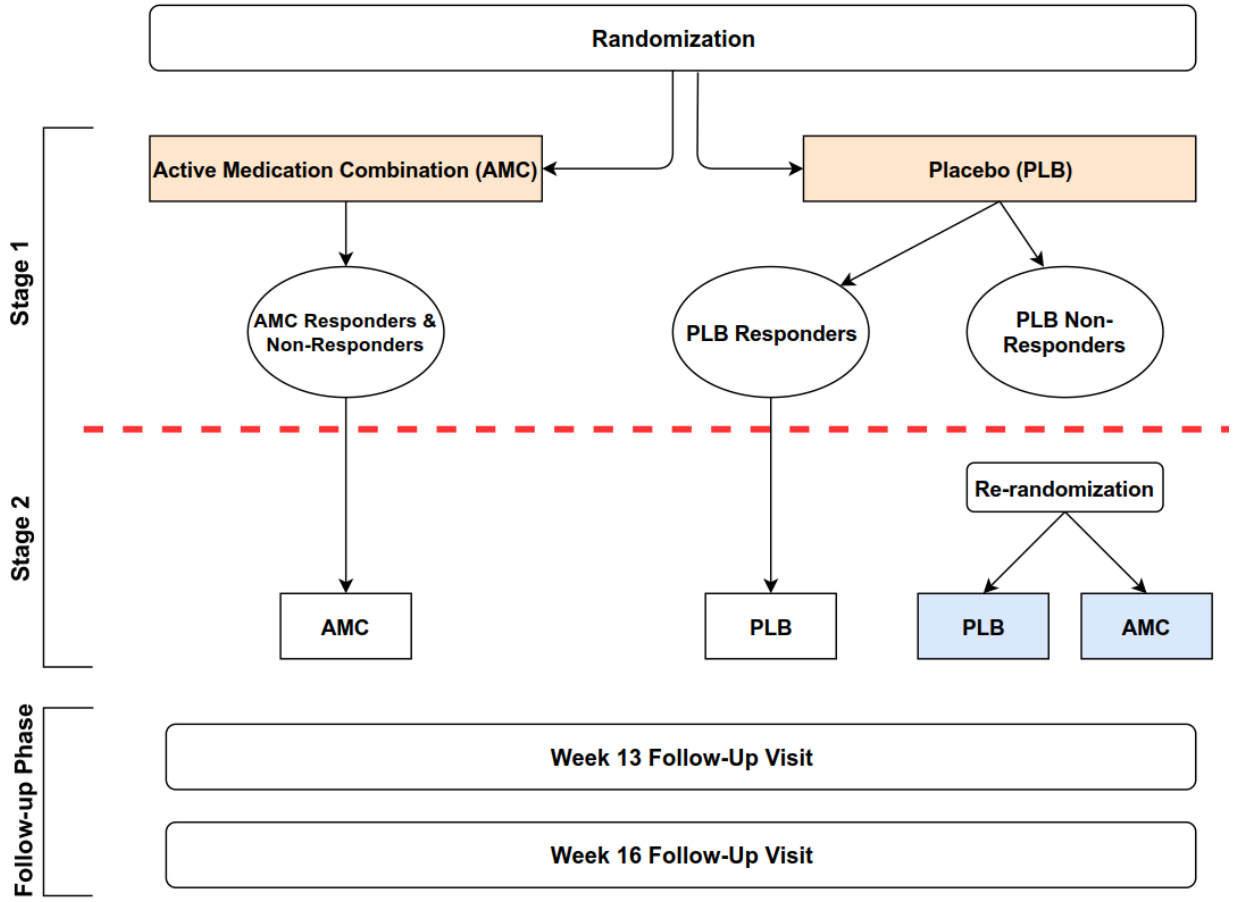
- Minimize placebo response
- Efficiency
  - Trial duration
  - Cost
  - Sample size
- Medication adherence
- Population severely affected

ADAPT-2 Key Inclusion Criteria

1. Meet DSM-5 criteria for moderate or severe methamphetamine use disorder (4 or more criteria)
2. Self-report (TLFB) meth use ≥18 days in 30 days prior to consent
3. At least 2 of 3 UDS + for meth within a 10-day period during which clinic visits occur with at least two days between visits
4. Fairly medically healthy and psychiatrically stable individuals
5. Not concurrently enrolled in formal addiction treatment

ADAPT-2 Design & Unmasked Schema

- Double-blind, placebo-controlled, randomized SPCD
- 8 study sites
- Randomized to AMC vs. PLB
- PLB non-responders **re-randomized** to AMC v. PLB
- 12-week Medication Phase
  - Visits: twice weekly
  - Oral meds: dispensed weekly
  - Injections: every 3 weeks



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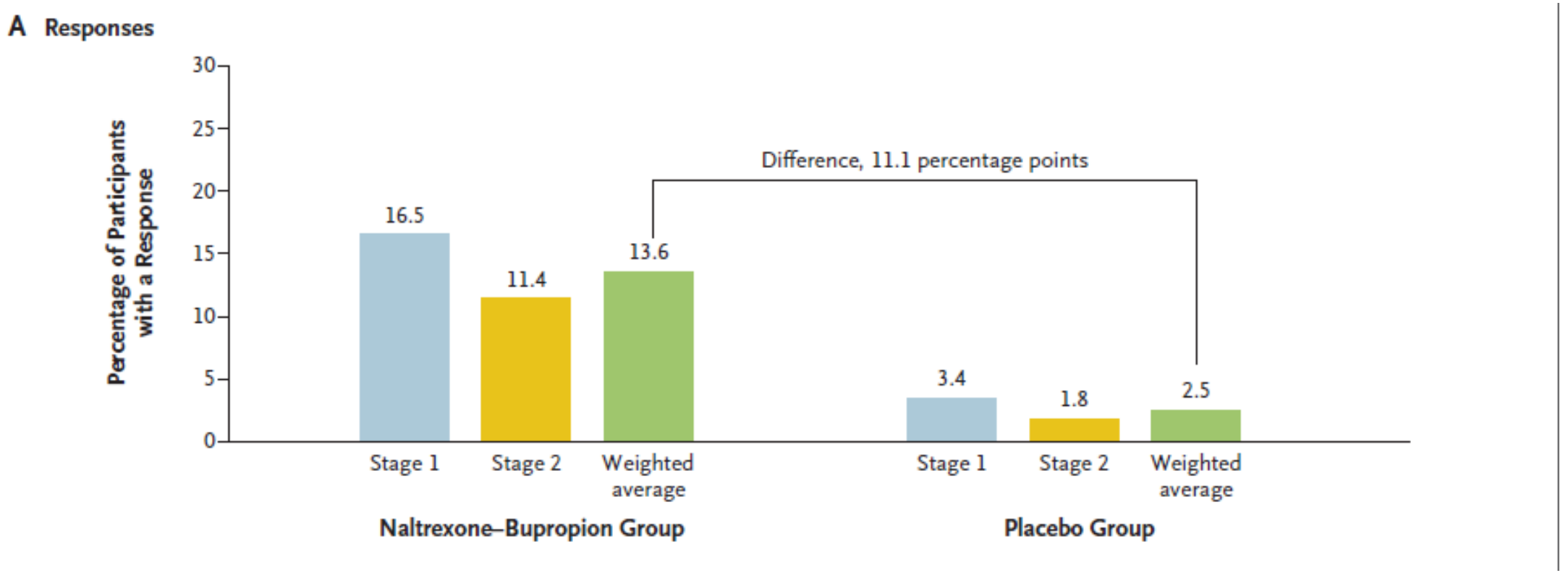
ADAPT Primary Outcomes

- **Primary efficacy outcome measure:** Meth-negative UDS results for AMC vs PLB

- "Responder": Any ppt who provided ≥3 (out of possible 4) meth-negative UDS during the evaluation period:
    - Stage 1 evaluation period: Weeks 5 and 6
    - Stage 2 evaluation period: Weeks 11 and 12
  - This definition provides a more real-world representation of addiction behavior and allows for some return to use, but in the context of *mostly* abstinence, to be considered as treatment response.

- **Primary safety outcomes**: Adverse Events and Serious Adverse Events

Weighted Outcome Primary Result



Trivedi MH, et al. *N Engl J Med*. 2021;384(2):140-153.

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Self-Reported Methamphetamine Use & Craving Decreased

Methamphetamine Abstinence: Timeline Followback (TLFB)

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results
PLB	AMC	PLB	AMC	p-value
14.0%	27.2%	16%	25.3%	**<0.001**

Note: The baseline measure is the proportion of abstinent days in the 30 days prior to randomization. The outcome is the change in proportion of abstinent days. Study parameters: weight 0.43, continuation rate 0.792, test statistic (Z) 5.666

Reduction in Methamphetamine Craving: VAS

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB VAS craving	AMC VAS craving	PLB VAS craving	AMC VAS craving	Treatment effect	p-value
-21.860	-29.599	-20.119	-31.339	-9.724	**<0.001**

Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (Z) -4.69

NIDA UG1DA020024

Cigarette Use and Depressive Symptoms Decreased

Cigarette Abstinence: TLFB

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB	AMC	PLB	AMC	Treatment effect	p-value
5.4%	10.3%	3.8%	11.9%	0.067	**<0.001**

Note: The baseline measure is the proportion of abstinent days in the 30 days prior to randomization. The outcome is the change in proportion of abstinent days. Note: N = 392, Weight 0.43, continuation rate 0.792, test statistic (z) 4.353

Reduction in Depressive Symptoms: PHQ-9

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB	AMC	PLB	AMC	Treatment effect	p-value
-2.946	-4.458	-3.362	-4.042	-1.039	**0.016**

Note: N = 403, Weight 0.43, continuation rate 0.792, test statistic (z) -2.41

NIDA UG1DA020024

Quality of Life Measures

Improvement in patient-reported progress in recovery: Treatment Effectiveness Assessment (TEA)

Stage 1: Mean Change from Baseline		Stage 2: Mean Change from End of Stage 1		Results	
PLB	AMC	PLB	AMC	Treatment effect	p-value
2.178	6.495	2.450	6.222	4.006	**<0.001**

Note: N=306, Weight 0.43, continuation rate 0.792, test statistic (z) 4.558

Other QoL Outcomes:

- 3 separate types: Physical Health, Mental Health, Activities
- More improvement (from baseline) in AMC than PLB, in both stages
- Not significant

Number Needed to Treat (NNT) Comparison to Other SUD Treatments

Medication	Effect	NNT
Bupropion + Naltrexone (extended release)	Response Rate in MA Use Disorder (ADAPT-2 Primary Outcome)	**9**
Naltrexone (oral)	Prevent relapse to heavy drinking in Alcohol Use Disorder	9-12
Naltrexone (extended release)	Abstinence in Opioid Use Disorder	8
Bupropion (oral)	Smoking Cessation	8

There are no other published multi-site RCTs demonstrating successful outcome of pharmacotherapy for methamphetamine use disorder.

NIDA UG1DA020024

ADAPT-2 versus Coffin (2019)

Proportion of Abstinent Days in ADAPT versus Coffin (2019)

	ADAPT AMC	ADAPT Placebo	**ADAPT Effect Size#**	Coffin Mirt	Coffin Placebo	**Coffin Effect Size#**
Baseline	0.0	0.0		0.15	0.25	
Week 6	0.29	0.09	**0.26**	NA	NA	
Week 12	0.36*	0.09*	**0.32**	0.34	0.22	**0.11**

*Subjects in AMC or Placebo for 12 weeks

#Cramer's V: guidelines 0.1=small effect, 0.3=medium effect, 0.5=large effect

Summary

- Adaptive designs can lead to more efficient trials
  - *Fewer patients may be required for the study*
  - *Reduces the chance of an underpowered trial*
  - *The patient population most likely to benefit from a treatment may be identified by eliminating the noise of placebo-response*
  - *Treatment effects may be estimated with greater precision*

- Adaptive designs can be exciting to design, implement, and interpret, but also challenging.

Thank You

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Session 2: Optimizing Clinical Trial Design for Stimulant Use Disorder

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters:

David McCann, PhD, *National Institute on Drug Abuse*
Madhukar Trivedi, MD, *UT Southwestern*

Panelists:

Sarah Akerman, MD, *Alkermes*
Maria Sullivan, MD, PhD, *Pear Therapeutics*
Jessica Hulsey, *Addiction Policy Forum*
Frances Levin, MD, *Columbia University*
Robert Walsh, RAC, *National Institute on Drug Abuse*
Maryam Afshar, MD, *U.S. Food and Drug Administration*

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Break: 2:15-2:30

Session 3: Identifying Clinically Meaningful and Patient-Centric Endpoints

REAGAN-UDALL FOUNDATION FOR THE FDA

Presenters:

Brian Kiluk, PhD, *Yale School of Medicine*

Panelists:

Michelle Peavy, PhD, *University of Washington*
Philip Rutherford, *Faces and Voices of Recovery*
Deborah Hasin, PhD, *Columbia University*
Ivan Montoya, MD, MPH, *National Institute on Drug Abuse*
David Reasner, PhD, *U.S. Food and Drug Administration*
Celia Winchell, MD, *U.S. Food and Drug Administration*

Identifying Clinically Meaningful and Patient-Centric Endpoints

Brian D. Kiluk, Ph.D.
Associate Professor of Psychiatry

Yale SCHOOL OF MEDICINE

Presented at Virtual Public Workshop Monday October 18, 2021
Hosted by Regan-Udall Foundation for the Food and Drug Administration

FDA Guidance on Endpoints

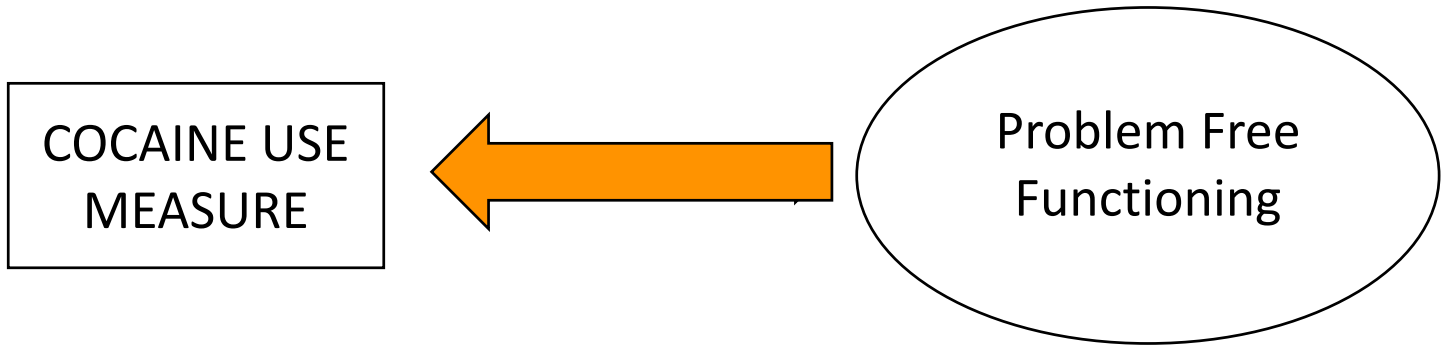
- Recommended primary efficacy endpoint is a decrease in drug use based on comparison of responders
- Commonly used threshold to define treatment "responder" is ABSTINENCE

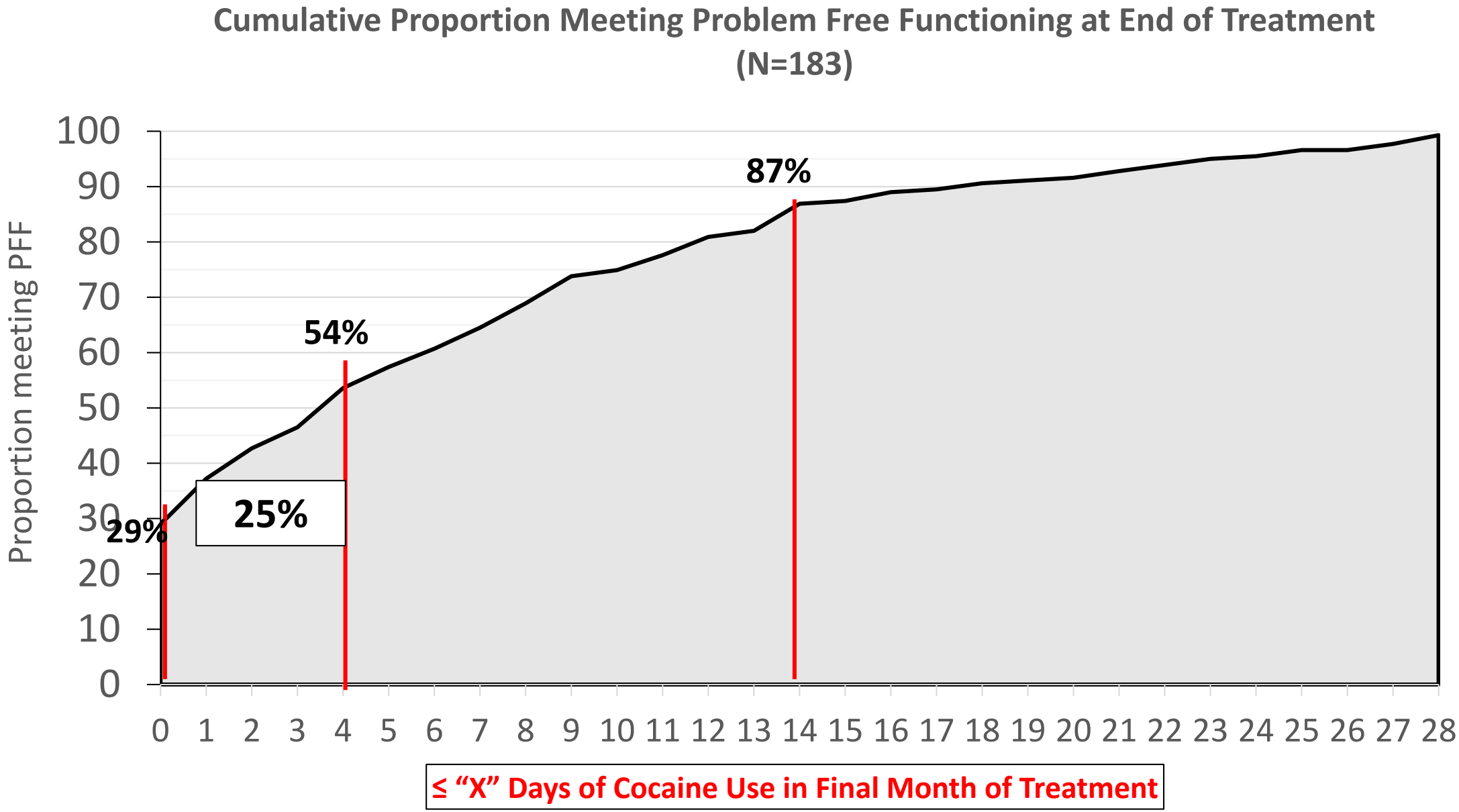
- **ABSTINENCE IS NOT REQUIRED AS ENDPOINT**
  - Thresholds other than abstinence are acceptable
    - BUT, need to show that drug use pattern predicts clinical benefit

What Defines Clinical Benefit?

- Data pooled across 7 RCTs conducted at Yale (N = 718)

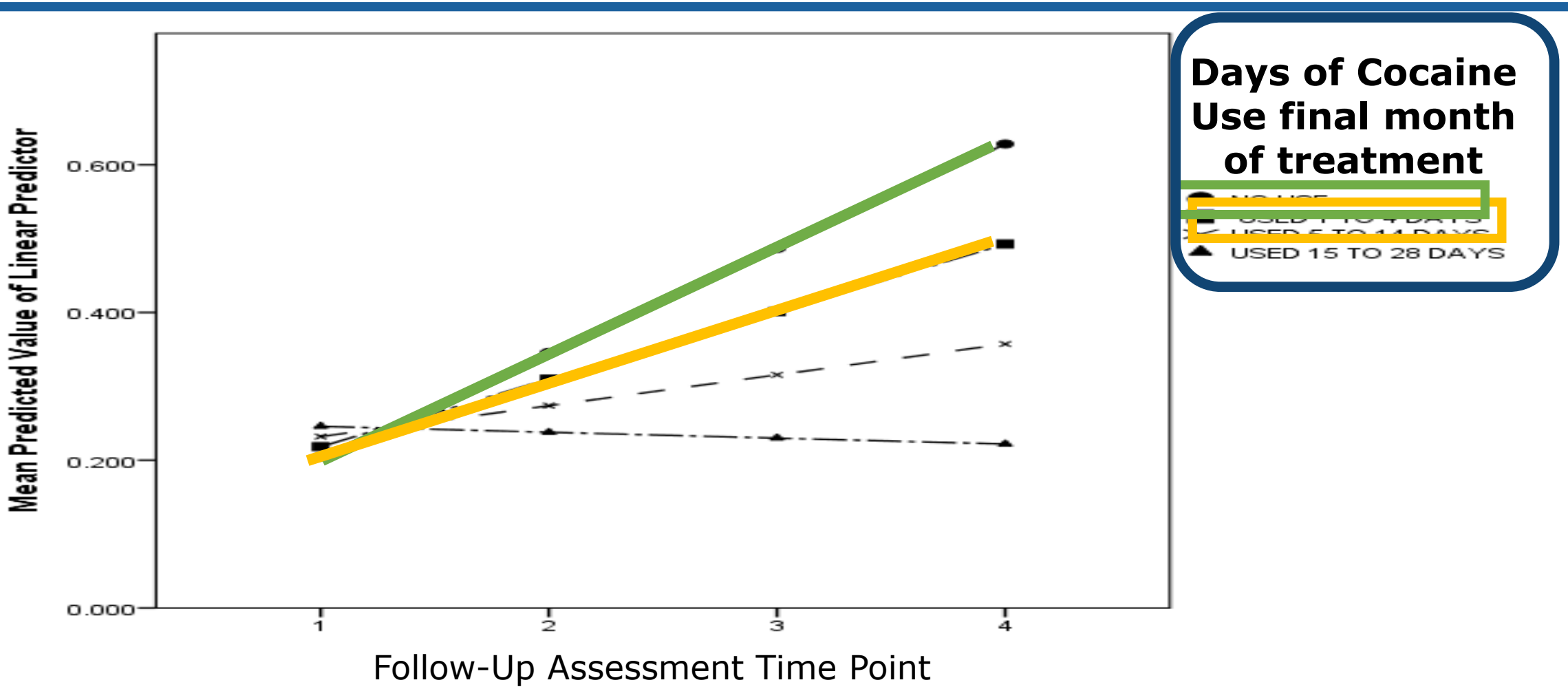
- Establish an indicator of clinical benefit ("Good" functioning)
  - Absence of physical and psychosocial problems
  - 'Problem Free Functioning' (PFF) derived from Addiction Severity Index





Kiluk et al., 2017, *Drug Alcohol Dependence*

Probability of Achieving Problem-Free Functioning During Follow-up Based on Days of Cocaine Use at End of Treatment



Kiluk et al., 2017, *Drug Alcohol Dependence*

Cocaine Frequency Levels as Endpoint

- Pooled sample across 7 RCTs (N = 718)

Cocaine Frequency Level	Baseline n (%)	EOT n (%)
Abstinence (0 cocaine use days in past month)	0 (0%)	83 (16.1%)
Low Frequency (1-4 cocaine use days in past month)	119 (16.6%)	147 (28.5%)
High Frequency (5+ cocaine use days in past month)	597 (83.3%)	285 (55.3%)

Roos et al., 2019, *Drug and Alcohol Dependence*

Change in Cocaine Frequency Level

Change in Cocaine Frequency Level from Baseline to EOT	n (%)
Increase 1 Level	34 (6.6%)
No change	284 (55.1%)
Decrease 1 Level	**134 (26.0%)**
Decrease 2 Levels	**63 (12.2%)**

- **Reducing from high freq → low freq similar to high freq → abstinence**

Roos et al., 2019, *Drug and Alcohol Dependence*

Endpoints in SUD trials

- Outcomes typically based on frequency of use/abstinence

- **Frequency of substance use is not a criterion for disorder**

> "A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period"

DSM-5 Criteria for SUD

1. Substance
2. Persistent
3. A lot of tim
4. Craving or
5. Failure to f
6. Persistent s
7. Important
8. Use in phys
9. Physical or
10. Tolerance
11. Withdrawal

an intended

trol

me

substance use

Severity Category

"Mild" = 2-3 criteria

"Moderate" = 4–5 criteria

"Severe" = 6+ criteria

Early Remission

≥3 months to <12 months without meeting SUD criteria (except craving)

Change in Symptom Criteria or Severity

- Measures of change in disorder severity or remission rates commonly used in treatment trials for psychiatric disorders
  - Depression
    - Montgomery-Asberg Depression Rating Scale (MADRS)
    - ≥50% reduction in total score on standardized observer rating scale
    - Self-report scale (QIDS, PHQ-9)

- SUD trials have not prioritized severity or remission as an outcome

Change in Disease Status

Diagnostic criteria for OUD encompass both drug use and its effect on patient well-being. If all trial patients meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for moderate-severe OUD at baseline,[2] the sponsor could use the proportion of patients meeting DSM-5 criteria for remission of OUD at the end of the trial as a primary or secondary efficacy endpoint.

FDA Draft Guidance 2018: Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication Assisted Treatment; Guidance for Industry

End-of-Treatment DSM-5 Status

- RCT evaluating CBT4CBT for primary alcohol users (Kiluk et al., 2016)

	End of Treatment Severity Category				
6-month Follow Up	Absent (n=23)	Mild (n=10)	Moderate (n=12)	Severe (n=8)	Post-hoc
Percentage of days abstinent	91.3	70	58.2	74.1	Absent > Moderate
Percentage of heavy drinking days	4.1	12.6	19.4	16.1	Absent > Moderate
SIP score	6.8	8.9	9.2	21.6	Absent < Severe

Kiluk et al., 2018, *Alcoholism: Clinical and Experimental Research*

Change in DSM-5 Cocaine Use Disorder Severity

- Recently completed trial with treatment-seeking cocaine users (N=99)*
  - DSM-5 severity at baseline: Moderate = 17%; Severe = 82%
  - At End-of-treatment (12-weeks; n=68):
    - No longer met disorder threshold past 30 days = (n=26; 38%)

- No longer met disorder threshold at end-of-treatment
  - Days of cocaine use in last 4 weeks of treatment: Mean = 0.23 (sd=0.78)
  - Percent days abstinent during 12-month FU: Mean = 90.5%

* PRELIMINARY DATA; not yet published

Conclusions

- Promising Endpoints
  - Cocaine use levels to define 'responder'
    - Reduction in frequency level (high to low; low to abstinence)
  - DSM-5 diagnostic threshold, or reduction in severity category
- Challenges
  - Validation of self-reported frequency of stimulant use
  - Structured Clinical Interviews for DSM
  - Time frame
- Opportunities
  - NIDA-modified ASSIST
  - In Development (OUDSS): NIDA U01DA051639
    - Patient reported measure of DSM-5 criteria for OUD

Opioid Use Disorder Severity Scale*

- Measure frequency (severity) of disorder criteria
- Greater sensitivity to detect change
- Advance measurement-based care approach
- Variation in severity of individual DSM criterion unknown

In the past month...

	Never	Rarely	Sometimes	Often	Almost Always
I ended up using more opioids than I meant to	○	○	○	○	○
I used opioids for a longer amount of time than I meant to	○	○	○	○	○

* Currently being developed and validated

THANK YOU

- NIH NIDA R21/33 (DA041661)
- NIH NIDA U01DA051639
- Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION)

- Collaborators & Co-authors
  - Kathleen Carroll, Ph.D.
  - Corey Roos, Ph.D.
  - Charla Nich, M.S.
  - Theresa Babuscio, M.A.

Session 3: Identifying Clinically Meaningful and Patient-Centric Endpoints

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David Reasner, PhD, *U.S. Food and Drug Administration*
Celia Winchell, MD, *U.S. Food and Drug Administration*

Session 4: Future Directions for Stimulant Use Disorder Research

REAGAN-UDALL FOUNDATION FOR THE FDA

Panelists:

Marta Sokolowska, PhD, *U.S. Food and Drug Administration*
Nora Volkow, MD, *National Institute on Drug Abuse*
Brandee Izquierdo, MPA, *SAFE Project*
Denise Leclair, MD, *Novartis*
F. Gerald Moeller, MD, *Virginia Commonwealth University*
Pamela Scott, MS, *U.S. Food and Drug Administration*
Nicole Caffiero, PharmD, *Cigna*

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Thank you!