Prescription Digital Therapeutics and Drug/Software Combinations for Treatment of Serious Medical Conditions

VinFen 40th Anniversary

September 8, 2017
Prescription digital therapeutics have the opportunity to transform healthcare by standardizing care, collecting data, enhancing access, and improving outcomes.

To bring digital therapeutics to scale, PEAR Therapeutics is pursuing “the biotech/therapeutic model” featuring:

- Strong efficacy data demonstrated in randomized clinical trials
- Regulatory approval with medical claims for disease treatment
- Product codes to enable standardized reimbursement by payors
- Evidence-based neurobehavioral treatment, consistent with guidelines for standardization and quality

PEAR Therapeutics is the only fully integrated, prescription digital therapeutics company, creating regulated, reimbursable products with best-in-class efficacy claims.
PEAR Therapeutics overview

**Digital as prescription products**
PEAR is the leader in developing *prescription patient-facing software to treat disease, products we call eFormulations™*

**Fully-integrated digital therapeutics company**
We’ve *built a 50 person team in Boston and SF* with expertise in software design & engineering, clinical development, regulatory affairs, health-economic outcomes research, product commercialization, and reimbursement

**Proprietary platform with blocking IP**
We have developed a *modular, cloud-based infrastructure* to deliver eFormulations™ and our approach is protected by *IP surrounding drug/software combinations*

**Pipeline of validated eFormulations™**
PEAR has developed a *portfolio of eFormulations™* and we have already engaged both the FDA and payors on pipeline programs treating Substance Use, Opiate Dependence, Schizophrenia, PTSD, and others

**The first FDA approved digital therapeutic**
PEAR’s lead product, reSET®, significantly improved abstinence in 6 randomized controlled trials in Substance Use Disorder, paving the way for it to be the *first FDA-approved prescription digital therapy*

**Demonstrated medical value reimbursement**
We’ve created a *pathway for third-party reimbursement* of reSET®; it can be reimbursed via product codes with medical value creation supported by health economic outcomes research
PEAR is positioned to address the issues currently limiting the impact of digital therapeutics

### Traditional business model

- **Focus on health and wellness use cases**

- **Limited clinical evidence** for efficacy; small longitudinal studies relying on patient reported data

- Due to regulatory limitations, **unable to speak to disease treatment claims** or modify drug dosing

- **Unclear distribution channels** with physician & payer confusion regarding benefit to patients

- **Lack of third-party payer reimbursement** without clear means for coding and payment

### PEAR’s approach

- **Focus on diseases with high unmet need**

- Efficacy evaluated via **RCTs versus current standard of care** utilizing existing approvable endpoints

- Filing for **FDA approval with claims to assess/treat disease** and integrate with medication

- **Distributed directly to physicians as a prescription product** with access codes conferring patient access

- **Medical devices with product codes** and reimbursement supported by **health economic analyses**
PEAR’s *eFormulation*™ platform is based on clinical evidence that digital therapeutics can enhance medication efficacy.

Medication with clinical benefit + *eFormulation*™ Digital therapeutic designed to enhance medication efficacy = Multi-modal therapy with proven synergistic effect
eFormulations™ bridge the gap between home and clinic, enabling demonstration of enhanced outcomes

1. Patient receives a prescription for an eFormulation™ including a software access code
2. Patient downloads PEAR app and enters code to access prescription digital therapeutic
3. Drug and software work synergistically to treat disease
4. Data is collected from patients and displayed to care team
5. Data enhances clinician decision-making and provides population outcome insights
We have focused our initial pipeline on CNS diseases with high unmet medical need.

**High Unmet Need**

The US spends ~ $1.3 Trillion per year on CNS illnesses (psychiatry, neurology, and pain) with 80% of the world market currently unserved or underserved.

**Few New Therapies**

Few new drug therapies are set to come to market for CNS diseases, and the pipeline is particularly thin for mental health and addiction conditions.

**Favorable Reimbursement**

The Affordable Care Act and the Mental Health Parity and Addiction Equity Act are driving reimbursement of care for brain related diseases including new devices and drugs.

**Clinical Proof of Concept**

Software-based therapies have shown efficacy in treating brain related diseases and also in enhancing the efficacy of approved CNS medications.
We have developed a pipeline of eFormulations™ treating areas of high unmet medical need.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Product</th>
<th>Stage</th>
<th>Partner</th>
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</thead>
<tbody>
<tr>
<td>Substance Use Disorder</td>
<td>reSET®</td>
<td>Prototype</td>
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<tr>
<td>Opiate Dependence</td>
<td>reSET-O™</td>
<td>Pilot study</td>
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<td>Schizophrenia</td>
<td>Thrive™</td>
<td>FDA PreSub</td>
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<tr>
<td>Combat-PTSD</td>
<td>reCALL™</td>
<td>Pivotal studies</td>
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<td>General Anxiety Disorder</td>
<td>reVIVE™</td>
<td>FDA submission</td>
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<td>Multiple Sclerosis</td>
<td>PEAR-006</td>
<td>FDA approval</td>
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<td>Traumatic Brain Injury</td>
<td>PEAR-007</td>
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<td>Insomnia</td>
<td>PEAR-009</td>
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<td>Acute &amp; Chronic Pain</td>
<td>PEAR-010</td>
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</table>
The PEAR Infrastructure provides modular delivery of FDA-approvable, prescription eFormulations™

“Dead app” available on App Stores with access codes to unlock prescription-only content

Patient Facing Applications

PEAR SDK

“Dead app” available on App Stores with access codes to unlock prescription-only content

Online Dashboards

Clinician dashboards with additional analytics for review by payors and providers

Access Codes

Analytics Engine

Messaging

Assessments

Data Storage

Real-time data analytics engine for identifying at-risk patients

Validated clinical assessments for outcomes tracking

HIPPA-compliant data storage

Push notifications for medication dosing reminders and badges for rewards

SDK for modular integration across mobile platforms, browsers, and VR

• All design and code created under Quality Management System (QMS) following good manufacturing practices (CGMP’s) according to FDA’s 21 CFR 820

• Automation of traceability matrix and Validation and Verification (V&V) process for rapid and repeatable regulatory submission
Substance Use Disorder (SUD) is a major public health problem: only 11% of Americans receive needed treatment.

**Substance Use Disorder (SUD) is a chronic, relapsing disease with high societal costs**
- Associated crime, lost work productivity and healthcare costs exceed $400 billion annually in the US\(^1\)

**Opioid abuse has reached epidemic proportions**
- More than 2 million individuals abuse or are dependent on opiates\(^1\)
- Prescription opiate and heroin overdoses caused more than 24,000 deaths in 2013\(^2\)

**Only a fraction of those who need treatment receive care\(^1\)**
- Although 22.7 million were classified with substance dependence or abuse in 2015, only 11% received treatment\(^1\)
- Limited access to care is the major reason patients do not receive care

**While Legislation, like the Affordable care act requires insurers to cover SUD treatment, expanding access to care for millions of people\(^2\)**
- Limited capacity of the current system\(^3\)
- Lack of standardization in delivering guideline, neurobehavioral intervention with high quality which improves measurable outcomes

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Our lead program **reSET®**, is the first FDA-approved digital therapeutic

**Introducing reSET® for treatment of SUD**

- reSET® is a *prescription digital therapy* for treating Substance Use Disorder (SUD)
- The digital therapy delivers addiction-specific Cognitive Behavioral Therapy (CBT), Fluency Training, and Contingency Management
- reSET® has been evaluated in 6 *randomized clinical studies involving over 1500 patients*, and has attracted more than $45M in National Institute of Health (NIH) funding\(^1\)-\(^4\)
- In a multi-center randomized trial consisting of 507 patients seeking treatment for Substance Use Disorder (SUD), reSET® *enhanced abstinence versus in-office treatment (p = 0.003)*\(^5\)
- reSET® is on pace to be cleared in 2017 as a class II medical device (De Novo submission) with claims for treatment of Substance Use Disorder (SUD) and enhancement of abstinence and retention in treatment

\(^1\) Experimental & Clinical Psychopharmacology. 2008. 16(2):132-143.
\(^4\) Journal of Substance Abuse Treatment. 2014. 46: 43-51.
**reSET®** combines patient-facing interventions, assessments, and clinician dashboards to treat Substance Use Disorder.

**Patient**
- CBT Modules
- Fluency Training
- Contingency Management
- Craving & Trigger Assessment
- Mobile Dashboard

**Physician & Therapist**
- Module Use
- Cravings and Triggers
- Concept Proficiency
- Abstinence and Appointments
In patients with Substance Use Disorder, reSET® doubles rates of abstinence versus face to face therapy.

507 patients with Substance Use Disorder at 10 nationwide treatment centers were randomized to 12 weeks of typical outpatient treatment (TAU) vs reSET® with limited clinician exposure and abstinence was measured through urine analysis and self reports.

![Graph showing % Abstinent over weeks for TAU and reSET® groups]

<table>
<thead>
<tr>
<th>Population</th>
<th>Time Point</th>
<th>reSET® (n=255)</th>
<th>TAU (n=252)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comers</td>
<td>Week 9-12</td>
<td>29.7%</td>
<td>16.0%</td>
<td>2.22 (1.24, 3.99)</td>
<td>0.0076</td>
</tr>
<tr>
<td>Non-abstinent at start</td>
<td>Week 9-12</td>
<td>10.1%</td>
<td>3.0%</td>
<td>3.59 (1.36, 9.48)</td>
<td>0.0099</td>
</tr>
</tbody>
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reSET® shows high rates of patient engagement and enhances retention in treatment versus face to face therapy.
**reSET®** will be the first FDA-approved, prescription digital therapeutic with clearance on track for 2017

**Device classification**

reSET® was submitted as a Class II medical device via the *de novo* pathway

**Indications for use**

reSET® is indicated for *all patients* with substance use disorder (SUD) including those who are using opioids, cannabis, cocaine, alcohol, and stimulants

**Therapeutic claims**

reSET® improves abstinence and retention in treatment compared to standard of care (intensive outpatient treatment)

**Special controls**

Clinical testing must demonstrate *both safety and efficacy* for subsequent filings claiming reSET® as a predicate
Pilots with leading organizations, like VinFen
reSET® Patient Feedback

- Patients are **more engaged in treatment when using reSET®**

- Patients find reSET’s® content **helpful for learning relevant coping skills for dealing with triggers and cravings**

- Patients feel **more accountable for their sobriety** when they are responsible for regularly reporting their drug use through reSET®

- Patients feel that they can be more honest about reporting their drug use, cravings, and triggers through reSET®

- “Using reSET® made me feel like I had a counselor with me all the time to help me through treatment”

- “When specific challenges came up in my life I would turn to reSET® to learn coping skills”

- “Being able to “check-in” with reSET® every day made me feel like I was being held accountable for my drug use”

- “It is useful to report my drug use in an honest way without being judged”

Feedback generated from patient focus groups during a reSET pilot
**reSET® Provider Feedback**

- **reSET®** enables providers to provide **more effective treatment** for their patients.

- Providers appreciate the ability to **easily identify topics that their patients are struggling with** through **reSET®** and the clinician dashboard.

- Providers value the **deeper insight** they get into their patient’s treatment progress through **reSET’s®** clinician dashboard.

- “My clients that received **reSET®** seemed more motivated in their over-all treatment, shared new insights, and asked more advanced questions.”

- “**reSET®** has been helpful in generating targeted conversations with my clients. What were loose conversations before are now concrete.”

- “Watching patient-entered triggers over time helps me to better understand my patients’ drug-use patterns.”

Feedback generated from patient focus groups during a reSET pilot.
Introducing **reSET-O™**: the first multimodal therapy treating Opiate Dependence

Buprenorphine + **reSET™**: Digital therapeutic to enhance abstinence in Opiate Dependence = **reSET-O™**: branded drug/device combination with best in class efficacy for Opiate Dependence
**reSET-O™** enhances the efficacy of pharmacotherapy in Opiate Dependence

3 Randomized trials consisting of 465 total patients completing outpatient buprenorphine\(^1,3\) or methadone\(^2\) maintenance treatment

Patients received either the current standard of care or **reSET-O™ with limited clinician exposure**; abstinence was measured through urine analysis

Patients using reSET™ displayed a **significantly greater ability to remain abstinent**

The combination enhanced abstinence outcomes and **reduces the required clinician intervention**

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\(^1\) Marsch et al. J Substance Abuse Treatment. 2014.
\(^3\) Christensen et al. 2014
THRIVE™ improves schizophrenia, schizoaffective disorder, and bipolar disorder on existing approvable endpoints

Introducing THRIVE™

- THRIVE™ is a **clinically validated digital therapy** applying evidence-based, multi-modal, and reinforcement therapy to target Positive Symptoms in Schizophrenia; the product is comprised of a patient-facing smartphone application and clinician-facing web interface

- THRIVE™ has been evaluated in **3 clinical studies, involving over 1,279 patients**²-⁴
  - In a 1 month longitudinal study (n=33), patients interacted with THRIVE™ 5.2 times per day (63% of use was patient-initiated), and showed 8% average reduction in total PANSS³
  - In a multi-center usability study (n=342), patients across socio-economic backgrounds and disease severity showed continued engagement with THRIVE™ across the 6 month study duration⁴
  - Two additional studies (n=40; n=160) are currently ongoing and will provide additional information on health outcomes, safety, efficacy, and usability

¹clinicatrials.gov
⁴Ben-Zeev et al. 2016. JMIR Mental Health. 3(3) e34.
The time is right to create regulated digital therapeutics and drug/software combinations

1. While multimodal therapy is standard of care, **few patients receive adequate wrap-around care** as qualified providers are in short-supply.

2. **Reimbursement has become increasingly data-centric** providing further incentive for technologies that can track and monitor outcomes.

3. Data demonstrates that combination, multi-modal treatment of pharmacotherapy + neurobehavioral therapy enhances outcomes compared to either alone.

4. The **ubiquity of smartphones** allows us to push medical/neurobehavioral interventions and collect medical data from the population at large.

5. The FDA has **clarified regulatory requirements** for therapeutic software as a medical device, enabling regulation as therapeutics.

6. Learnings from consumer media enable us to make mobile therapies sufficiently engaging, enhancing dose, and hence response.

7. Patient-facing **digital therapies have shown efficacy** across clinical conditions, enhancing outcomes and expanding access.

8. **Real-world data collection technologies** have shown the ability to track and quantify patient outcomes.

9. **Machine learning, predictive algorithms, and AI** create the opportunity to enhance and to individualize care paradigms.

10. **Printable pill technologies** create the opportunity for a fully integrated and technology-enabled pharmacotherapy.
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