Digital Therapeutics
for Substance Use Disorders:
Research Priorities and Clinical Validation

Will M. Aklin, Ph.D.
Director, Behavioral Therapy Development Program
Division of Therapeutics and Medical Consequences (DTMC)
NIH, National Institute on Drug Abuse (NIDA)

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Disclosures

- No one involved in the planning and presentation of this activity has relevant financial relationships.

- All speakers have been advised that any recommendations involving clinical medicine must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. All scientific research referred to, reported, or used in the presentation must conform to the generally accepted standards of experimental design, data collection, and analysis.

Target Audience

- The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.

Educational Objectives

At the conclusion of this activity participants should be able to:

- Review research to support the development of safe and effective Digital Therapeutics (DTx)

- Describe strategies to accelerate the delivery of Digital Therapeutics to patients and improve SUD treatment outcomes

- Illuminate NIH-supported and FDA-authorized DTx options for patients

  - Discern which technologies constitute DTx

  - Gain an understanding of DTx as stand-alone treatments or integrated with FDA-approved SUD treatments

  - Identify the FDA authorization process for DTx

Why the Need for New Treatment Options?

- As evidenced during the COVID pandemic:
  - Traditional methods of delivering health care are limited and can be difficult to access
  - Rural and urban healthcare "deserts" highlight the need to expand options to increase access

- One of the most promising methods is the use of digital therapeutics (DTx) to address this public health challenge

- April 1, 2001—White House Office of National Drug Control Policy (ONDCP) announced its priority to expand access to evidence-based treatments
  - which includes…"reimbursement for motivational incentives and digital treatment for addiction, especially stimulant use disorder."

NIDA Views on Digital Therapeutics

What are DTx and What are they not?

- DTx **are** mobile, web, or other software-based platforms that can deliver effective treatments

- DTx **are** designed to prevent, manage or treat a medical disorder or disease

- DTx **are not** general wellness apps or telehealth – remote access to a clinician

- Behavioral treatments requiring face-to-face interactions can be delivered whole or in part by DTx

NIDA Priorities on Digital Therapeutics

- Improve treatment efficacy

- Integrate behavioral treatments having defined mechanisms of action with a standardized therapeutic delivery

- Boost effects and increase efficiency of interventions

- Produce technology-enhanced treatments that are implementable and self-sustaining

Notable Advantages of Digital Therapeutics

Reproducibility – Reliably delivered treatment with limited staff training, following evidence-based guidelines (quality control)

Engagement – DTx can encourage patient engagement by having the intervention available 24 hours a day, as needed

Reach – Limited treatment access partly accounts for the reason over 80% of individuals in need of SUD treatment do not receive it

Privacy – Stigma is a critical issue for many patients when considering treatment; enhanced privacy could help address stigma

Cost – DTx delivery does not require active interaction with a clinician, reducing face-to-face cost (blended care approach combines in-person and DTx strategies)

Data Recording – DTx can facilitate the recording of data that physicians collect during their in-person treatment sessions, and they can also facilitate patient recording of symptoms, feelings, cravings, and other information

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Discussion #1 -- Unanswered Questions

- Are there ways to establish or maintain rapport? What is the balance between digital health and interpersonal contact?

- How will digital therapeutics intersect with health disparities populations in the area of addiction research?

- Health-care system requirements including HIPPA compliance?

Overall DTx Landscape

- Rapid shift over the last decade has resulted in a surge of DTx development, yet many have not been clinically studied

- Development efforts have far outpaced validation studies

- As such, there is a need to bring order to the "Wild West" with a trusted entity responsible for:

  - Review of clinical effectiveness and usability of DTx

  - Authorize DTx that are worthy of patient consideration

Less Chaff, More Wheat…

To Validate or Not to Validate— That is the Question!

- The importance of validation in the target population is as important for DTx as more traditional medications and/or devices

- NIDA values FDA's role providing independent assessment of risk, safety, and effectiveness

  - Currently, digital interventions can be given to patients without FDA review and authorization

  - Whether FDA review is required depends on several aspects, including the level of risk associated with the treatment population or the intervention

  - While several products on the market were tested in clinical studies and shown to be effective, there is no standard that patients can rely on to be assured of their efficacy

NIDA and FDA Partnership MOU

NIDA/FDA (Center for Devices and Radiological Health) Memorandum of Understanding (MOU) was established in 2019 and allows regular interaction and sharing of information about DTx

Three major actions items were prioritized:
- NIDA funding opportunity on DTx development for SUDs
- FDA/NIDA collaboration on presentations to applicants on authorization process
- Development of a joint commentary on NIDA/FDA DTx research priorities and clinical validation

Focus on opportunities to:
- Provide guidance to grant applicants to help navigate the FDA submission and authorization process
- Accelerate the progression of these technologies through the regulatory pathway

FDA Regulatory Pathways for DTx

General Wellness— low risk devices, do not make diagnostic or therapeutic claims (do not need clearance)

Pre-Market Approval (PMA) Pathway—high risk/class III medical devices, FDA inspection required, not relevant to DTx

510(k) Pathway—low to moderate risk devices, must demonstrate equivalence to predicate device, FDA decreasing 510k submissions in favor of de novo

De Novo Pathway—novel, low to moderate risk devices, new product classification

Breakthrough Devices Program—program to give priority review—for medical devices and device-led combination products; goal is to give patients timely access to breakthrough technologies (De Novo, 510(k), or PMA placed towards top of queue)

Sample Early Interaction Progression

Mechanism:
Pre-submission Program

Pre-Submission(s)

IDE or Marketing Submission

VOLUNTARY
Highly effective

Pre-Submission (Q-Submission)

- Provides an opportunity to obtain FDA feedback prior to IDE or marketing submission
- FDA provides written feedback and an optional meeting
- Pre-submissions are NOT intended for "pre-review" of data
- The purpose is to clarify feedback, not to respond in real-time to new information or proposals

Guidance Document

"Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

Medical Device Definition

- Definition of a medical device is specified in section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321) *

- Section 201(h) states in part:

  - The term "device"…means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is…"

    - "…intended for use in the <u>diagnosis</u> of disease or other conditions, or in the <u>cure, mitigation, treatment, or prevention</u> of disease…" or

    - "…intended to <u>affect the structure</u> or any <u>function</u> of the body …and which does not achieve any of its primary intended purposes through chemical action.…and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

When is an IDE Needed?

- When a device is a significant risk device
- 21 CFR 812.3(m) defines "Significant Risk" as and investigational device:

  (1) Is **intended as an implant** and presents a potential for serious risk to the health, safety, or welfare of a subject;
  (2) Is **purported or represented to be for a use in supporting or sustaining human life** and presents a potential for serious risk to the health, safety, or welfare of a subject;
  (3) Is **for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health** and **presents a potential for serious risk to the health, safety, or welfare** of a subject; or
  (4) Otherwise presents a potential for **serious risk to the health, safety, or welfare of a subject**

Study Risk Determinations

- An opportunity to obtain FDA feedback on whether your proposed study is a significant risk or non-significant risk study

- FDA provides a written letter outlining whether the proposed study is determined as significant risk or non-significant risk

Guidance Document

"Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies"

https://www.fda.gov/media/75459/download

Developing a Digital Therapeutic for SUD: Points to Consider

- Design considerations:
  - Type of behavioral therapy
  - How does device implement the principles of this behavioral therapy
  - Indicated for use as an adjunct to usual best medical care or
  - indicated for use as a standalone DTx?

- Non-clinical testing considerations:
  - Software validation

- *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices

Developing a Digital Therapeutic for SUD: Points to Consider

- Clinical testing considerations:
  - Human factors/Usability testing
  - *Applying Human Factors and Usability Engineering to Medical Devices*
    (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices)
  - Clinical trial - to evaluate safety and effectiveness of the DTx

Developing a Digital Therapeutic for SUD: Points to Consider

- Medical device trials differ from drug studies

- Device studies are designed to support a "reasonable assurance of safety and effectiveness"

- Endpoints of interest can be highly diverse between studies
  - Dependent on indication for use being sought

- Clinical trial should be designed to support the indication for use and target population

Developing a Digital Therapeutic for SUD: Points to Consider

- Recommend evaluating the safety and effectiveness of the device in the population for which it is to be indicated

- Specific use vs. general use
  - Guidance for Industry: General/Specific Intended Use (https://www.fda.gov/media/71966/download)

- Time frames for evaluating the primary endpoint should be defined
  - Consider time course of the specific SUD
  - Do patients have an initial immediate response and then tend to relapse?

- Endpoints should be prespecified
  - 1 or more "safety" endpoints
  - 1 or more "effectiveness" endpoints

Developing a Digital Therapeutic for SUD: Points to Consider

- **Well-controlled study**
  - Sham control vs. usual care (or treatment as usual)
  - Considerations:
    - Need to account for the placebo effect and treatment groups having equivalent "time on task"

- **Adjunctive use vs. standalone**
  - If used as adjunct:
    - Patients should be on usual care
    - Protocol should delineate what usual care constitutes
    - If patients are allowed to be on medications, protocol should include a plan for how medications will be managed and monitored
  - If used as a standalone
    - Protocol should have specific plan for patient safety if patients will not be on medication or other usual care
    - Protocol should have a plan for how patients will be "washed" from medications or other usual care
    - Need to account for placebo effect and device effectiveness compare to usual care

- **Inclusion/exclusion criteria should meet the target population for indication for use**
- **Some statistical considerations:**
  - Pre-specified plan for handling missing data
  - Pre-specified success criteria for secondary endpoints if you plan to make labeling claims based on secondary endpoints and to further support device safety and effectiveness

- **Randomization**

- **Blinding**
  - Patients, investigators, and study staff blinded along with a plan for blinding assessment

- **Generalizability to the US population**

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Discussion #2—
# Endpoint Measures for DTx

- Measures obtained from a DTx or clinician can be used to provide clinically meaningful data on how a patient feels and functions

  - Independent measures collected from the DTx or by other means, such as assays of biofluids, may be an independent biomarker in confirming subjective reports

  - Concerns DTx could give biased assessments; outcome measures from different domains should confirm one another

- FDA only has the ability to authorize non-medications, which is distinct from the approval given to medications

Changing Landscape: Key Breakthroughs

- 2017 - FDA approves 1st Digital Therapeutic for SUD Treatment from Pear Therapeutics
  - NIDA-funded efficacy trial
  - reSET provides CBT/CM as an adjunct to treat stimulant, cannabis, cocaine and alcohol use
  - reSET-O approved in 2018 for OUD as adjunct to medication treatment

A. Percent of Tested Weeks of Opioid Abstinence $F_{(1,158)} = 8.81$, p<0.01

B. Retention — Standard Therapy + reSET (80%); Standard Therapy (64%)
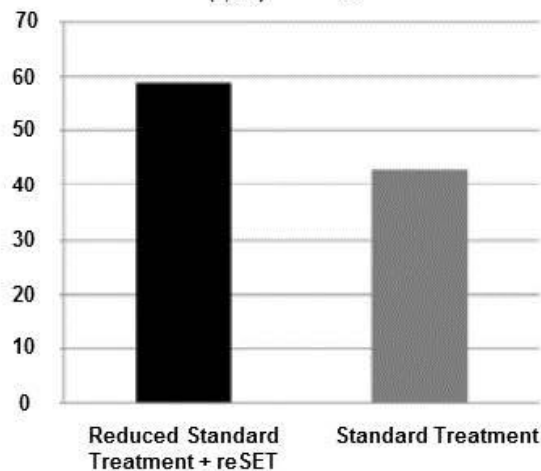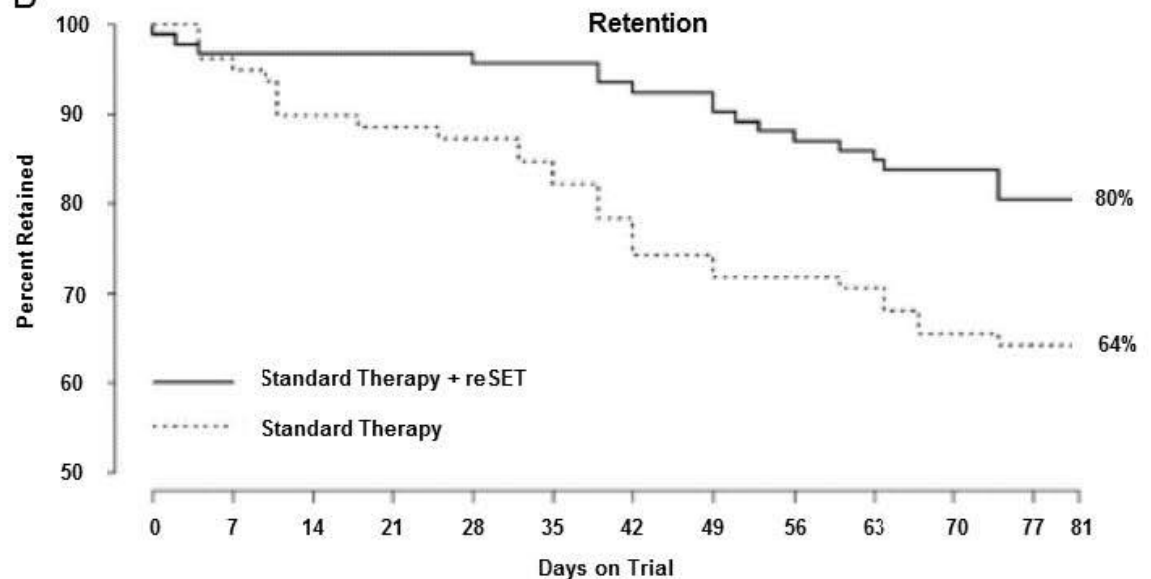
NIDA Supported DTx Studies

Loyalty and Reward-Based Technologies to Increase Adherence to Substance Use Disorder Pharmacotherapies (R43/R44—RFA-DA-19-014; 015)

- DTx as an adjunct to increase medication adherence
- Primary endpoint: adherence to FDA-approved medication for SUD (e.g., buprenorphine, naltrexone, NRT)
- Rewards and contingencies delivered in a self-sustaining manner

Developing Digital Therapeutics for Substance Use Disorders (UG3/UH3—PAR-21-183)

- Research to develop and test DTx for stand-alone treatments or integrated with FDA-approved SUD treatments
- DTx indications: prevention of SUD initiation, medication adherence, treatment retention, treatment of withdrawal, abstinence or reduction of relapse

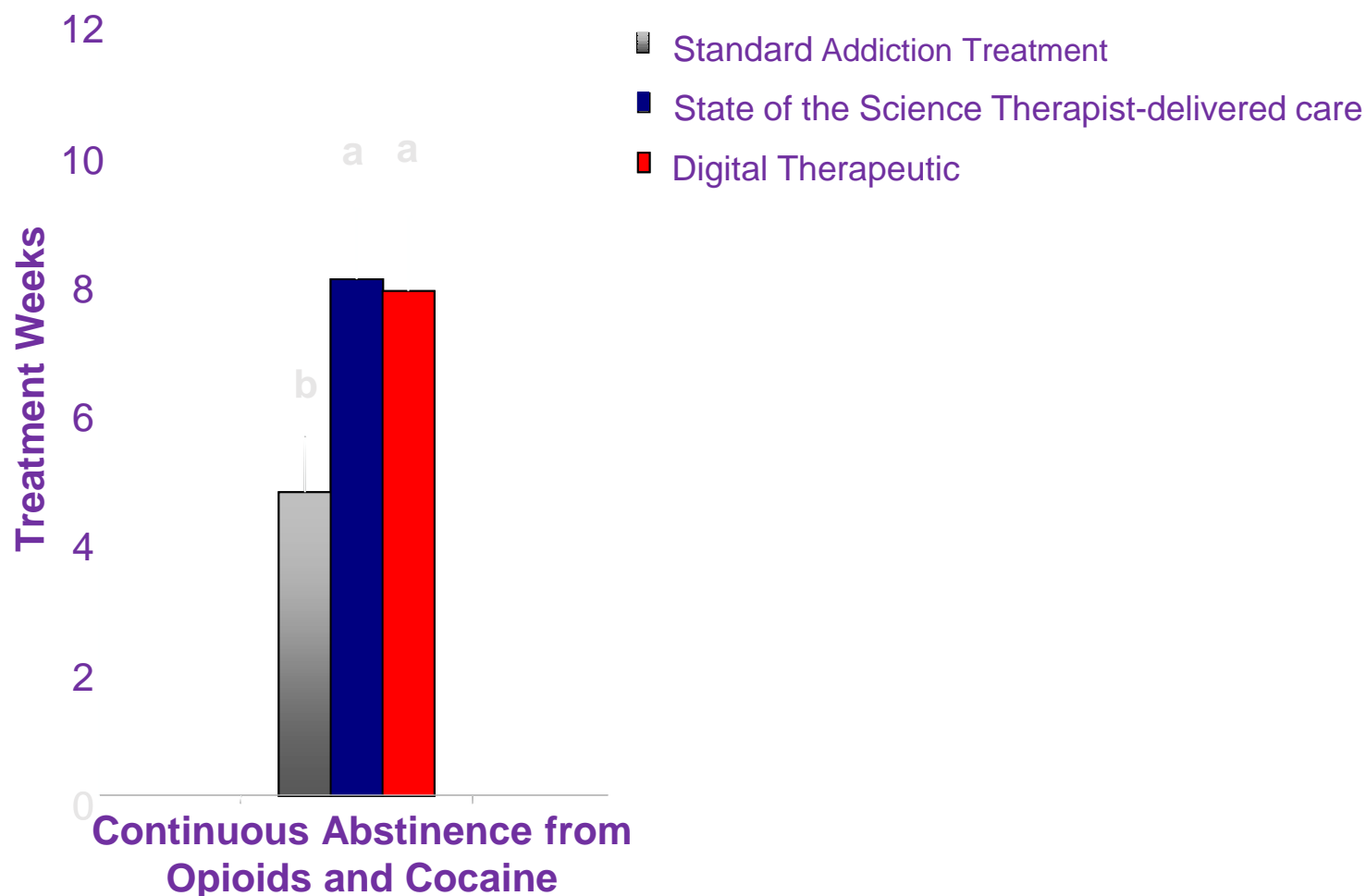# Examples of Research Activities Funded through NIDA During UG3

- Development of a finalized version of the DTx and validation in the study population;

- Evidence that the intervention effects efficacy related endpoints
  - For example: craving, dependence, days of abstinence, etc;

- Evidence the intervention effects behavioral endpoints as they relate to SUD
  - For example: measures of working memory, impulsivity, risk-taking propensity, distress tolerance, self-regulation, stress reactivity, etc;

- Evidence an adequate dose range/treatment duration for the DTx intervention(s) can be applied with acceptable safety, tolerability, adherence, etc;

- Evidence when integrated with an FDA-approved treatment, there is enhanced adherence, retention, efficacy or effects on other measures relevant to the approved treatment;

- Completion of a proof-of-concept, feasibility clinical trial;

- Q-submission to obtain FDA feedback on the regulatory pathway; Filing an IDE;

Smartphone-based financial incentives to promote smoking cessation during pregnancy

- Primary endpoint: biochemically confirmed smoking abstinence

- Best practices: brief smoking cessation counseling at start and at two assessments

- Incentives: best practices and remote financial-incentives intervention

- Assessments: breath and saliva tests were submitted remotely in the form of videos of participants completing the tests
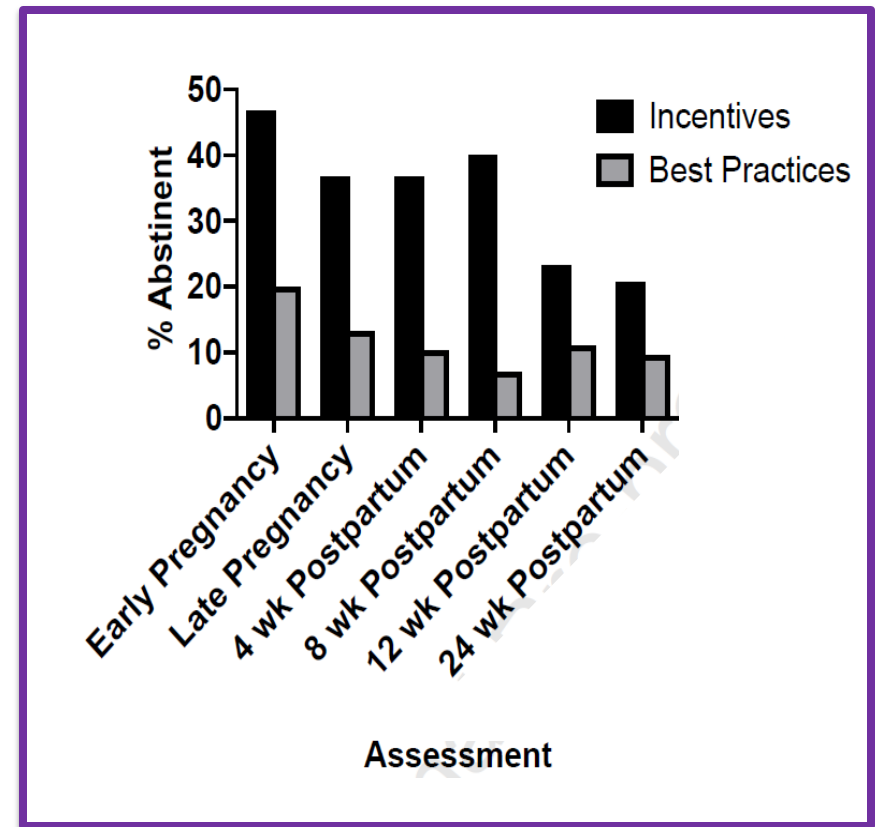
Digital Therapeutic is as Effective as "Gold Standard" Clinician-Delivered Treatment in Medication Treatment for OUD (n=135)

Legend:
- Standard Addiction Treatment
- State of the Science Therapist-delivered care
- Digital Therapeutic

Y-axis: Treatment Weeks

X-axis: Continuous Abstinence from Opioids and Cocaine

Bickel, Marsch et al., 2008

RCT of a Novel Smoking Cessation Application for Individuals with Serious Mental Illness

- Grant funded to test Learn to Quit, a smoking cessation app tailored to individuals with SMI

- Combines Acceptance and Commitment Therapy with nicotine replacement therapy

- Data from pilot study, pivotal trial funded

	Learn to Quit	Quitguide
USABILITY AND ENGAGEMENT		
System Usability Scale	85.2	78.4
Days Used	34.1	32
App Interactions	847	205
App Duration in Hours	4.24	2.14
SMOKING BEHAVIOR		
Reductions in CPD	12.3	5.9
Quit Attempts	5.3	8.96
SMOKING ABSTINENCE		
30 day PPA, Week 16	12.1%	3.1%

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Closing Remarks

- FDA premarket review is especially important given the growing number of marketed digital health solutions w limited/ no validation

- FDA marketing authorization provides an important line of demarcation, giving patients and healthcare providers assurance about safety and effectiveness of the DTx

  - DTx meets the definition of a medical device and safe and effective for its intended use

- A prescription DTx receiving FDA regulatory authorization is required to demonstrate

  - Good manufacturing practices including robust software development
  - Data integrity/security practices
  - Compliance to applicable medical device Quality Systems regulations

Closing Remarks, Cont'd

- NIDA is committed to treatment of substance use disorders investing in scientific and theory-informed DTx with a focus on clinical validation studies

- DTx helps treatments to: (1) maintain potency, (2) become more easily implementable and sustainable (state-of-the-art practices)

- NIDA/FDA partnership goals focus on improving design, development, and methods for delivering regulated and clinically-validated DTx to patients
  - Guidance to investigators to help navigate the FDA submission and authorization process
  - Accelerate the progression of these technologies through the regulatory pathway
  - Add exponentially to the armamentarium of SUD treatment options

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General Discussion

- How does the information presented today apply to your discipline/practice?

- Can you think of <u>one thing</u> that you could do in your own work setting with your healthcare team to change practice based on the information presented today?

FDA Guidance Documents

- General Wellness Guidance Document
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-wellness-policy-low-risk-devices

- Policy for Device Software Functions and Mobile Medical Applications
https://www.fda.gov/media/80958/download

- Significant Risk/Non-Significant Risk Guidance Document
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

- FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-procedures-section-513g-requests-information-under-federal-food-drug-and-cosmetic

- "Software as a Medical Device (SAMD): Clinical Evaluation"
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/software-medical-device-samd-clinical-evaluation

FDA Guidance Documents

- Benefit Risk Guidance for IDE Submissions
  https://www.fda.gov/downloads/MedicalDevices/DeviceRegulation
  andGuidance/GuidanceDocuments/ucm451440.pdf

- Benefit-Risk Guidance for Medical Device Premarket Approval and
  De Novo Classifications
  https://www.fda.gov/regulatory-information/search-fda-guidance-
  documents/factors-consider-when-making-benefit-risk-
  determinations-medical-device-premarket-approval-and-de

- Benefit-Risk Guidance for 510(k) Submissions
  https://www.fda.gov/regulatory-information/search-fda-guidance-
  documents/benefit-risk-factors-consider-when-determining-
  substantial-equivalence-premarket-notifications-510k

FDA Guidance Documents

- IDE Submission Information http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm#reqele

- Design Considerations for Pivotal Clinical Investigations Guidance https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf

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PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in **addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD)**.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit:

https://pcssNOW.org/mentoring/

PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medications for opioid use disorder. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register

PCSS is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

Addiction Technology Transfer Center	American Society of Addiction Medicine
American Academy of Family Physicians	American Society for Pain Management Nursing
American Academy of Pain Medicine	Association for Multidisciplinary Education and Research in Substance use and Addiction
American Academy of Pediatrics	Council on Social Work Education
American Pharmacists Association	International Nurses Society on Addictions
American College of Emergency Physicians	National Association for Community Health Centers
American Dental Association	National Association of Social Workers
American Medical Association	National Council for Mental Wellbeing
American Osteopathic Academy of Addiction Medicine	The National Judicial College
American Psychiatric Association	Physician Assistant Education Association
American Psychiatric Nurses Association	Society for Academic Emergency Medicine

Educate. Train. Mentor