Wearables and Patient Reported Outcomes in Research and Post-Market Surveillance

CRT Plenary Meeting 2019
Tallin

04.10.2019 / Dr. Christian Müller

Agenda

- Digital (Health) Transformation
- Real World Evidence
- Breelib, BreeConnect, Ventavis®
- Ventastep study
- Evidence Matrix
- ePRO collection

Disruption - Letterpress

- Self referring on written words creates own reality
- Radical reduction on character shape
- Social need
- Development of additional technology skill: reading
- Data doubling the world

Disruption - Digitalization

- Identifies probabilistic patterns in datasets
- Infinity, ubiquitious, loss of control
- Binary coded functional systems in society
  - Economy (payment/ no payment)
  - Politics (power/ no power)
  - Medicine (ill/ healthy)
- Binary code enables endless operational opportunities
- For which problem digitalization is a solution?

Digitalization assesses social complexity

Real World Data

electronic health records (EHRs),

claims and billing data,

data from product and disease registries,

patient-generated data including in home-use settings,

data gathered from other sources that can inform on health status, such as mobile devices

www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf

Real World Evidence

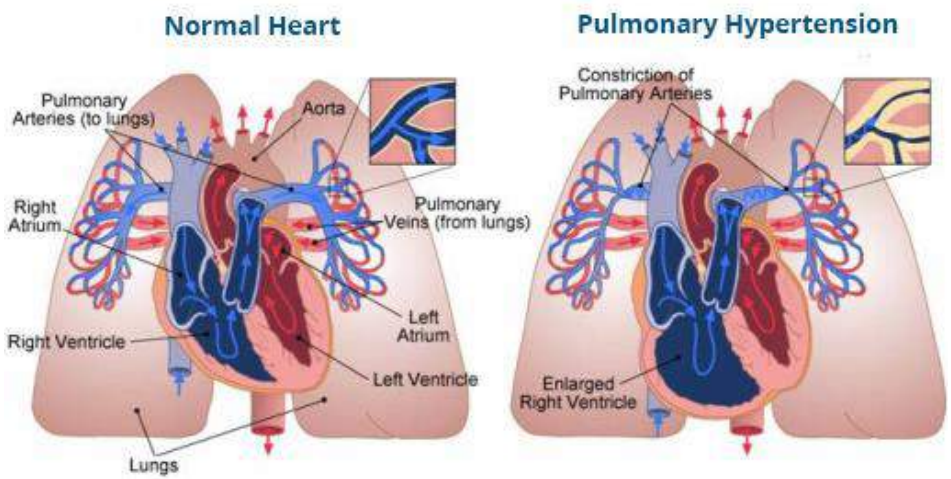
clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data

Corrigan-Curay J, Sacks L, Woodcock J. Real-World Evidence and Real-World Data for Evaluating Drug Safety and effectiveness. Jama. 2018;320(9):867-8.

Digitalization leverages box-stop medicine to Real World Evidence

Pulmonary arterial hypertension (PAH) & Ventavis®

- Characterized by endothelial cell proliferation, pulmonary vascular remodeling, culminating in right heart failure and death
  - Symptoms include: shortness of breath, fatigue, chest pain, syncope, swelling (legs/ankles)
    - Dual combination therapy : endothelin receptor antagonists (ERA`s) and phosphodiesterase-5 inhibitors (PDE5-i`s) or stimulators of soluble guanylate cyclase (sGC)

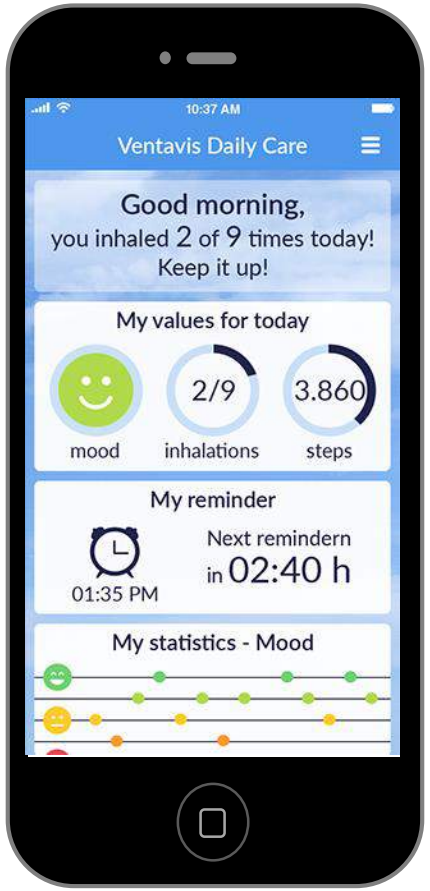


- synthetic analogue of prostacyclin PGI2
  - dilates systemic and pulmonary arterial vascular beds
    - approval in Sept 2003 for the treatment of PAH NYHA/World Health Organization (WHO) FC III, may be added to dual combination therapy

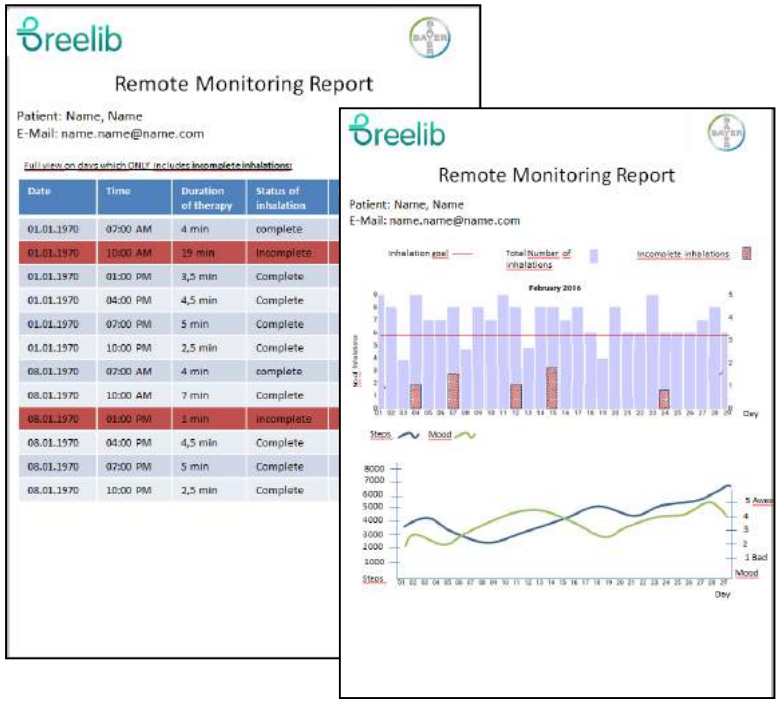
VENTAVIS
iloprost trometamol

Date, time and duration of iloprost inhalations are captured continously and displayed to the patient

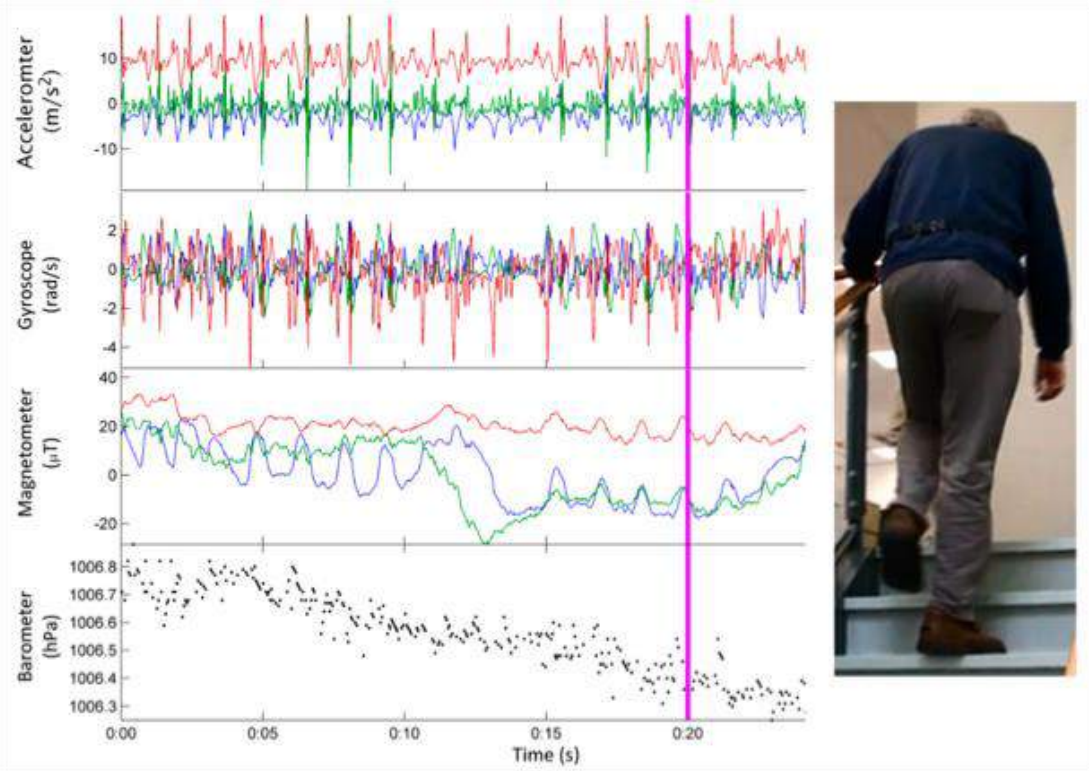
- Date of inhalation, inhalation time, inhalation frequency, inhalation complete/incomplete
  - Data is stored for about 9 months of inhalations
    - BreeConnect™ app can be actively connected to Breelib via Bluetooth



SHARING OF INHALATION DATA WITH PHYSICIAN



Detection of micromovemet & translation into real life activities by xbird GmbH

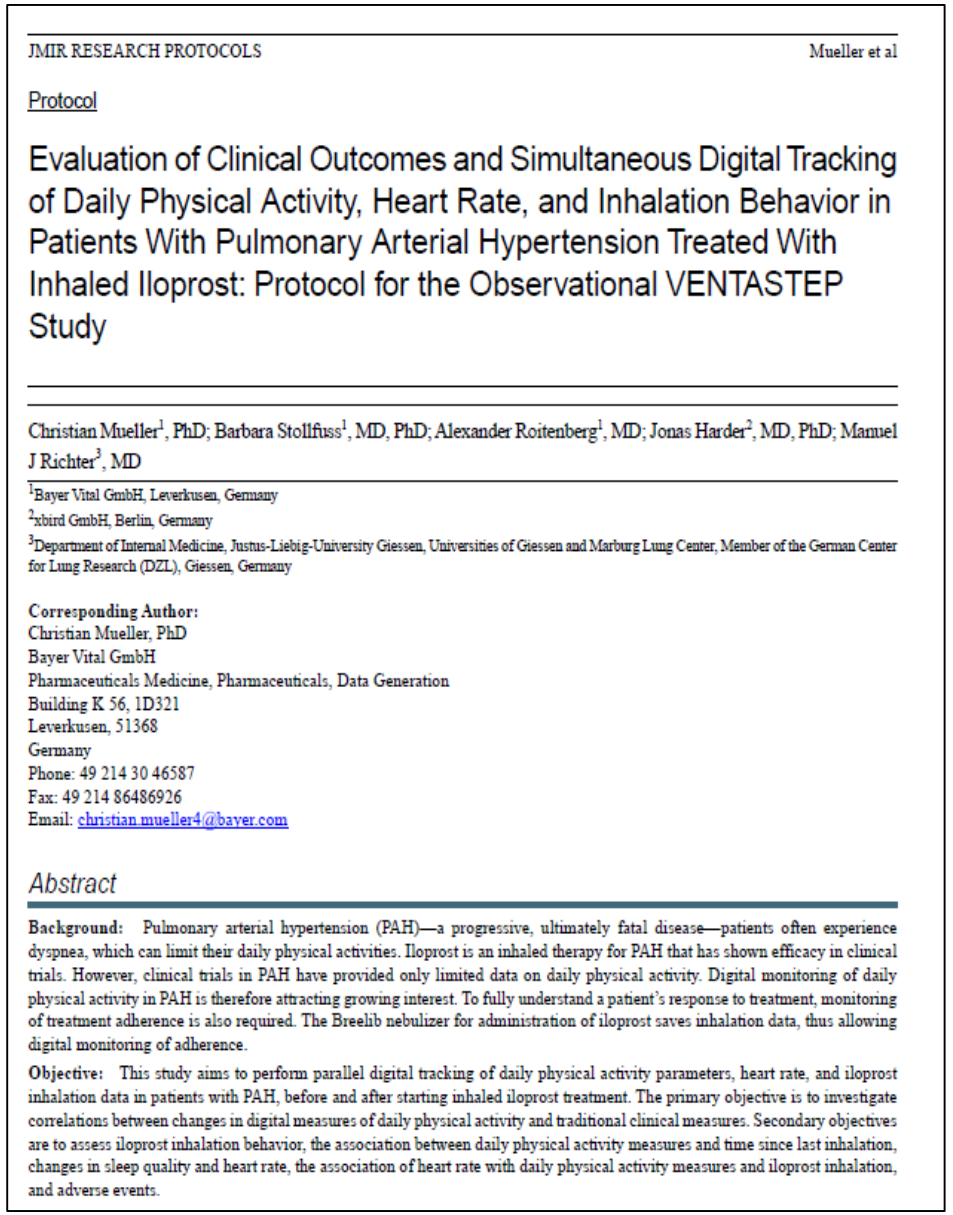


Identification of micromovements during real life activities and transfer into study variables

VENTASTEP

Ventavis® (Iloprost): Evaluation of inhaled ilopro**st** effects using the Br**e**elib™ nebulizer, clinical outcomes and physical activity of patients with advanced **p**ulmonary arterial hypertension.

- Local, German, prospective, uncontrolled, non-interventional, digital cohort study
  - 31 Ventavis® treatment naïve patients recruited at 9 sites
    - 2 observation periods per patient (baseline period; before start of Ventavis® treatment & observational period; 3 months after start of Ventavis® treatment)



JMIR RESEARCH PROTOCOLS Mueller et al

Protocol

Evaluation of Clinical Outcomes and Simultaneous Digital Tracking of Daily Physical Activity, Heart Rate, and Inhalation Behavior in Patients With Pulmonary Arterial Hypertension Treated With Inhaled Iloprost: Protocol for the Observational VENTASTEP Study

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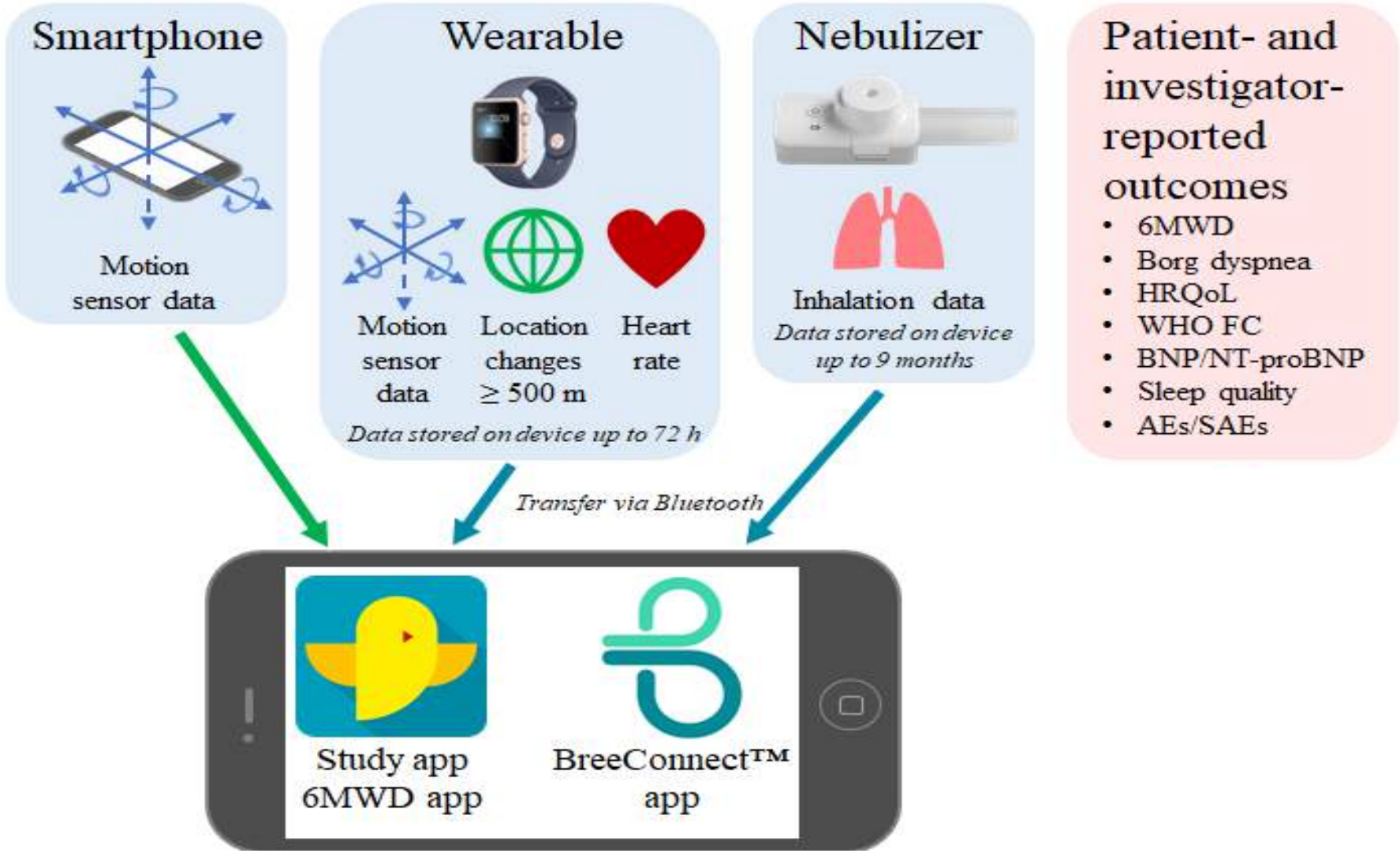
Abstract

Background: Pulmonary arterial hypertension (PAH)—a progressive, ultimately fatal disease—patients often experience dyspnea, which can limit their daily physical activities. Iloprost is an inhaled therapy for PAH that has shown efficacy in clinical trials. However, clinical trials in PAH have provided only limited data on daily physical activity. Digital monitoring of daily physical activity in PAH is therefore attracting growing interest. To fully understand a patient's response to treatment, monitoring of treatment adherence is also required. The Breelib nebulizer for administration of iloprost saves inhalation data, thus allowing digital monitoring of adherence.

Objective: This study aims to perform parallel digital tracking of daily physical activity parameters, heart rate, and iloprost inhalation data in patients with PAH, before and after starting inhaled iloprost treatment. The primary objective is to investigate correlations between changes in digital measures of daily physical activity and traditional clinical measures. Secondary objectives are to assess iloprost inhalation behavior, the association between daily physical activity measures and time since last inhalation, changes in sleep quality and heart rate, the association of heart rate with daily physical activity measures and iloprost inhalation, and adverse events.

https://www.researchprotocols.org/2019/4/e12144/pdf

Fusion of classical and digital biomarkers out of 4 data sources



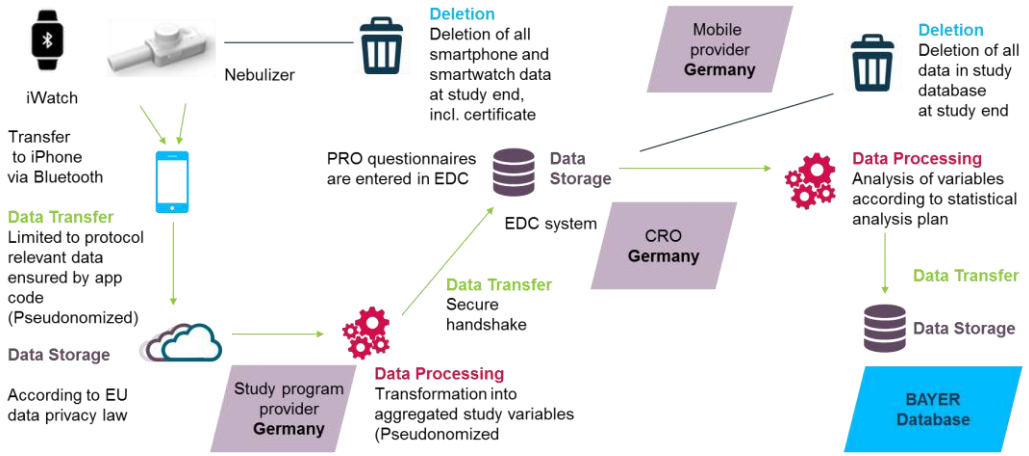
Using wearables in a digital research ecosystems enables identification of relevant digital biomarkers

Secure cloud server
Data storage and processing

Digital study variables

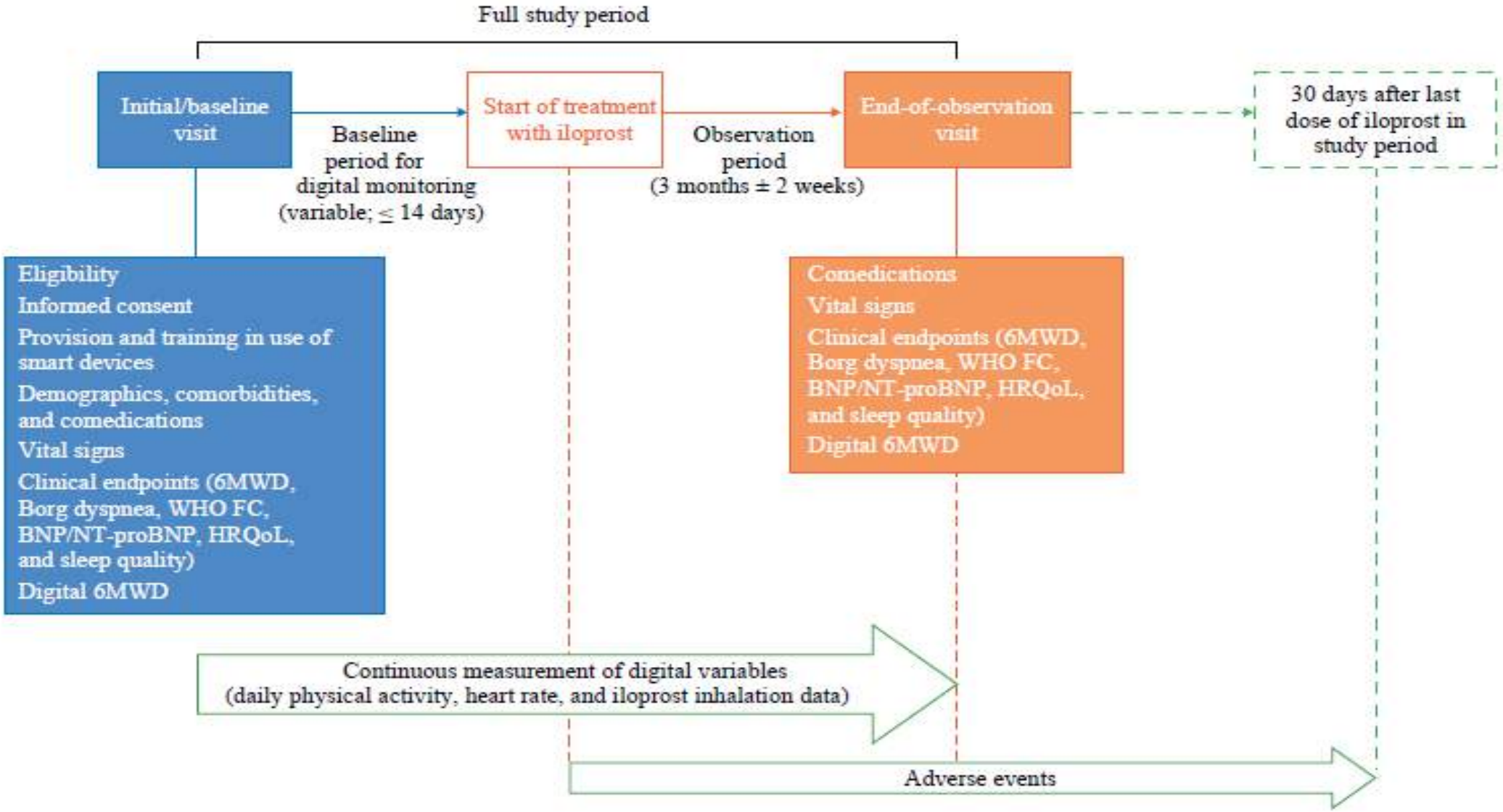
- Daily physical activity
  - Distance walked
  - Number of steps
  - Number of floors climbed (10 feet)
  - Number of times standing up
  - Time spent at home
  - Number of relevant location changes
  - Number of times leaving home
- Status distribution:
  - Active (any activity)
  - Inactive (sedentary/lying down)
  - Watch not worn
- 6MWD
  - Number of steps
  - Distance
  - Heart rate
- Heart rate
- Iloprost inhalation behavior
  - Average number of daily inhalations
  - Average daily proportion of complete/incomplete inhalations
  - Average daily inhalation duration per session

Electronic data capture system of CRO
Analysis of variables according to statistical analysis plan



25 MB per patient per day

Study visits & data collection



Source: Mueller et al. 2019

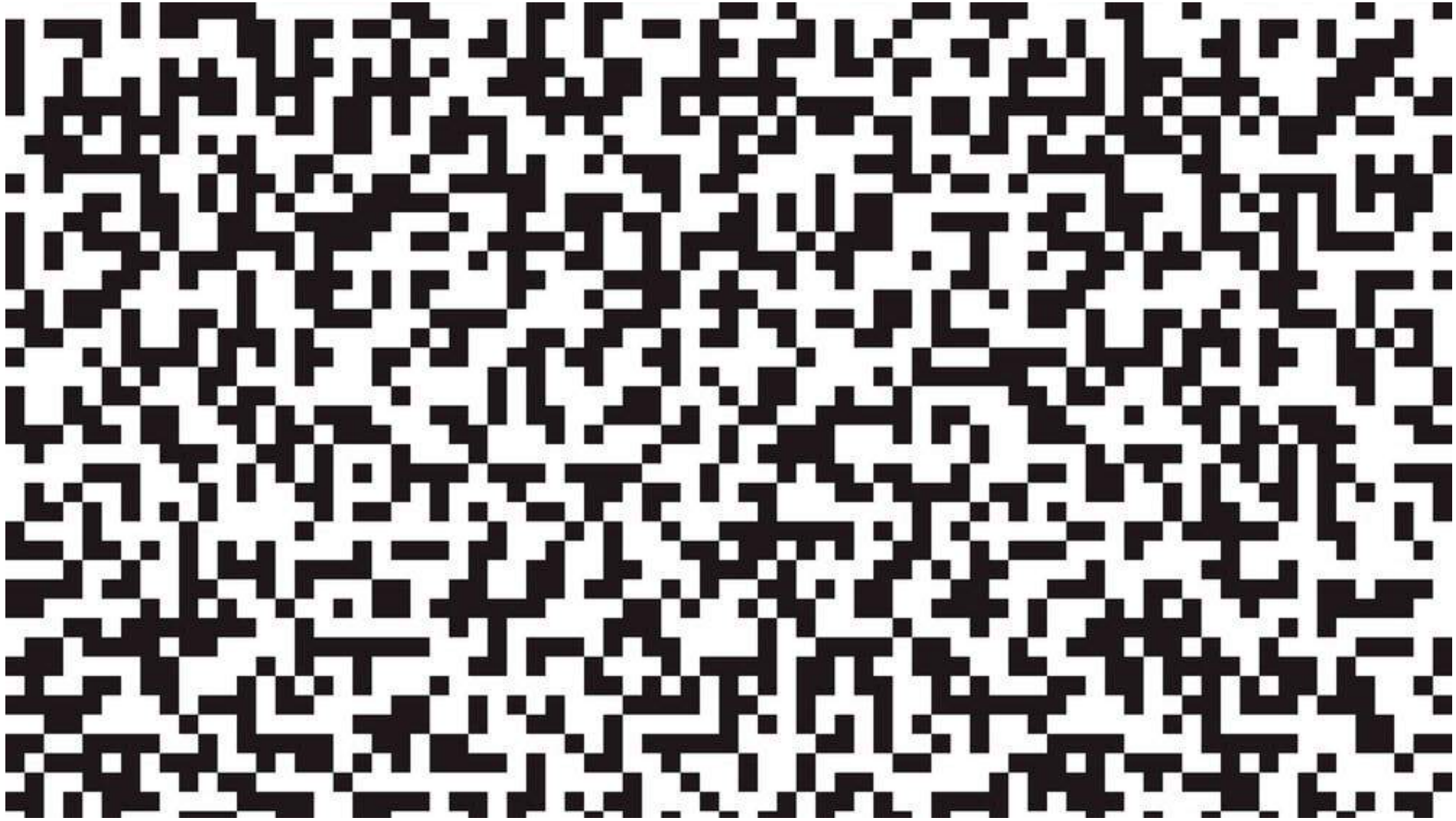
VENTASTEP objectives

PRIMARY OBJECTIVE:

// to evaluate the potential use of device-based measures as outcome-surrogates for clinical assessments. This is done by assessing patient-wise correlations between of 3-month/ baseline differences of clinical measures (i.e. 6MWD, QoL, WHO FC and proBNP species) and wearable-based measures (physical activity)

ASSOCIATION BETWEEN CHANGES IN CLINICAL OUTCOME MEASURES AND CHANGES IN DIGITAL OUTCOME MEASURES

From correlation to pattern identification



From correlation to pattern identification

Pearson Correlation Statistics (Fisher-Z-Transformation)			
Variables			
6MWD (investigator)	Borg Dyspnea Scale (investigator)	EQ-5D	WHO-FC
Borg Dyspnea Scale (investigator)	EQ-5D	WHO-FC	NT-proBNP/BNP
EQ-5D	WHO-FC	NT-proBNP/BP	Distance walked (device based)
WHO-FC	NT-proBNP/BNP	Distance walked (device based)	Number of steps (device based)
…			

Real world evidence generation in a digital world - using an **evidence matrix** for primary data collection

Patient

Sensor/Device

Indication

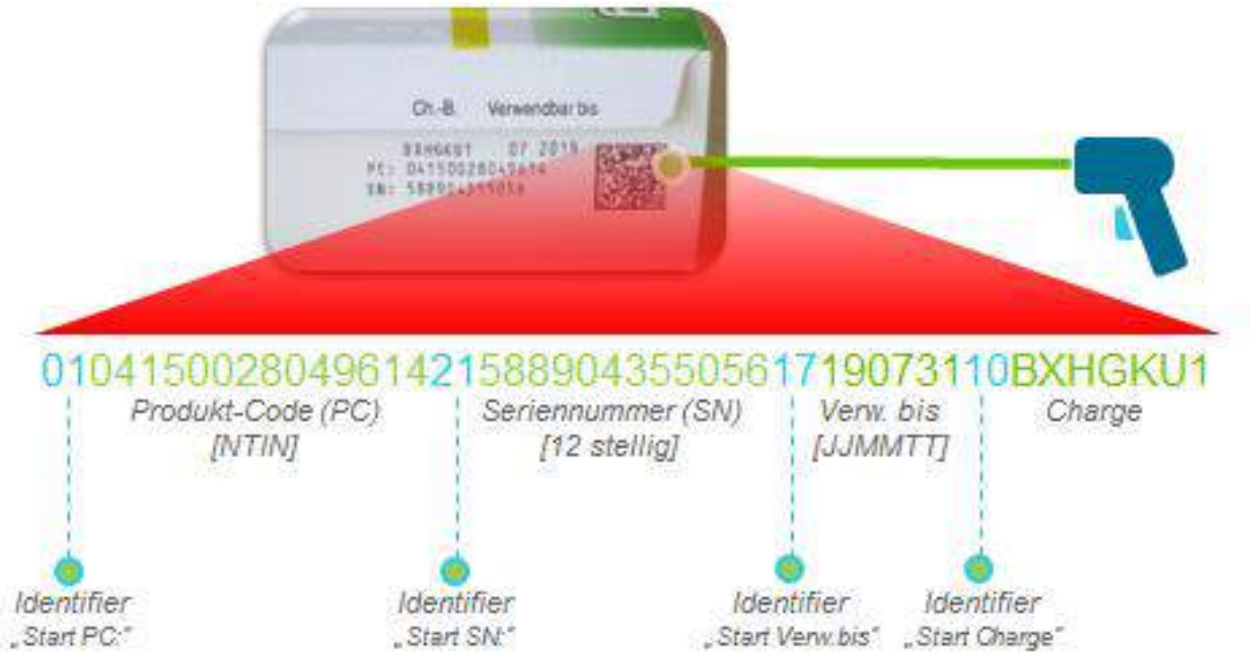
Validity

Biomarker

Endpoint

Falsified medicines directives 2D Matrix Code can work as patient authentification in remote, patient centric real-world data collection

Outer package is our hardware in the household of patients – just deliver software to collect data

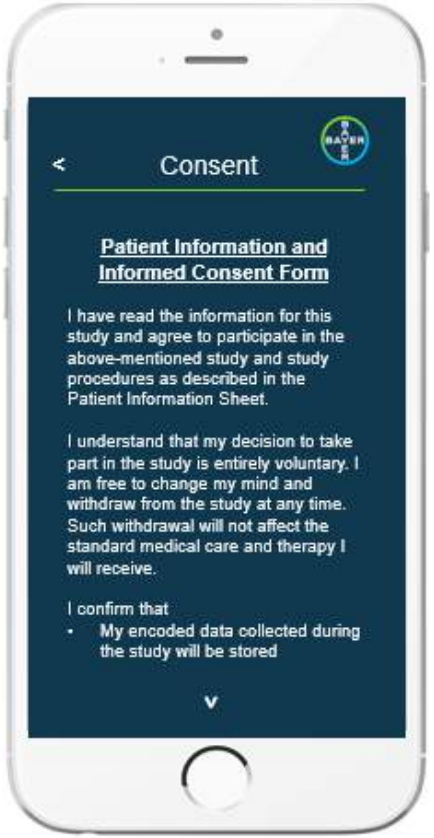


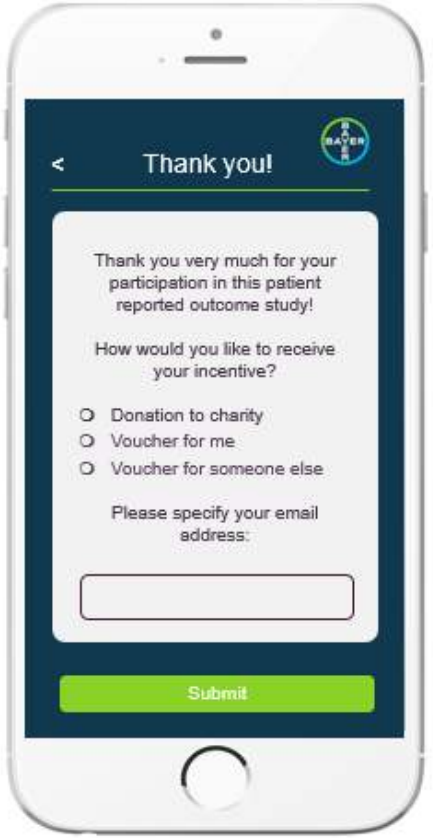
- Primer
- Country Code
- Product Code (PZN)
- Serial number
- Expiry date
- Charge

my ePRO app in a nutshell
Download - Scan - Consent - Answer - Compensation

Experimentation & Customer Focus

Download	Scan 2D Matrix Code	Consent	Answer PRO	Compensation
my ePRO app from public app store	**for authentification as BAYER drug taking patient**	**to PIIC electronically**	**using validated PROs & additional data sources**	**based on time needed for answering PROs**





With my ePRO app we help patients to report their outcomes – PRO – with a compensation for their time required

Take home message

- need for RWE research with digital features
- digital support to identify patterns
- overcome box-stop medicine
- implementation into routine care

Forward-Looking Statements

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The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Science for a better life

Thank you!

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