NAADAC

Advances in Technology in the Addiction Profession, Part I

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>> JESSIE O'BRIEN: Hi everyone I'm letting everyone trickling before we get started, we will begin in about two minutes and we will begin the specialty series, advances in technology in the addiction profession

All right welcome everybody to today's webinar Advances in technology in the addiction profession part one, digital therapeutics clinically validated Haverhill treatments were substance abuse disorders presented by Dr. Will Aklin.

My name is Jessie O'Brien the training and professional develop and content manager here at NAADAC the Association for addiction professionals, I will be the facilitator for this training experience.

The permanent homepage for webinars is www.NAADAC.org/webinars, bookmark this page with the latest in addiction education, closed captioning is provided by CaptionAccess today so please check your most recent confirmation email or our Q&A and chat box for the link to use closed captioning.

We are using Zoom webinar for today's life event have moved away from go to webinar so it may look a little different if you have not been with us in a little while you'll notice the Zoom control panel that looks like the one on my side at the bottom of your screen, there are too many humane items to be aware of on the menu, the first is the chat box you can now chat, with the host analyst and attendees so feel free to chat away, the second is the Q&A box if you open the Q&A window you can ask questions to the host and panelist any questions you have and they will either reply to you by text in the Q&A with window or answer live and we will gather the questions and towards the end have a live Q&A with our presenter.

You can also opt vote questions you see that are there, and that will move the questions up depending on the number of votes a great way to get your question answered, and lastly the handouts the slides are available in the chat box so look for those, and let us get started.

Every webinar has its own webpage with everything you need to know about the webinar so immediately following this life event you can go back to where you registered and access the online CE quiz link so for this one is www.naadac.org/technology-series-2021-session-1 and you will be able to access the CE quiz as soon as this webinar is over and if this is your first time going through the process make sure to follow the instructions guide that is right underneath the online link to guide you through the process. You can also email us at ce.naadac.org, please note if you need your certificate to stay live on it please complete the CE quiz within the next four hours.

Let us introduce our present your today, Dr. Will Aklin is director of the behavioral therapy developed program within the division of therapeutics and medical consequences at the

national Institute on drug abuse, University of Maryland Dr. Aklin area research include development of treatments with theory derived behavioral targets, studies that integrate behavioral/pharmacological treatments, and clinical validation/optimization of digital therapeutics interventions. Dr. Aklin has extensive experience in behavioral and cognitive behavioral treatment for substance abuse disorders, adaptive brief interventions and adherence court trials he has courted several National Institutes of Health trip initiatives and develop and testing of behavioral therapies for substance abuse disorders, and find initiatives helping to end addiction long-term heel initiative and partnerships with the FDA and digital therapeutics and device based treatments for substance abuse disorders.

Dr. Aklin if you want to turn on your camera, I will stop sharing my screen and turn myself off and myself.

>> WILL AKLIN: Thank you Jessie for that introduction.

Okay, good morning, or good afternoon everyone, happy Friday, I am excited to discuss with you today intriguing topics that have to do with digital therapeutics clinically validated behavioral treatments for substance abuse disorders.

I like to consider direct behavioral therapies building program, and I will talk a little bit about where some of the future of behavioral therapies are involving digital therapeutics, I think there has been a lot of development and in digital therapeutics, and less so with regard to the clinical validation aspects so I will talk a lot about that today, and hopefully I will impart some information having to do with the regulatory process and how we view digital therapeutics for the future for substance abuse disorders.

There are several goals and learning objectives I plan to discuss today, the goal is really to highlight research that supports the development of safe and effective digital therapeutics, devices, and treatment options for patients and I will discuss strategies to accelerate their delivery to patients and to improve substance abuse treatment outcomes.

I also will illuminate different studies that are currently funded, several exemplars for you today, that will walk you through the process of approval. And funded opportunities that we currently support at the NIH.

At the end of this I will provide some information on discerning which technologies constitute digital therapeutics, gain an understanding of digital therapeutics as standalone treatments or those that are integrated with FDA approved medications.

And also learn about the FDA authorization process.

In this presentation and workshop, I will posit that digital therapeutics offer a complete model of care, I will also discuss how treatment packages may benefit patients by delivering interventions with fidelity and state-of-the-art practices, into a unified seamless delivery platform.

All that will make up today's workshop I will highlight those in-depth and hopefully at the end I will open it up for questions and answers at the time.

Why the need for new treatment options? This has been very clear and apparent to all of us that as we have been through one of the worst pandemics in history, some of the traditional methods for delivering treatments have really been exposed, and are limited and can be difficult if not impossible in some cases to access.

If there is not one major magnifying glass on this issue, it is after this pandemic, we showed that, we have witnessed that there are a lot of vulnerabilities with regard to traditional interventions, traditional healthcare systems, we are looking to think about what are some ways as to how this can be resolved.

If you think about rural as well as urban healthcare, there are some deserts that highlight the need to expand options to increase access and this is not a complete overhaul, rather, a way to improve what we have already, we know some that work, ways we can improve treatments that may not work as well, but I think, thinking about this in terms of expanding the options to increase access is one way that really speaks to why we need at this moment new treatment options.

One of the most promising methods is the use of digital therapeutics, to address this locale challenge. I would say crisis and that is not an overstatement but I would say, you can view that as a crisis and we need treatment options that could really couple meant the existing interventions that we have.

Earlier this year the White House office of national drug control policy, and lo and behold reimbursement or motivation incentives as well as digital treatments for addiction were listed as one of the top priorities. Clearly this is one area that is really on the radar of many as to why we should use these types of interventions for one, but making it accessible to people who need it most, so that is really where I see this as the unique need for delivering, or developing, and testing new treatment options for patients.

Overall, I really want to set the stage by discussing what NIDA views are on digital therapeutics, and I think before I get into what they are and what they are not, it is important to really understand the landscape.

The landscape is such that there are a number of digital health solutions out there in the market place, anyone of us can go on to Google play or any type of marketplace like that, and see what options are available, and if you look at smoking cessation, for example, you will likely pull up hundreds of digital health solutions.

Let me talk about what digital therapeutics are and what they are not.

Digital therapeutics themselves or clinical grade software programs, that can deliver the behavioral interventions themselves. These are technologies that were only available for direct face-to-face interactions with the clinician but digital therapeutics are the software programs themselves that can deliver the behavioral intervention.

They are designed to prevent, manage, and treat substance abuse disorder or some other medical condition or disease. It is the intent to manage and/or treat medical condition or disorder.

Digital therapeutics are available via mobile, web and other related platforms, so it is really agnostic to the type of delivery platform, but it is available in a variety of platforms and remote fashions ways that really reach patients remotely so that spans mobile, web, and other platforms.

What they are not, are wellness apps. The intent is not general wellness, digital therapeutics as we are really operationalizing them focus on those that prevent, manage and treat, wellness apps or telehealth that access to a clinician, you and I talking on one end of the screen providing treatment is normal, that would not classify as digital therapeutics. We do not classify wellness apps or telehealth in that category, in that bucket of digital therapeutics. Just as, to really set the stage and frame my discussion today, I am only focusing on those with the intent to prevent, manage, and treat substance abuse disorders.

Along these priorities, we have several priorities we have listed over the next five years at NIDA, what are some of these priorities? Regarding digital therapeutics?

The first is to improve treatment efficacy, there are a number of ongoing clinical trials a lot of the intricacies that my going to a treatment plan, for example, and leave a lot of the therapeutic content to digital therapeutics.

Is one way to think about strategically how to boost the effects and increase the efficiency of interventions.

Another priority is to focus on technology and enhanced treatments that are ample amendable as well as self-sustaining, we are very much keen on ensuring that these interventions can really stand the test of time, that want to project is complete, for example, a grant process goes anywhere between 3 to 5 years and if there is an efficacy trial echoes and for that five year period want to ensure that the results, the treatment outcomes, everything that goes into that study can be found to have some self-sustaining ability, and is ultimately ample mental, we want to make sure what is being developed and tested can reach the population intended and is used.

With that is very clear for us from a funding perspective, is to ensure there is a clear dissemination plan, a clear strategy, with the ultimate product, the ultimate digital therapeutics

reach patients in the end, I cannot over emphasize this enough to ensure these treatments are implementable and self-sustaining.

and increasing options for remote treatment delivery, that is really important to ensure that it can reach those in rural populations and urban populations in patients who need treatment.

Let me walk through some notable advantages of digital therapeutics before I get into some of the questions that are still unanswered.

Digital therapeutics really highlight several areas that call for assessing feasibility, and we think about assessing something works, whether or not it is feasible, digital therapeutics offer important information on how treatments can be delivered reliably, and that is one way that digital therapeutics are utilized currently in many studies that are currently funded, they provide robot reliable treatment delivery with limited staff training and follow evidence-based guidelines, so many companies for example, many researchers are using digital therapeutics to really ensure quality control and it is not to place the clinician but it is to help complement the clinician in the work and load one might have, so this is seen as a way, as a tool that I have to treat patients, is to have a digital tool that can really help to delivery therapeutic content in a reliable and reproducible way.

Secondly engagement, digital therapeutics can encourage engagement by having the intervention available 24 hours a day, so essentially it is like having a clinician in your pocket, so the patient can have access to therapeutic content, to respective modules that might be available for that digital therapeutics, anytime a patient might be in crisis we can certainly use that technology anyway that can be used on demand, so that is something that is a notable advantage that digital therapeutics can offer.

Reach is another important feature of digital therapeutics, there are limited access accounts for over 80% of individuals in need of substance abuse treatment do not receive treatment, and a lot of that has to do with Reach, as I mentioned in the outset it has a lot to do with access, so digital therapeutics really help to address that problem, not, I would say entirely but it does address that problem to a large degree.

I will say if we were to think about couple advantages that digital therapeutics offer, it is really, it can illuminate or minimize travel to a clinician to that should not be understated because it can really eliminate a lot of the travel time, so if the patient may have difficulty with transportation for example, this could help to offset going into a clinic or going into a session 3 times a week or two times per week, you might have a digital therapeutic help to offset the travel.

It brings into a good position that digital therapeutics offer helps advantage in terms of reaching can offer.

Privacy is another notable advantage for digital therapeutics regarding stigma, having to do with patients not wanting to go out and seek treatment, so I think it can really help to eliminate

or reduce stigma involved, that many patients are reluctant to seek treatment, I think the goal is to reach that 80% of individuals who are not seeking treatment, and stigma really is a main culprit in terms of why individuals do not want to seek treatment.

It is not a silver bullet but it provides advantages.

The last is cost, delivery does not require active interaction with the clinician, it reduces face-to-face cost, less time maintaining treatment fidelity, more time on evaluation and optimizing treatment effect and getting back to the point of using this as a comprehensive or complete model of care, that is something that I think digital therapeutics can offer in terms of cost reduction and really focusing on aspects of the treatment plan that need direct attention or direct in person interactions, and those that really can be addressed with digital therapeutics.

As I noted on some of the positives, there are a number of unanswered questions, and some of these unanswered questions really have to do with the ability to maintain rapport as clinicians, it is important as you will know that rapport is a very important feature to the clinical enterprise, the clinical interview, going down to the treatment plan and the treatment execution is rapport.

What is the balance that digital therapeutics offer between digital health and interpersonal contact, those are some of the unanswered questions, do digital therapeutics intersect with health disparities population in the area of addiction? When we think about individuals may or may not have access to high-speed Internet, or access to a smart phone example, those are some of the challenges that might arise, so it is how digital therapeutics will interact with that, with health disparity population and could that decrease the gap or expand the gap, those are some important unanswered questions.

Lastly, the healthcare system requirements including HIPAA requirements, all these questions are very important in terms of how this can be a viable treatment option, and really adapted into the larger clinical enterprise.

Again, as I present today, I want you to think about, these are some of the remaining questions, some of the questions that still need to be answered but I think moving forward and well on their way, I want to highlight not only the positives but questions that are still remaining going forward.

I highlighted before, I discussed this before but I want to go over the digital therapeutic landscape and why NIDA have partnered with FDA and this area in particular.

As I noted there are over 300,000 touted digital health solutions in the market place, and hundreds focus on smoking cessation alone, that is available right now through Apple Store, through Google play, and very few have clinical validation, so that is an enormous number when you think about touted health solutions, I'm not saying this is all focused on substance issues but no health, digital health, there are over 300,000, which is mind-boggling.

In the research efforts that have gone into the development of these technologies, have far outpaced validation studies, so the development of digital therapy or health solutions as far outpaced validation studies, and as such I will call it wild West and I will say there is a need for a trusted entity to be responsible for evaluating the effectiveness, the efficacy and usability of digital therapeutics.

There is also a need for a trusted entity to authorize digital therapeutics that are worthy of patient consideration.

In short, the goal here to focus on making it where it is less chaff and more week, really getting at, cutting through the 300,000 and getting it down to how do patients know which one of these digital therapeutics, which one of these treatment options are viable, which one is really undergone important clinical testing, for example.

It is really focusing on less chaff, more week, focusing on getting through which one of these digital strategies are worth their time and health.

I want to really go over this in full, in full view to validate or not to validate, that is a question. I will say, the importance of validation in this target population of substance abuse issues is important, it is as important as it is for FDA approval of medications, clinical therapies.

The pathway is much more difficult, all medications in the US need to be approved by the FDA before being prescribed by physicians but anything about digital therapeutics on the other hand, you think of any back to that 300,000 number, these technologies can be given to patients without FDA review or authorization, and I will say, whether a FDA review is required largely depends on several aspects including the level of risk associated with the treatment, it also involves the treatment population, and so if it is a treatment population, say you have a population that is vulnerable or a population that might have a high risk suicidal ideation or suicide risk, it goes into the treatment population for the intervention so that is an important note there.

While several products available on the market were tested, and clinical studies, and shown to be effective, not every product is gone through the FDA regulatory process, but there are studies out there that have shown to be effective, and there is no standard

To be assured of efficacy, there is a huge disconnect that we are very much interested in helping to remedy.

That brings me to the NIDA and FDA partnership which is a memorandum of understanding with the FDA, and this was established back in 2019 and allows regular contact and sharing of information between the agencies. I am a primary contact and that along with several others across agencies, and over this time period between 2019 and now, we prioritized several items across his partnership. One of those is a guide notice for information on FDA authorization of digital therapeutics.

Essentially what that is, it is to provide applicants, it is to provide those who are investigators or submitting applications to the national Institute on drug abuse, information and this process going forward.

Provide information on what are some aspects of their project that could be improved, what are aspects of the project that would be essential in order for funding and support, and also providing joint presentations and the authorization process, as well as a commentary on what is the regulatory pathway for digital therapeutics in our priorities respectively across the agencies.

Also, there are two areas refocused on primarily and that is guidance to grant applicants, to help navigate this FDA process. And accelerate progression of these technologies through the regulatory pathways, so again this is a partnership that we want to ensure that there is a trusted entity to have a pathway for digital technologies to help, to ensure that their really clear rigor and reproducibility across these technologies.

Let me walk through very briefly some of the regulatory pathway for digital therapeutics, some apply and some did not, and I will talk about this further in depth, but I want to show some of the pathways that are germane to digital therapeutics.

As I mentioned when we focus on digital therapeutics we are not discussing or not classifying wellness, which are low risk devices that do not make diagnostic claims or therapeutic claims, so those that fall into this category, wellness, do not need clearance, so again, digital therapeutics that I am discussing really involve those that intend to treat, manage, or prevent disorder or disease.

If you think about it along the continuum wellness would be an end, digital therapeutics would be on the other, entity PMA pathway or premarket approval pathway focuses on high-risk class III medical devices which FDA inspection required, and this is not relevant to digital therapeutics, these would likely fall into the category of pacemakers for example, or deep brain stimulators, that is not applicable to digital therapeutics, but I wanted to go over the level of risk associated with this to highlight some of these areas.

The 510(k) is a low to moderate risk device must demonstrate equivalence to particular device and FDA is decreasing 510(k) submissions in favor of de novo.

De novo pathway is novel low to moderate risk devices and new product classification.

Both of those are applicable to digital therapeutics, and lastly, breakthrough devices program which gives priority review for medical devices or device led the nation products; the goal here is to provide timely access to breakthrough technologies, and those that might have come in for de novo, 510(k) or premarket approval are placed orders the top of the queue and I will talk about one in particular, when exemplar I will talk about that received breakthrough designation really to provide promising treatment options to patients.

That is a program that has received a lot of attention.

This is to go over a sample direction progression with the FDA in considering, these are considerations for digital therapeutics, so there is a resubmission program, and that is to provide input on digital therapeutics are the beginning and to ensure or to provide feedback on the potential digital therapeutics.

This is a voluntary, highly effective program, and it is really the beginning I would say of the process of interacting with the FDA.

I will talk a little bit about when an IDE, for example, is required, so investigational device exemption, when something along those lines is required. This resubmission or Q-submission process provides an opportunity for FDA feedback, that is prior to the IDE or marketing submission as you go along a straight line that I just showed you, that arrow ahead of the previous slide.

The FDA provides written feedback and an optional meeting on your proposed device, or digital therapeutics; pre-submissions are not intended or pre-review of data, it is really intended to provide clarify feedback, not intended to provide real-time or new information on proposals, but to give written feedback on digital therapeutics prior to the IDE.

I provide here some guidance documents for your review and consideration, just to supplement some of this information, and a lot of the information can be somewhat detailed, I would encourage everyone to take a look at that information at your leisure.

Let us talk about medical device definition, when does it classify as a medical device? We are talking about the intent.

This gets into the term device it means and instrument or apparatus implementation, machine, and getting into how any of the component parts or accessories which are intended for the use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention.

When you look in those terms of digital therapeutics would be to classification of medical device. Given the intended use is the diagnosis, cure, treatment or prevention.

Intended also to affect the structure or any function of the body, so again, this is the long definition I want to highlight purpose is really in the intent, if the intended use is to treat, then it would fall under the medical device definition and thereby require most likely the regulatory review.

When an IDE is needed. And IDE is needed when a device is a significant risk device. It takes into consideration not only the device, but also the target population, and the intended use of the overall study design, so as mentioned the target population with patients who are suicidal, even with risk mitigations, the study could be considered high risk, so 21 CFR defines significant risk as an investigational device, it is intended as an implant, and presentable to risk to health, safety, or welfare of a subject; purported or represented before use in supporting or sustaining

human life, not applicable here to me: Or use of substantial importance in diagnosing, curing, mitigating, or treating disease, so that the fall in the digital therapeutics camp as to when an IDE is needed, and again IDE is investigational device exemption.

Serious risk to health, safety, or welfare of a subject.

I will move into the study risk determinations, and an opportunity, this is an opportunity for FDA feedback on whether your proposed study is significant risk, or nonsignificant risk study.

Similar to the Q submission this provides opportunity and whether there is a significant risk or not, it gives you a sense of where that will fall on that continuum and whether the review is required, and again, I have noted some guidance document for your review and consideration to supplement this slide here.

I wanted to go through some of the points to consider when developing digital therapeutics for substance abuse disorders, and I will highlight again several exemplars but I wanted to walk you through the process, clinical validation process and points to consider through this from top to bottom.

Design considerations, they are most important when you think about the approach of your study design, the approach, how the study will be executed, how the digital therapeutic will not only be developed but executed in terms of clinical validation. First and foremost, obviously I think, is the behavioral therapy itself. How does the device implement the principles of behavior therapy, principles of behavior change, as I noted before, some of the mechanism of action our research we know have been shown to really predict behavior to a large extent, like self-regulation or stress reactivity, how might those principles be integrated in the digital therapeutics themselves?

Indicated for the use as an adjunct to usual best medical care, or indicated as a stand-alone treatment, those are two important distinctions that are important in terms of design considerations, so as an adjunct to existing treatment or a stand-alone intervention itself.

Nonclinical testing consideration involved software validation, and that is important to ensure the safeguarding of data, that is an important including the aspects of development, and whether or not the information is protected.

Software validation is equally important to the design considerations, and here's more guidance document on the content or premarket submission or software contained in medical devices.

Other points to consider are clinical testing considerations, such as human factors, usability testing, and applying human factors and usability engineering to medical devices, so a lot of this really is just to highlight what all of the important points that going to the study design, whether it is usability testing, clinical trial to evaluate safety and effectiveness of the digital therapeutics, so these are report points to consider of how you plan, or how the digital therapeutic is tested.

As I would say an obvious point to many is that medical devices trials differ from drug studies. Device studies are designed to support a reasonable assurance of safety and efficacy. Point of interest can be highly diverse between studies, so you may have an endpoint such as craving, or an endpoint focusing on retention and treatment, there might be another endpoint that focuses on substance use reduction or substance use abstinence, so these endpoints of interest can be highly diverse between studies, but it is important to really have some clear understanding or clear plans of what is the specific indication that you're looking at specific indication of the digital therapeutics.

Clinical trial should be designed to support your indication or use, and the target population, these are important aspect of digital therapeutics that really fall into the critical validation and why it is important to ensure separating the wheat from the chaff, back to that analogy.

Other points to consider, going to the command evaluating the safety and effectiveness of the device in the population for which it is to be indicated, so we have specific use for one, versus general use; we have timeframe for evaluating the primary endpoint should be clearly defined, it should have some very clear guidelines in terms of what is the path for evaluating these endpoints, the time course of the specific use disorder and do patients have an initial immediate response and then tend to relapse? These are important questions regarding primary endpoints, and they should be prespecified, so it is important to ensure or important to outline what are the endpoints and that should be done a priori.

One or more safety endpoints, one or more effectiveness endpoints.

I don't want to get too detailed in some of the aspects of the considerations for digital therapeutic but I want to go through briefly ensuring that the study is well-controlled and I highlighted some of the important considerations, sham versus usual care accounting for placebo effect, and I bring up a point of adjective use versus standalone use, and patients should be on usual care, protocol should be delineated, what usual care constitutes, and if used as a standalone, these are important points to consider the patient will not be on medication, or patient safety if patients will not be on education, there needs to be a clear plan, a specific plan for patient safety if they will not be on medication during that specific trial or other usual care.

And lastly, I want to highlight the placebo effect and device effectiveness compared to usual care.

Inclusion/exclusion criteria a target population or indicated use, statistical considerations as well, handling missing data, prespecified criteria for secondary endpoints, randomization and blinding.

Patients, investigators and study staff blinded along with the plan or blinding assessment.

And generalizability to the US population.

Given this interaction in this partnership with the FDA what are some of the views that we have gleaned, some of the interactions and some of the takeaways of the FDA views on digital therapeutics? First and foremost is while digital therapeutics can collect endpoint measures the FDA may not accept measures collected by the digital therapeutic cells to validate the treatment.

They may require independent collection of data such as why a study physician, or a study staff, such that it would not bias or give a biased assessment, so that is a concern of having digital therapeutic collect endpoint measures, so again, that is really wanting to separate the endpoint method for data collection and really making sure they are not biased in any way.

Currently FDA only has the ability to authorize non-medications which is distinct from giving approval to medications. I want to see that point again, so that that point is not lost, the FDA has the ability to authorize non-medications which is distinct from the approval of medications. There are folks lobbying to have the same level of validation for these digital therapeutics as there is for medication, they want to have the same level of evaluation such that you want to be able to help patients make a decision as to what digital therapeutics have been clinically validated which has really undergone important scientific rigor that is important to establish, that is one path, it is not to say it is the only path forward but to help patients make a decision that the app or digital technology or tool or platform has some level of clinical testing and validation, and so there are organizations lobbying Congress to pass a law to give FDA that authority, because right now as it stands the only have a few approval given to medications.

Now that the regulatory aspects have lay the groundwork for the second part of my discussion, is really outlining what was the changing landscape, the breakthrough that really moved this process forward? In 2017 the FDA approved the first digital therapeutics for substance abuse treatment, from Pear Therapeutics, an exemplar of a digital therapeutic that underwent the FDA authorization process, suppose a NIDA authorized trial, and this was the data I want to highlight and we look into section A, when used with outpatient treatment and contingency management we set significantly approved abstinence in substance abuse, and increased retention compared to standard treatment, so there you will see reduced standard treatment, plus re-SET which is the digital therapeutic and then standard treatment alone, there you can see there was improved abstinence in substance abuse and increased retention compared to outpatient therapy alone.

These data of the study were used to support the FDA authorization of reSET that was approved in 2018 or opioid use disorder as an adjunct to medical treatment so becoming the first digital therapeutics approved this indication.

What I think is interesting about this, if you look into section B you can see the level of retention, and it appears that digital therapeutics improves retention, abstinence, particularly among those who are non-abstinent treatment entry, so over time you see that increase here

in retention so 80% versus 64%, I think that is very significant in terms of making sure, ensuring patients are retaining treatment.

I want to highlight -- making sure I'm on time – or highlight several of the efforts that have been under development and have really NIDA has spearheaded.

One is the loyalty rewarded technologies to increase adherence to substance use from pharmacotherapies, and several applications very meritorious obligations with the goal of using digital therapeutics as an adjunct to increased medication adherence. The primary endpoint that we sought to support for adherence to FDA approved medications for substance abuse disorder including buprenorphine, nicotine placement therapy, and reporting contingencies delivered in a self-sustaining manner, I will highlight a study, it is a study that really shows significant improvement among pregnant women, among smokers, by dynamic care, digital therapeutics that was found to be highly effective, I will highlight that, it came in under this fire funding opportunity announcement.

There is currently another digital therapeutics funding opportunity announcement for substance to abuse disorder which really focuses on resource developing tests digital therapeutics as standalone treatments for those that are integrated with FDA approved substance abuse disorder treatment with a specific indication to prevent substance use disorder indications, medication adherence, treatment retention, withdrawal, abstinence, and or reduction of relapse, so those are the specific indications that is a federal agency that we are prioritizing for this funding opportunity announcement, that is currently available.

I want to walk you through some of the activities and through NIDA during the UG3-phase, when you think about and points think about what are the specific indications we are highlighting and prioritizing, craving, dependence, days of abstinence for example, these are some of the important highlights that we prioritize in our develop in phase of these digital therapeutics, establishing feasibility, establishing aspects of the treatment efficacy related endpoints, evidence of the intervention affects behavioral endpoints as they relate to substance use disorders, so as I mentioned some of the important mechanisms of action for example, distress tolerance regulation, these are aspects of behavior change, and how does the behavioral endpoints relate to the substance use disorder as well? Evidence that adequate dose range treatment duration for digital interventions can be applied with applicable, sorry, acceptable tolerability and inherence, and effects and other measures are relevant to the approved treatment. Proof of concept, feasibility, and as I mentioned at the outset before, in the regulatory process the submission to feedback on the regulatory pathway and or filing the IDE, all acceptable activities and examples of what really we support in the initial phase of the process.

The project I wanted to highlight, another exemplar in addition to the Pear Therapeutics example is a study by Alison Kurti that looked at in a digital intervention based on contingency management that showed increased smoking cessation in women smokers during and after

pregnancy compared to best practices. In this study biochemically conserve confirmed smoking abstinence had a comparison between the incentive group versus the best practices group, and here you can see in early pregnancy see the absence here the percent abstinence on the y-axis, up to 50% in early pregnancy with the incentive and financial incentive group, compared to best practices. Less than 20%. You go down all the way through the course of late pregnancy, four weeks postpartum all the way to 24 week postpartum and still infant incentive group is found to be highly effective compared to best practices. Again, this was remote financial incentive intervention, that has really showed significant for this important population, when we think about smoking cessation during pregnancy, this is an important exemplar of the process of clinical validation of a digital therapeutics, so that is an important highlight.

Point of the slide is to really show the comparability of standard addiction treatment compared to state of the science, therapist delivered care, compared to digital therapeutics, so if you look at the blue bar as well as the red bar, that is in person, state of the science delivered intervention by a therapist, compared to a digital therapeutics, and there you can see equally effective when it comes to the same type of treatment being delivered by a therapist compared to continuous abstinence from opiates as well as cocaine use, compared to a digital therapeutics delivered format.

That is very for promising and again this is an important step an important slide to highlight this is not as a way to replace a clinician, but to help complement, extend the reach and to use this as a clinician extender.

This is an important last exemplar I wanted to highlight, and I mindful of the time, we are just past the hour, but as I go through this last exemplar and close on several points I wanted to reiterate, this is an important study to highlight, an important pilot study.

Is a study looking at patients with serious mental illness, comparing learn to quit based on acceptance and therapy focusing on smokers. This is a pilot, these data are from a pilot trial a pivotal trial, subsequently funded and what I wanted to highlight is if you look at the learn to quit orange section here, the learn to quit, compared to the NCI quit guide, a digital comparator used in the study, smokers showed a greater reduction, and if you look at reduction in cigarettes per day listed in the smoking behavior, reduction in cigarettes per day, you can see 12.3 under learn to quit versus 5.9, respectively, and a higher percentage of thirty-day point prevalence, 12.1% compared to 3.1% respectively.

That is an important aspect of this digital therapeutic to highlight here in the study, but also outside of the significant reduction in cigarettes per day, thirty-day point prevalence I want to highlight a focus on engagement, if you look at the number of app interactions, in the learn to quit, 847 app interactions, compared to 205 app interactions, and look at app durations, in hours, four hours compared to two hours, that is an enormously different, in terms of app interaction.

When you think about engagement, that is critical to digital therapeutics, to ensure that engagement is one of the most important drivers of behavior when you think about digital therapeutics and why it is important to really ensure those are essential aspect of research with dirigible through therapeutic/sure these are highly engaging, and to emphasize that point we look at how significant that difference was, 847 versus 205.

I want to, before we open it up to question and answers, to emphasize the FDA regulatory authorization is important for several reasons, and chief among them is the growing number of marketed digital health solutions in the marketplace, going back to that 300,000 number, not all specific to substance abuse or smoking cessation, wood grain, when you think about the available options in the market place, many include those with limited or no validation, that is an important, I think that is the one important aspect wanted to highlight as to why the FDA authorization process is important to consider.

It also provides an important line of demarcation, giving patients and healthcare providers assurance about safety and effectiveness of the digital therapeutics. A prescription digital therapeutics receiving FDA authorization is required to demonstrate good manufacturing practices including robust software developer; data integrity ends safeguarding of data; compliance and applicability to medical device quality systems regulations.

NIDA is specifically committed to the treatment of substance use disorders investing in scientific inquiry theory informed digital therapeutics that the focus primarily on clinical validation, and the reason why getting back to why the clinical validation aspect is so important is that the development really has outpaced this part of the process of the clinical validation aspect, that is really why NIDA is committed to treatment of substance use disorders investing in scientific and theory informed treatments in this way.

As I highlighted technology helps treatments to maintain potency of the intervention, to ensure that it is reproducible, it is delivered reliably, it becomes more easily able mental as well as self-sustaining, so we want to make sure that any investment, any funded opportunity, any funded project is a plan for dissemination, has a plan for ultimately how the intervention will be used and integrated in healthcare, and clinics etc., it is an important aspect that technology helps to improve and supplement.

The FDA/NIDA MOU that I focused on improving design, developing, and methods for delivering regulated and clinically validated treatments to patients.

Guidance to investigators to help navigate the process, and accelerate the progression of these technologies through the regulatory pathway.

And finally, all this effort and all the process really ensuring ultimately patients and clinicians provide care divisions really can have tools in their armamentarium to treat substance abuse disorders have options at their disposal.

I wanted to end with highlighting some FDA guidance documents, this is for reference, and again, everything I discuss is really cited in these guidance documents, so going down from the general wellness, policy for device software, save significant risk, software as a medical device, clinical evaluation, the risk guidance for IDE submission, and five 10K submissions as well, IDE submission information and design consideration for pivotal.

Highlighted several references, and I believe we can open it up, or I can turn it back to Jessie if you want to open it up for Q&A at this time.

>> JESSIE: The first one is, what types of organizations are primarily submitting applications or digital therapeutics, academic institutions, hospitals, private companies

>> WILL AKLIN: We have small companies, investigators from academic institutions, research institutions, we also have a lot of industry from pharmaceutical companies and a lot of pharmaceutical companies are really using digital technologies to really ensure that the treatments are delivered with fidelity in their trials, it is a nice mix of individuals and academic settings, those who are in industry, as well as small businesses, it is a very nice mix, and I think it is important to really have that diversity in terms of those who are trying to develop these technologies and assure the clinical validation, and ultimately it reaches the patients who need them.

>> JESSIE: Next, as a consumer or patient, what would you want to look for to ensure digital therapeutics has been authorized?

>> WILL AKLIN: Fantastic question, it is important, and we are working very hard on making sure that patients have the information that they need to ensure, if for example the Pear Therapeutics example that I mentioned, is a prescription digital therapeutics, so that is used in conjunction with outpatient treatment, cognitive behavioral treatment, in addition to contingency management, and it requires a prescription of that digital therapeutic of reSET, that is one way a prescription period therapeutic.

Another is, really to ensure that it has the clinical testing that say a medication as head, we are working on the process to make sure that it is abundantly clear what are some of those that have really stood the test of time, that really have, that you can rely on, that you can be very confident that it went under important scrutiny medications to digital therapeutics don't have that same level so it is important to ensure that that is what we are working on very closely

>> JESSIE: A follow-up, does NIDA have a list somewhere of approved digital treatments?

>> WILL AKLIN: I didn't want to provide a listing, because I don't want to have this as an endorsement but I wanted to highlight the process of the clinical validation, but I think the point is important, it is important in that there needs to be, and I agree there needs to be some line of demarcation of what did some digital therapeutics undergo, what was the testing, what were the study samples, what were the actual data? All that is very clear for medications, it is very clear what study, what was the safety profile of the study, all that is very clear for medication, I agree, I think that same level of information should be provided for digital therapeutics, irrespective of if it is the FDA pathway or some other pathway. I think there needs to be some information that follows any type of technology, we have someone options in the market place, it is really important to try to do that, really important, so that is a great follow-on

>> JESSIE: It is an important resource for providers, there used to be a list of evidence-based practices and forgetting the name of the agency that had that, so you knew there was an evidence-based practice to use, so I think this is a similar question to that.

As mentioned, NIDA is not the only pathway to get something approved and to have it vetted.

Departed of Veterans Affairs as to apps, PTSD coach and mindfulness coach especially using them for the PTSD coach and it is free without a bunch of pop bad spot with these be examples of digital therapy

>> WILL AKLIN: Is the intent – or what is the intent? I am not familiar with that app. Goes into the intent, if the intent is to treat, prevent, or manage disease, then the Q submission process is important and that is why I wanted to spend some time to walk through the process because that is the type of question that the FDA would answer on whether or not there is significant risk of population, the indication are going for, so that is precisely the type of question for the Q submission, that is a partnership we have with the FDA is ensuring that those types of questions are answered, whether or not that would classify as a digital therapeutics.

It gets back into a process of the Q submission whether that would categorize itself as a digital therapy

>> JESSIE: Need more information, yes!

What trends do you see in terms of what is getting approved as digital therapeutics?

>> WILL AKLIN: That is a fantastic question, and going back to the specific indication, we as an agency, I think functional outcomes are very important, while I think 100% abstinence is certainly the goal, 100% abstinence is where the gold standard is, for medication, and for digital therapeutics, I think there are some important aspects of behavior change that if you were to look at it across the stages of change, if you were to look at that as one indicator, or you look at retention for example or whether or not your digital therapeutic retains individuals in treatment, you may use standard in person treatment or therapy you may get a digital therapeutics to focus on retention, making sure individuals are retaining treatment, so those are the aspects of digital therapeutics that we are seeing as trends in terms of the types of endpoints like retention, like reduction in craving, and moving outside of 100% abstinence, additional aspects of behavior change in addition to abstinence.

That is a great question, and those are some of the aspects of digital therapeutics that we see trending upward and high-priority

>> JESSIE: You mentioned discussion digital treatments, will all FDA approved digital permits require prescriptions or is there an over-the-counter approval

>> WILL AKLIN: the specific indication that particular company went out for, they sought to have a prescription digital therapeutics, that was their plan for. Without getting into the details of that particular company, that is what their goal was to have it were as a digital prescription model. Now, there are, there can be over-the-counter digital therapeutics, and again that is the other pathway that many are seeing themselves in, that one lane, so one lane is the prescription model, one lane is the over-the-counter models so there are different paths forward.

What we are most concerned about is that number, I keep going back everybody knows number by now, 300,000. Our goal is the dissemination, whether or not the path is a prescription or the path is over-the-counter, where the path is having some agreements with, for example, a treatment facility, there may be treatment centers that are focused on in their centers a specific therapeutic that works, so as long as there is a path forward that is what we are really focusing on, that is actually getting to the patient's and is providing, giving providers tools in their armamentarium.

>> JESSIE: Does NIDA ask for patient feedback on the product approves or do follow-up and approval process?

>> WILL AKLIN: We find follow-up studies, we find follow-up studies, I know the FDA has several meetings with patients and seek input from patients, patient reported outcomes they seek input on just their thoughts on what they need in treatments themselves, so the FDA does on occasion I'm not sure when that happens, but that is something that the FDA does quite regularly. But as far as NIDA is concerned, we certainly find follow-up studies and encourage studies that are larger in scope that we have some level of follow-up, upwards to one year, six months, one year, and upward for follow-up.

>> JESSIE: I'm not sure you can answer this but, someone was asking, the charge ahead with the standard addiction treatment in one column that was gray and we had one the digital therapeutic and pink that was pretty equivalent to the provider evidence-based -- they were asking, do you know why standard treatment was so much less effective?

>> WILL AKLIN: I am not certain as to, the standard treatment was equivalency between the digital therapeutic and the -- the standardized behavioral intervention, state of the science treatments they use in the study. I'm not exactly sure why that treatment, the standard outpatient treatment was not as effective, and I will say the state of the science treatment that was delivered was an in person version of that digital therapeutics, so it was the same treatment but it was delivered in a web-based format versus in person, and that was compared to the standard treatment, I would have to go back to the study to see what was actually done in that study, but the reference in there, but the goal was in the study to highlight whether or not there was any differences between an in person versus a web-based version of the treatment. It was found to be equally effective.

>> JESSIE: They suggested some possible reasons that it may be, and he may be able to infer from reading the study what may be contribute into the. Thank you.

Where can resources be found or high-quality efficacious digital therapeutic currently available?

>> WILL AKLIN: That is something that we at NIDA and agencies, as you mentioned, in terms of, SAMSHA at the list of empirically supported treatment, and I would advocate, I would argue, a similar list needs to happen for digital technologies. Those that have undergone the clinical

rigor, that line of demarcation, that patients can have confidence that is something that they should use in trust for their health. That is something I think would be important contribution to the field, it will be an important attribution to clinical milieu, that would be a high priority for our agencies to try to discuss

>> JESSIE: It sounds like there is not a really good recommend list if you're looking for good digital therapeutic product, if you're doing a search, you would have to look at the product first that you might find interesting and do your research on the vetting that was done and the study to make sure that it is a validated and evidence-based product. That would be, sounds like what you're saying until we are able to get a list that SAMHSA might post on their data

>> WILL AKLIN: I did not want to highlight, just some exam bars, but the NIDA, we have many independent studies and public information as to which product are funded, I highlighted two today, Pear Therapeutics and dynamic care but there are many others and it is not an endorsement but those are funded projects that have clinical studies that have shown over to her populations and different substances, to be efficacious and effective.

It is compiling that list will be important contribution, but again, all of the funded studies are publicly available or you to see.

>> JESSIE: It sounds like you can check out what studies are underway and have been done through NIDA, I thought we would have time for one more but I realized --

Thank you Dr. Aklin we really appreciate you, and all your expertise, thank you for being here and for answering all of our questions and for this valuable information or make has been recorded so you will be able to access it in the slides are all there, and any questions we did not get to will be available, we will consolidate and send to Dr. Aklin to answer and post on the webpage for you as a resource.

>> Thank you for having me and thank you for your time and attention everyone, I appreciate it

>> JESSIE: Take care.

Every NAADAC webinar has its own webpage with everything you need to know about the webinar immediately following this live event you can go back to the webpage where you

registered for the webinar and get access to the CE quiz as well as an instructional guide to guide you through, if it is your first time going through our CE process make sure to follow the instructions guide that is right underneath online like to guide you through the process and you can also email us at ce@naadac.org if you have any issues so again if you need your certificate to say live on that and some of you do sure to complete the CE quiz within the next 24 hours.

Here is the schedule for upcoming webinars we are pretty excited about on July 28 we have breaking the sounds, mothering and women sexually abused as children with Teresa Gill, and the second part of our technology series will occur on August 4 with Matt Demott see the power of peers in app or toll addiction recovery support I hope you can tune in for that.

If you have not had a chance yet make sure to check out and register for our NAADAC 2021 virtual annual conference, if you register before September 15 you can save up to $101 so I hope you'll join us for that, and addition we will have three preconference days, October 8, 15, 22nd, you can choose one of two tracks and get six CEs for each day you attend so exciting hopefully will check this out and sign up if you're interested.

If you missed either of our first two advancing awareness in LGBTQ care webinar series, they are available on demand, this is a four-part webinar series developed by NAADAC along with our LGBTQ plus subcommittee it has been really great so far and the next one is taking place on Friday, August 20 12 until 130 and we have the last one in September so hopefully you can sign up for that.

You are all here as part of our advances in technology in the addiction oppression series if you do take late in the series you can apply for the certificate in advances in technology in addiction profession that says you have completed all eight so hopefully you will continue with us.

We also had wellness and recovery series in the addiction profession which is also a specialty online training series it wrapped up in June, it had six different webinars and exclusive content that introduces techniques and strategies specific to implement and wellness, so if you missed it is available on demand.

If you are not a NAADAC number already consider joining, take a look you can learn more about joining NAADAC at the webpage on your screen and here are some of the benefits and otherwise a short survey will pop up the end of the webinar your feedback is appreciated we use it to inform our future content and what is coming up and thank you again for participating in the webinar at thank you Dr. Aklin your valuable expertise leadership and support in the field and hope everyone has a wonderful weekend and please stay connected with us on LinkedIn Facebook and twitter.

Have a great everybody take care