WHITEPAPER

Accelerating Biopharmaceutical Innovation With Digital Therapeutics To Improve Patients' Quality Of Life

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The last decade, and the emergence of a global pandemic, has ushered in personalized, AI-based technologies that are revolutionizing the way we approach medicine[1]. On the surface, digital health solutions have enabled consumers to take back control of their health and monitor key markers of their own well-being to reduce the risk of chronic disease. Even more important is the fact that digital therapeutics are strongly evidence-based and can predict and treat diseases more promptly and effectively[2]. This improved virtual care is giving rise to an era of improved clinical outcomes, while also importantly minimizing the cost burden to the patient. Innovative biopharmaceutical companies and dedicated digital technology companies are at the forefront of developing new, evidence-based digital therapeutics to help advance this period of personal, predictive care to improve patient outcomes[3].

1. Predictive healthcare is greater than the sum of its parts: How digital therapeutics are accelerating innovation at biopharma companies

Introduction to digital therapeutics

The Digital Therapeutics Alliance (DTA) defines digital therapeutics (DTx) as providing evidence-based therapeutic interventions, powered by high quality software programs aimed at preventing, managing, or treating medical diseases[4]. DTx can be considered as a type of software as a medical device (SaMD)[5]. They can be utilized exclusively or in conjunction with other devices, medications or therapies to enhance patient care and support personalized

disease, wellbeing and behavioral therapies. Best practices in design, usability, clinical evaluation and data protection are employed in DTx products. To ensure that risk, efficacy and intended use standards of DTx product design are met, they should undergo certification and clearing procedures by regulatory bodies.

Any product asserting to be a digital therapeutic must comply with the following principles[4]:

- The DTx product must improve a health function
- The product must be reviewed by the appropriate regulatory bodies to support product claims, and yield a medical intervention driven by software that incorporates patient privacy, quality design and product manufacturing, deployment and maintenance best practices
- DTx products should also aim to collect, analyze and implement real world evidence and/or product performance information
- The DTx product should make use of real-world outcomes, for example by conducting clinical trials and publishing results in accredited journals

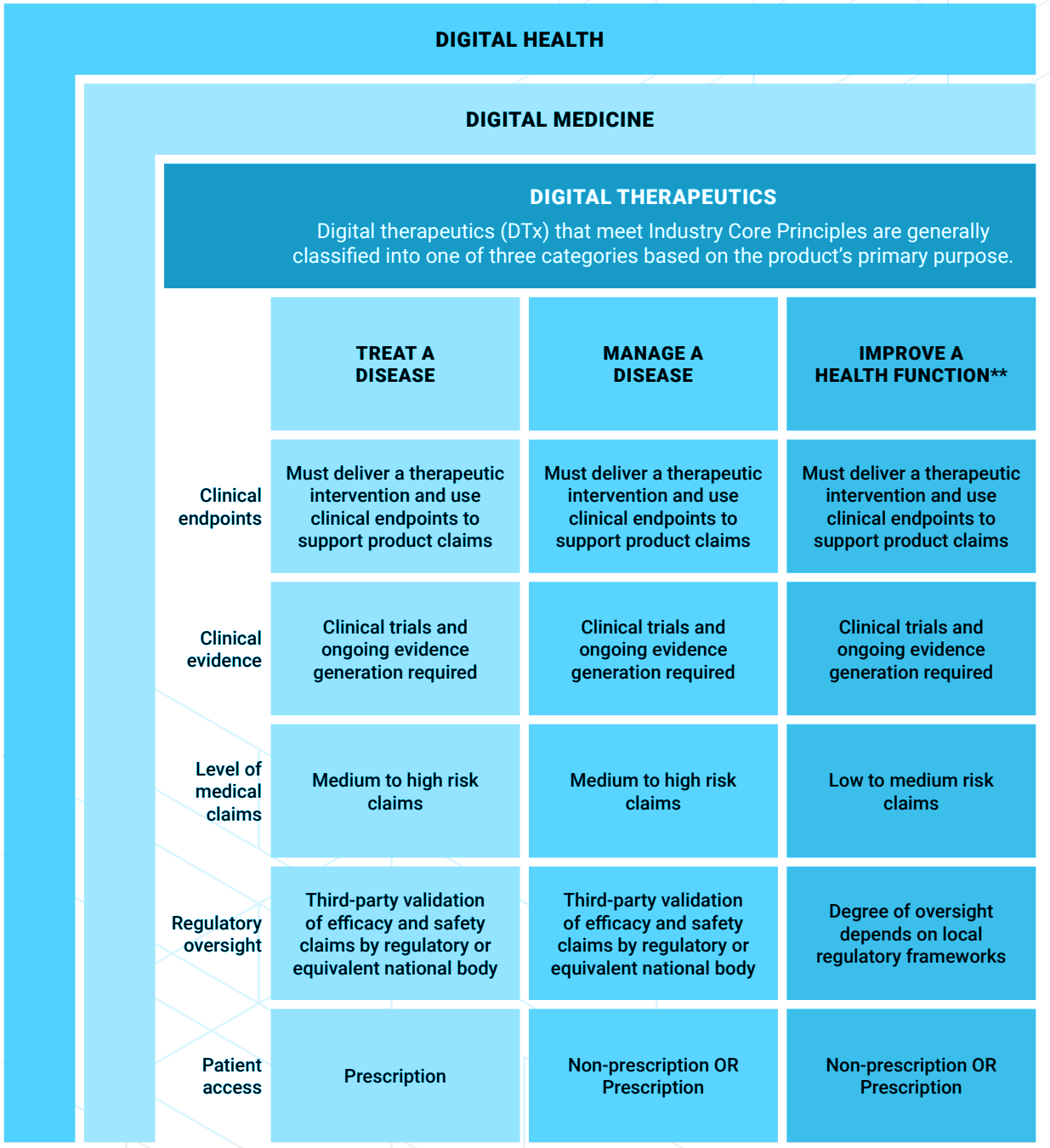
In summary, DTx products are akin to digital medication, often times necessitating the same level of real-world clinical evidence, regulatory control and approval as is required for traditional pharmaceutical products[6]. (See Figure 1)

How digital therapeutics uses clinical evidence and real-world outcomes

AI-powered analytics are applied to large clinical data sets to analyze real world behavior, ultimately to detect and prevent disease. Digital therapeutics make use of clinical evidence and real-world outcomes by leveraging this real-world evidence (RWE) and integrating knowledge from published papers to guarantee ongoing product monitoring (for safety, quality and efficacy) and to further refine the product for improved engagement, application and user experience[7].

Figure 1:

DTx Product Categories



*Update to the Industry Report, *Digital Therapeutics: Combining Technology and Evidence-based Medicine to Transform Personalized Patient Care* (p. 10).
**Includes digital therapeutics that prevent a disease.

Source: Digital Therapeutics Alliance

How biopharma companies can benefit from the addition of digital therapeutics

Digital therapeutics have the capacity to support patients in ways that supersede traditional medical care. Life sciences and pharmaceutical companies seeking a competitive advantage over other more traditional firms can leverage digital therapeutics to meet this unmet need in patient care.

A recent report by Frost and Sullivan (2021)[8] estimated a 40% growth rate in 2021 and a 29.8% compound annual growth rate in 2020-25 of the U.S. digital therapeutics market. Pharmaceutical and biomedical tech companies can greatly benefit from participating in the digital health revolution, by the addition of DTx. At the patient-level, DTx products provide better access to patients, improve clinical outcomes, as well as minimize the cost and burden of care. Indeed, previously implemented treatment plans by DTx vendors on digital platforms that combine expertise of health experts, coaches, care managers and patient providers led to a 50% reduction to the average number of hospital/emergency department visits[8].

Drug efficacy and non-adherence to care plans can be recorded quantitatively at the population-level to allow pharma companies to request regulatory approval for novel drugs/treatments and brand expansion. Further, digital therapeutics can provide greater evidence to support value-based reimbursement from payers. Indeed, the near real-time acquisition and transfer of contextualized patient data to healthcare providers allows these companies to adapt quickly and respond at the right time.

Many companies are now moving R&D investments away from core product lines toward more innovative ideas, recognizing the potential in DTx as the future of healthcare delivery[9]. DTx can build novel solutions and fill gaps in the market that conventional medicine might not be able to penetrate. For example, the cost of development of DTx solutions is vastly less than costs concerning drug development[10]. Existing business models can be improved by opening new markets, increasing R&D efficiency, extending product life and accelerating time-to-market.

Challenges to developing and launching a successful digital therapeutic

The adoption of DTx solutions is multifaceted, usually including numerous stakeholders from different disciplines, multiple decision-making processes and integration of several value judgements to come to any conclusion[11]. Despite the substantial solutions offered by digital therapeutics, they have not yet become fully established in day-to-day healthcare. To date, DTx have been approved by the FDA Center for Devices and Radiological Health following submission of trial data through similar pathways used for medical devices and some breakthrough DTx technologies have been expedited for regulatory review[12].

However, there is still no established FDA regulatory framework for software-as-a-medical-device (SaMD) products[5]. The Software Precertification (Pre-Cert) Pilot Program was launched

in August 2017 by the FDA to aid the evolution of a more streamlined and effective regulatory framework in the future[13], of which the latest version Pre-Cert 1.0 was released in January 2019[14,15]. In April 2020, the USFDA produced a guidance document to improve accessibility of DTx products for dealing with psychiatric conditions while also limiting conduct, mitigating risk of COVID-19 exposure[16]. However, the program is still in its pilot form and all FDA-cleared DTx products to date have had to go through conventional medical device clearance routes.

Launching these products on the market is the first hurdle amongst a series of more complex challenges. For example, the Centers for Medicare & Medicaid Services (CMS) currently does not have a defined benefit category for digital therapeutics, which makes it harder for prescribing clinicians to receive re-imbursement from public health insurance.

Thus, the evolving regulatory environment remains uncertain, and this presents a challenge to developing and launching digital therapeutics.

Furthermore, there are some risks associated with DTx products that may limit payer and provider acceptance and adoption. Unsubstantiated claims of the benefit of a product have been a concern in digital health applications, however as DTx is required to provide real-time evidence about the efficacy of the product to regulatory bodies, this risk is nominal. Another concern related to the use of DTx is their overdependence on technology and smartphones, which requires more attention considering many DTx products are now being used to treat mental health conditions[17]. As we are entering uncharted territory in healthcare with potential widescale application of DTx products, future research should focus on perceived risks associated with DTx products[2].

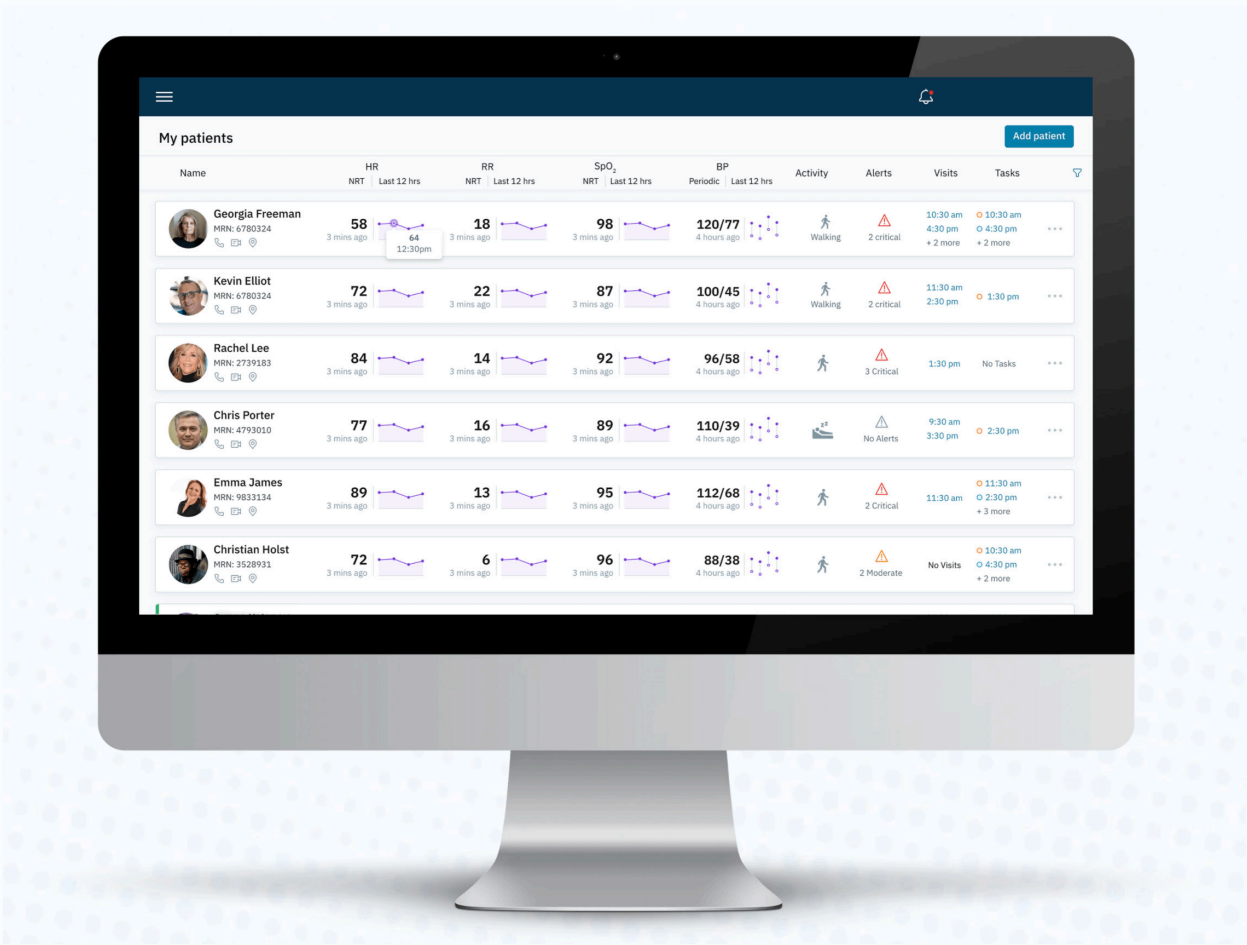
Key requirements for developing and launching a successful digital therapeutic

A company must consider certain key requirements in order to develop and launch a successful digital therapeutic. To begin, pharmaceutical companies should decide whether their DTx will be built in-house or if this work will be outsourced. Considering the path to developing a DTx contrasts to the traditional pharma industry model, often corporations will partner with digital therapeutic experts like Biofourmis to streamline this process.

The interests of the key-players (company, product, people and market) should be aligned as far as possible. All stakeholders must agree upon a universal model to outline, develop, commercialize and deliver these products in a way that maximizes patient health and accessibility and minimizes medical costs. For instance, software product development capabilities, peer-reviewed evidence, customer adoption, FDA-clearance of products, robust product pipeline are all factors to reflect on when developing a DTx. Digital therapeutics built with patients and care providers at the center will be critical to their successful adoption in the market (See Figure 2).

Figure 2:

Example of a digital therapeutic dashboard built with input from patients and care providers.



A recent review identified six key factors to ensure the success of DTx products[7]: Interoperability, socialization, outcomes, engagement, intelligence and integration. Interoperability comprises the use of advanced technologies to allow for data-sharing across several platforms. Intelligence also utilizes advanced technologies (such as machine learning, deep learning and AI) to yield personalized, evolving systems and interventions.

Socialization allows exchange of a patient's cumulative or real-time data with other member affiliates. Integration involves the use of DTx products as a part of a patient's lifestyle, spending more time managing their own care and less time with a clinician. Furthermore, from pilot studies to randomized control trials, outcomes are important for establishing successful DTx products. Finally, gaming principals should be applied to DTx interventions to satisfy engagement.

From all these factors, interoperability should be the focus, because it enhances big data processing, communication, qualified research and international collaboration[18]. This necessitates sophisticated datasets, standardized data formats and efficient communication

across digital platforms. There should also be emphasis on exploiting artificial intelligence to make robust predictions based on analysis of real-world trends and to enable clinicians to spend more time on building a relationship with their patients and less effort on repetitive tasks[19]. All key requirements discussed here should inform companies when developing and launching their digital therapeutic.

2. Case studies and best practices

Today, DTx products are on the market or in development to treat a variety of medical diseases and disorders. DTx frequently targets conditions that are poorly attended to by the healthcare system or behavior-modifiable including chronic diseases or neurological disorders such as Type II diabetes, cardiac disease, substance use disorder, autism spectrum disorder and major depressive disorder[20].

For example, Novartis is partnering with Biofourmis to monitor heart-failure patients who are taking Novartis' Entresto drug to reduce hospital readmissions and emergency-room visits[21]. The Biovitals HF program is designed to streamline the titration of medication dosage by collecting and analysing data from a wearable device[22].

Recently, Biofourmis also teamed up with Chugai to develop a digital and objective measure for clinically assessing a patient's pain caused by endometriosis[23]. The DTx comprises a wearable sensor that utilizes artificial intelligence to identify patterns that may be used to measure endometriosis pain and a smartphone app with game-design features to encourage daily monitoring of symptoms. This system is currently being verified and validated through an ongoing trial involving 120 women, with an estimated study completion date in April 2022[24].

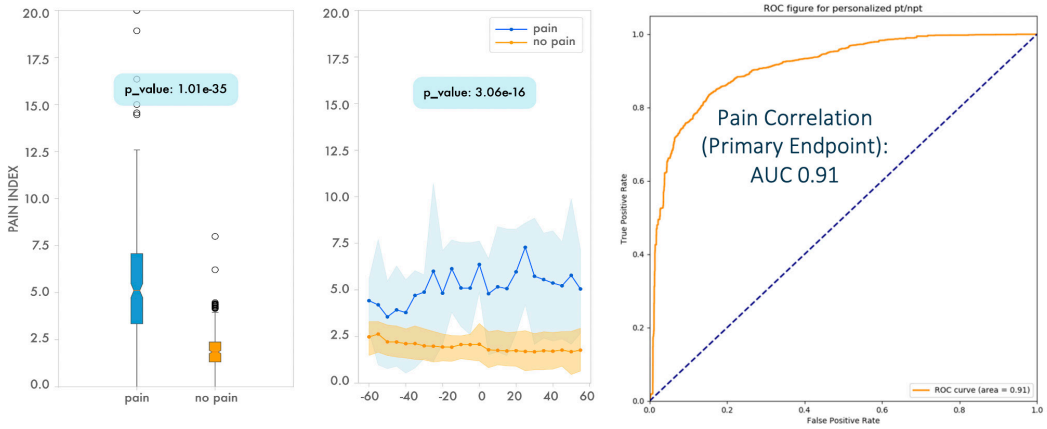
Biofourmis has developed other pain management solutions, such as painfocus™ in partnership with Mundipharma[25] which incorporates machine learning and several physiology biomarkers recorded with wearable devices to quantify the incidence and severity of pain[26]. (See Figure 3.) This DTx solution has been investigated in multiple studies with possibility to be extended to an ambulatory setting which would greatly enhance how clinicians evaluate and manage their patients.

Figure 3:

Overview of the Mundipharma painfocus(TM) study incorporating machine learning, physiology biomarkers, and wearable devices to quantify the incidence and severity of pain.

OBSERVEPAIN STUDY ClinicalTrials.gov Identifier: NCT03789630

- 115 patients undergoing Total Knee Replacement surgery
- Primary outcome: Objective qualification of pain levels patient reported pain levels correlate with deviations and multivariate physiology biomarkers which have shown to be associated with presence of pain
- Significant correlation between patient reported pain score (using VAS scale) and Biovitals® computed physiology deviations (pain biomarkers)



11th Congress Of The European Payne Federation EFIC® 2019

INDICATION

- Augmenting pain management by objective assessment of pain in an ambulatory at home setting to remotely guide therapeutic decision-making

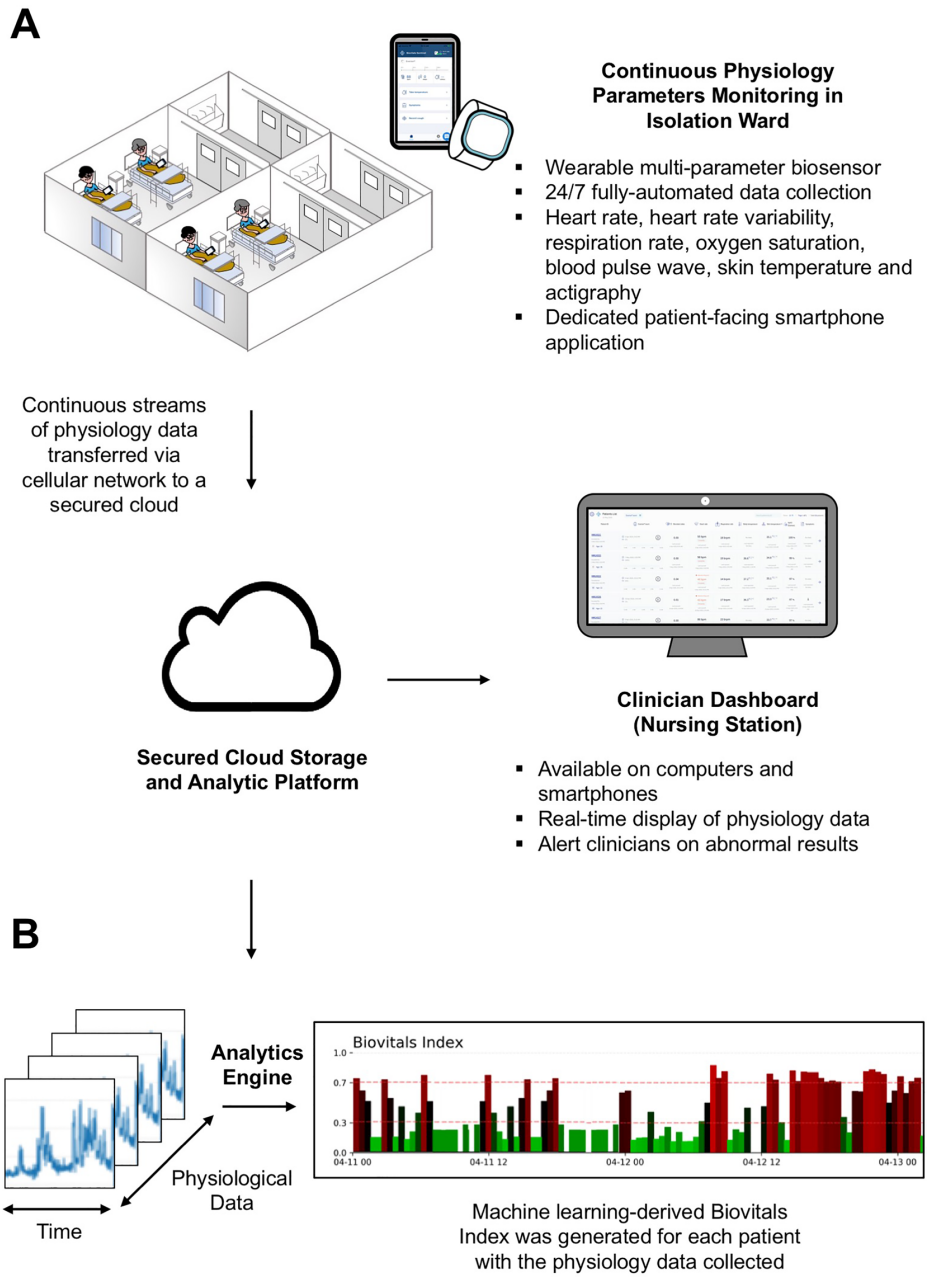
PROOF OF CONCEPT

- Feasibility/POC established to objectively qualify pain levels and evaluated clinical biomarkers for pain
- 2 Pharma-funded clinical trials ongoing in patients with postoperative pain (acute pain) and cancer pain (chronic pain)

Many of these aforementioned DTx solutions such as BiovitalsHF and painfocus™ leverage the Biofourmis Biovitals™ index. The University of Hong Kong is also utilizing this Index to remotely monitor and identify COVID-19-related physiological biomarkers that indicate clinical progression[27]. It was shown that the Biovitals™ index could predict deterioration in patients with 93% accuracy[28]. (See Figure 4 on next page)

Figure 4:

Overview of the Biofourmis Biovitals Index utilized by the University of Hong Kong to remotely monitor and identify COVID-19-related physiological biomarkers.



(A) Isolation ward setting and study design. (B) Machine learning-based derivation of Bio vitals index with continuous streams of physiology data from wearable biosensors.

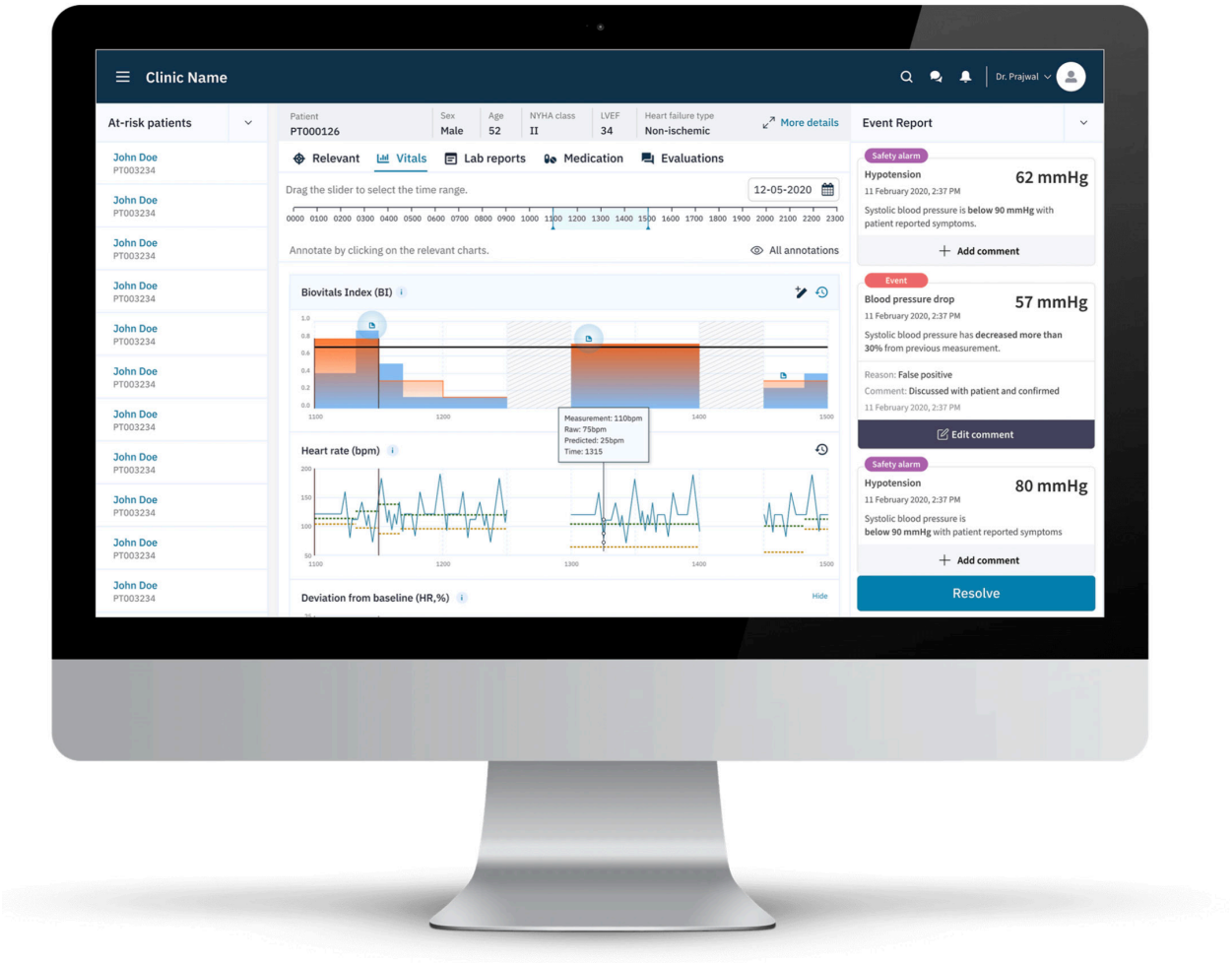
Statistical analysis. Continuous and discrete variables were expressed as mean ± standard deviation and percentages, respectively. Chi-square test or Fisher's exact test was used to compare categorical variables between groups. Students *t* test or Mann-Whitney *U* test was performed to compare continuous variables. Pearson correlation test was used for evaluating the linear association between two variables. Analysis of variance (ANOVA test) was used to compare the sample mean between multiple groups. Receiver operating characteristics (ROC) curve was used for evaluating the trade-off between sensitivity and specificity. Area under the curve (AUC)of (ROC) was used for evaluating the predictive accuracy for classification models. All tests were two-sided, and a *p*-value <0.05 was considered significant. All statistical analysis were performed using SPSS software (version 21.0,) R (version 3.6.1), and Python (version 3.6) programming languages.

Nature Scientific Reports, (2021) 11:4388

The FDA-cleared Biovitals™ index combines disease data and artificial intelligence to ensure patients receive the right care at the right time. Innovative analytics process active and passive data, and use machine learning to interpret and analyze a patient's vital signs, measuring deviations from a personalized baseline. (See Figure 5)

Figure 5:

Representative dashboard from the Biofourmis Biovitals Index, incorporating AI-driven predictive analytics of real-world patient data.



Based on a patient's condition, Biovitals enables the delivery of optimal dosing and can notify clinicians of significant changes, thereby facilitating earlier intervention in the case of a clinical event. In each of these case studies, the use of the Biovitals Index ensures industry core principles on best practices for digital therapeutics[4] are being adhered to.

3. What can we expect for the future?

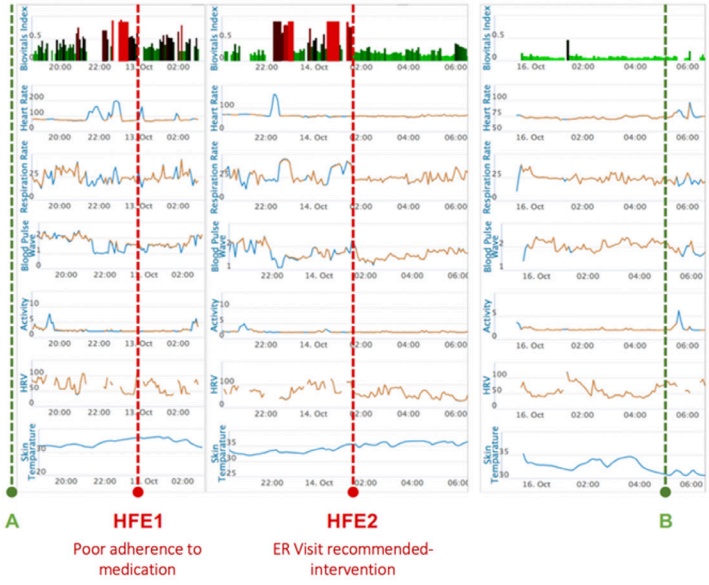
Transforming digital therapeutics: Biofourmis' approach

The future of digital therapeutics relies on gaining quicker, but appropriately granted regulatory approval. As the first company to have received FDA breakthrough designation[22] for heart failure, Biofourmis demonstrates how solutions that are digitally innovative can detect adverse events and predict disease in both clinical trials and in real-world commercial outcomes.

For example, their Care@Home platform enables clinicians to deliver personalized predictive care to patients outside of a traditional hospital or clinic across the continuum of care, including acute, post-acute and chronic care. (See Figure 6) The Biovital analytics engine, a highly sophisticated AI-powered, machine-learning platform, utilizes medical-grade wearables to continuously collect patient data to predict clinical exacerbation in advance of a critical event—enabling earlier interventions and leading to better clinical and financial outcomes. Spearheaded by companies like Biofourmis, digital therapeutics can reach a new level of care.

Figure 6:

68 years old white male, ICM (EF=38%), NYHA III, CABG, HTN, CKD,AF enrolled in at-home monitoring program



Patient	68 years old white male, ICM (EF = 38%), NYHA III, CABG, HTN, CKD, AF
A **9 Oct**	Discharged after treatment for diagnosed acute coronary syndrome, unstable angina & HF exacerbation. Discharged: 9 Oct 2017
HFE1 **13 Oct**	Intervention by Care team Missed his medication Furosemide; forgot to replenish his medicine.
HFE2 **14 Oct**	Intervention by Care team: ER visit Patient experiences severe SOB at-night. Outpatient treatment/ER: Carloc 25mg, Spiractin 25mg, Furosemide 40mg/4ml IV
B **15 Oct - Present**	New baseline post-intervention: Stable physiology, good medication compliance, increase in activity levels

Digital therapeutics will continue to disrupt biopharma, as they provide a cheaper, more proficient alternative than conventional pharmaceutical drugs. The future impact of digitalization on health and healthcare systems will be profound, altering all the stages of health care delivery, prevention and forms of care[29]. This is changing the healthcare landscape to evolve around the consumer, allowing patients more responsibility for managing their own healthcare. There is a need to re-shape regulatory approval by creating clearer re-imbursement pathways and more defined categories for digital therapeutics.

As a company that specializes in integrating personalized care and DTx, Biofourmis will be a key player in transforming the healthcare landscape by leading the way in evidence-based, digital therapeutics.

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Biofourmis is a global leader in virtual care and digital therapeutics, offering innovative solutions that enable clinicians to deliver personalized predictive care anywhere. Biovitals®, a highly sophisticated AI-powered health analytics engine, utilizes medical-grade wearables to continuously collect patient data targeted to predict clinical exacerbation in advance of a critical event, which enables earlier interventions and can lead to better outcomes. The Biovitals analytics engine has been clinically validated across multiple therapeutic areas for acute and chronic conditions, oncology, infectious disease such as COVID-19, chronic pain, and COPD, and is prescribed as a companion digital therapeutic with pharmacotherapy in value-based care.

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