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eHealth Applications & Digital Monitoring Devices

- An Enabler in Clinical Drug Development -

Dr. Frank Kramer
Director Medical Devices & eHealth Clinical
BAYER AG, Germany

DPhG Fachgruppe Industriepharmazie
Oct 21st 2020

Agenda

Background	// Digital Transformation of Pharmaceutical Industry
	// The Pharmaceutical R&D Value Chain
	// The Role of eHealth & Sensors in Clinical Drug Development

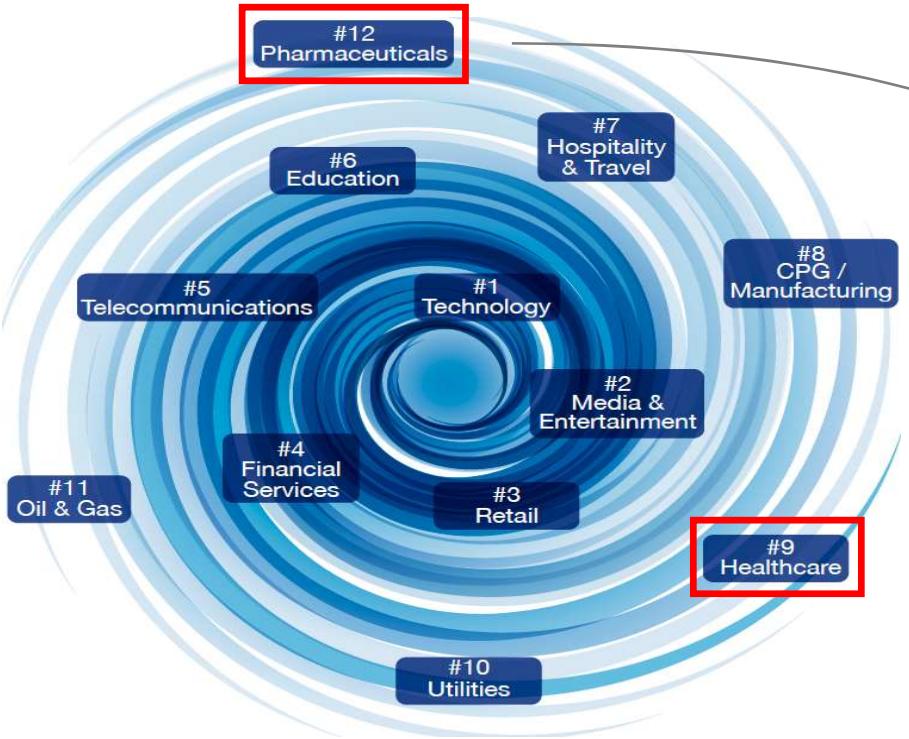
Why & Where to use eHealth	// Heart Failure: Characteristics, Prevalence and Relevance // Motivation to Implement eHealth Apps & Wearables in Clinical Trials

eHealth & Sensors at Work	// Tools for Remote & Continuous Patient Monitoring: Sensors & ePROs
	// eHealth,Sensors & ePROs in Observational and Interventional Studies
	// Challenges during Implementation

Regulatory Perspective & Outlook	// Generation of Standards
	// FDA and EMA view
	// Impact of eHealth on Quality & Efficiency in Healthcare
	// New Business Models

Digital Transformation of Industries

To Which Extend is Pharmaceutical Industry Affected ?



Areas of Digital Trans-formation

Research:
- Omics, Big Data

Development:
- Wearables, eHealth

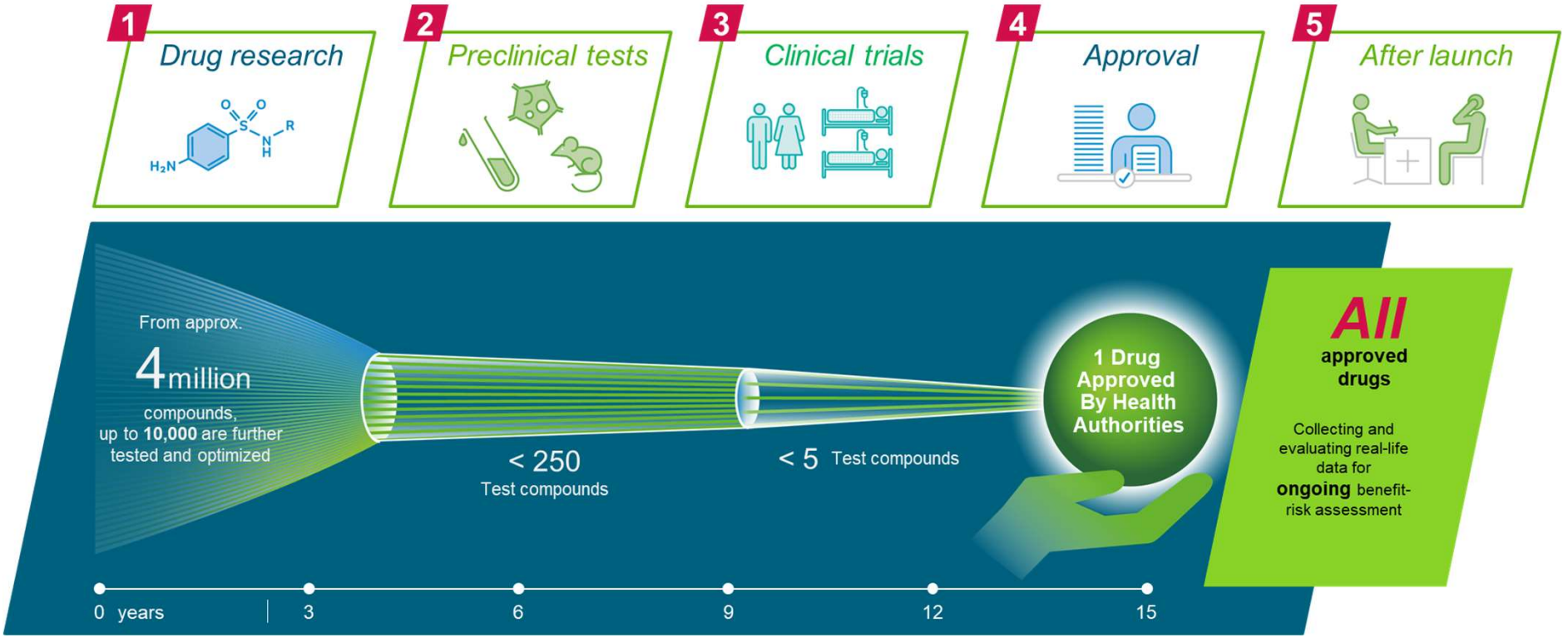
Production:
- IoT, Industry 4.0

Marketing:
- Social Media

Global Center for Digital Business Transformation at IMD/Lausanne 2015

Pharmaceutical R&D Value Chain

The long Process from Idea via Molecule to Medicine



The Role of eHealth & Sensors in Clinical Drug Development

Data Capturing in Clinical Trials: Complementary Information

- Demographics (Age, Sex…)
- Disease specific parameters (ECG, Ultrasound….)
- Lab parameters (Blood, Urine biomarkers…)
- Comorbidities
- Medication / Side effects
- **Wearable-derived data**
- **How patients feel and manage their disease (PRO)**

Point in time *versus* Continiuous Measurements
Objective *versus* Subjective Measures

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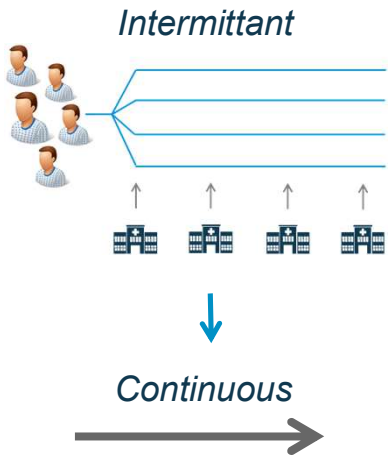
The Motivation to Implement eHealth Applications & Wearables

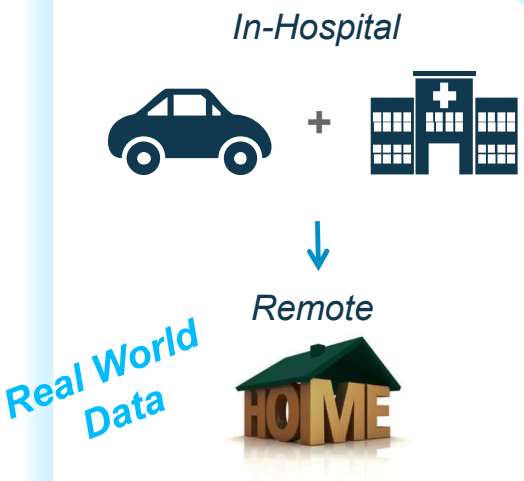
Benefits of Remote and Continuous Data Capturing in Clinical Trials

Better Profile Drugs



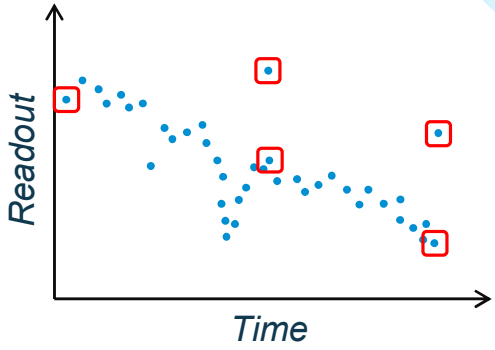
Data Capturing

Reduce Patient`s Burden



Patient Monitoring

Reduce Costs / Safe Time



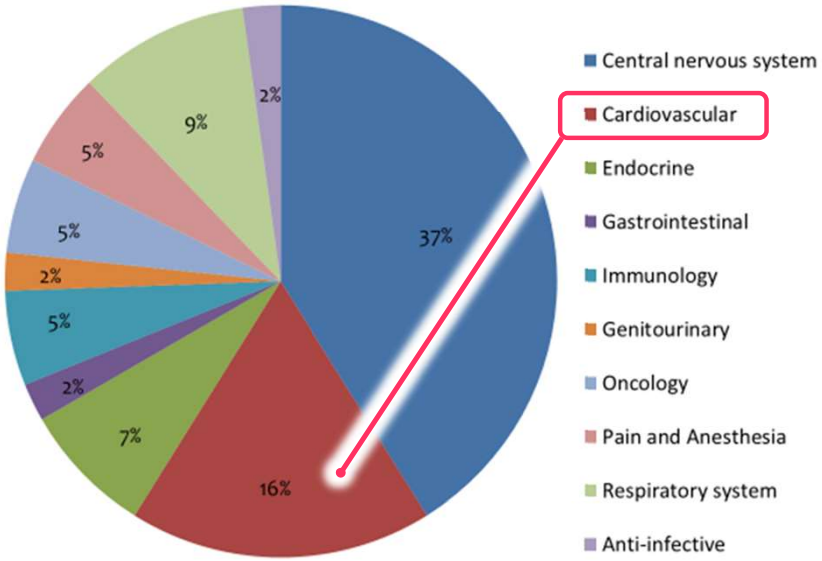
Reliably Capture Disease Course

Digital Devices Induced **Paradigm Shift** and Enable **Highly Innovative Trial Designs**

Where to Implement eHealth?

Registered Mobile/Electronic Health Clinical Trials

Clinical Trials.gov, accessed June 2017, N= 564 trials



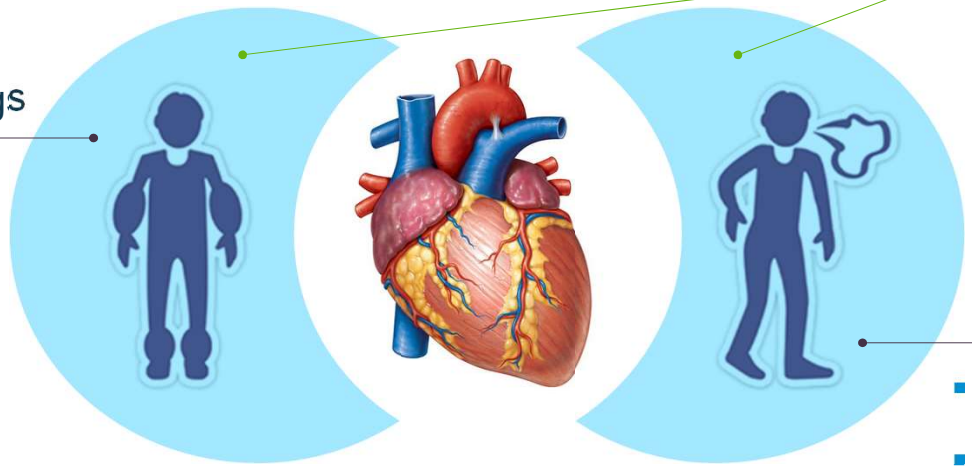
Sarwar CMS. et al., 2018, Int J Cardiol. doi: 10.1016/j.ijcard.2018.06.039.

Heart Failure

Symptoms are Impacting Quality of Life

- Vital Signs & Activity tracking
- ePRO

- Swelling of arms and legs



- Shortness of breath
- Reduced ability to exercise

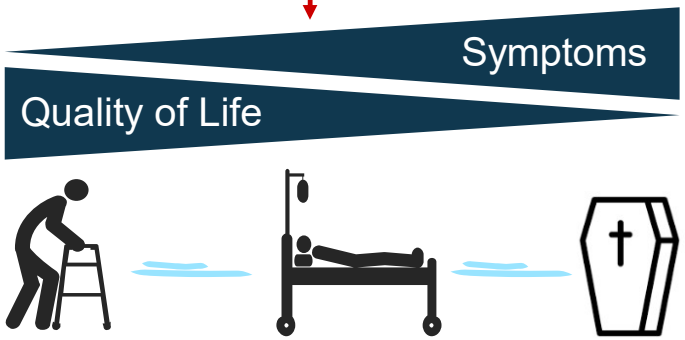
Innovative Therapies: Prolong Life, Reduce Hospitalization
Improve **Symptoms, Quality of Life** and **Exercise Capacity**

Heart Failure

A Progressive and Deadly Disease

1-year mortality

5-year mortality



Heart Failure

A Highly Prevalent Disease with High Socio-Economic Impact

- 518 Cases / 100 000 Individuals (2017)
- Doubling since 1995
- 47414 Deaths in 2015

- 5.1 million cases
- > 870.000 new cases per year
- 1-2 % of health care expenditure

- 26 million cases
- $ 108 billion worldwide annual costs

Source: American Heart Association (AHA), German Society of Cardiology (DGK), Press Release DGK 01/2018

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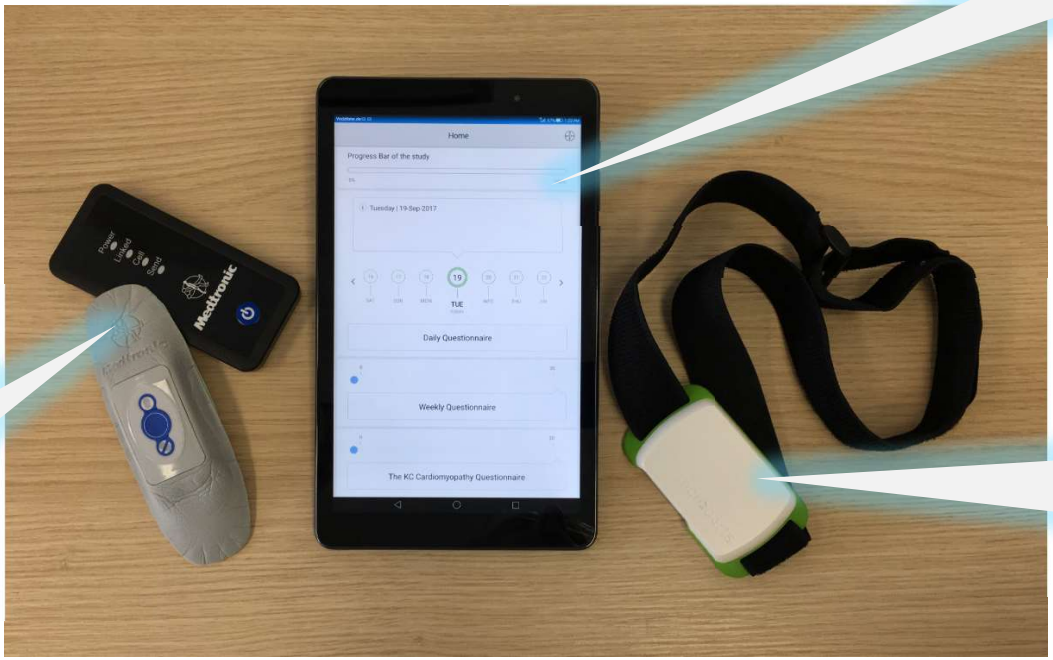
Tools for Remote & Continuous Patient Monitoring

Wearable Devices and eHealth Application in REALIsM-HF



VitalConnect

phys iQ

Mobile Cardiac Monitoring Patch

(24 hrs / 5-7 days)

Electronic Patient Reported Outcome

(daily, weekly)

Activity & Energy Expenditure Tracker

(24 hrs / 7 days)

https://www.mcroberts.nl/products/movemonitor/

https://www.physiq.com/

Definition Patient Reported Outcome (PRO)

US Food & Drug Administration

According to the FDA-NIH Biomarkers, EndpointS and other Tools (BEST) Working Group, a patient-reported outcome (PRO) is….

"…a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else."

PROs may capture symptoms such as itching as well as functioning in daily life such as the ability to carry groceries.
A patient-reported outcome measure (PROM) is the instrument or tool, typically a questionnaire or diary, used to gather the health status of the patient.

Examples
- Numeric rating scale of pain intensity
- Patient-completed diary of seizure episodes
- Verbal rating of severity of visual symptoms

Reference: DA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring (MD): Food and Drug Administration (US); 2016

Available PROs to Assess Heart Failure

Tool Description and Principle of Operation

Chronic Heart Failure Questionnaire (CHFQ)	Single-Item Health Status
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Multidimensional Fatigue Inventory
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Social Provisions Scale
Chronic Heart Failure Assessment Tool (CHAT)	EuroQol Dimensions Index
Heart Failure Functional Status Inventory (HFFSI)	Medical Outcomes Study 36-Item Short-Form Healthy Survey
QoL in Severe Heart Failure Questionnaire (QLQ-SHF)	12-Item Short-Form Health Survey
Left Ventricular Dysfunction Questionnaire (LVD-36)	Sickness Impact Profile
San Diego Heart Failure Questionnaire (SDHFQ)	Health Utilities Index Mark-3
Memorial Symptom Assessment Scale-Heart Failure (MSAS-HF)	Patient Health Questionnaire-9
Zung Self-Rating Depression Scale	Brief Symptom Inventory
Profile of Mood State	MacNew
Patient-Generated Index	Cardiac Depression Scale
London Chest Activity of Daily Living Scale	QoL Index-Cardiac Version
Generic QoL questionnaire	Health-Related QoL Questionnaire
Cumulative Illness Rating Scale	Dyspnea Fatigue Index
Duke Activity Status Index	

Butler J, ….Kramer F… et al. Exploring New Endpoints for Patients With Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016;9(11):e003358.

Example: Kansas City Cardiomyopathy Questionnaire (KCCQ)

23-item Questionnaire, *Six Domaines, Two Summary Scores, 4-6 min Completion Time*

Symptom Domain	// frequency and burden of clinical symptoms including **fatigue**, **shortness of breath**, paroxysmal **nocturnal dyspnea** and patients' **edema/swelling**
Physical Function Domain	// **limitations** patients experience, due to their heart failure symptoms, in performing **routine activities**
Quality of Life Domain	// patients' assessment of their **quality of life**
Social Limitation Domain	// extent to which heart failure **symptoms impair patients' ability to interact** in a number of gender-neutral social activities
Self-efficacy Domain	// patients' perceptions of **how to prevent heart failure exacerbations** and manage complications when they arise
Symptom Stability Domain	// recent **changes in patients' symptoms**; their shortness of breath, fatigue or swelling

Clinical Sum-mary Score

Overall Sum-mary Score

eKCCQ
In REALIsM-HF
Trial

Step Wise Implementation of eHealth

Assessment of Feasibility, Generation of Infrastructure & Building of Data Base Layer

Traditional Clinical Trial Concepts: Established Readouts & Endpoints

Pilot Patient Registry:
Wearables & Innovative Data Infrastructure

- Identify Technology
- Feasibility
- Establish Data Infrastructure
- Build Data Base Layer

REALISM-HF

VITALITY Study
(in between)

Interventional Trial:
Drug
+ Traditional Readouts
+ Wearables

- Drug Approval FDA
- EUROPEAN MEDICINES AGENCY

REALIsM-HF Patient Registry

An ePRO and Wearable Device Pilot Study in Heart Failure Patients

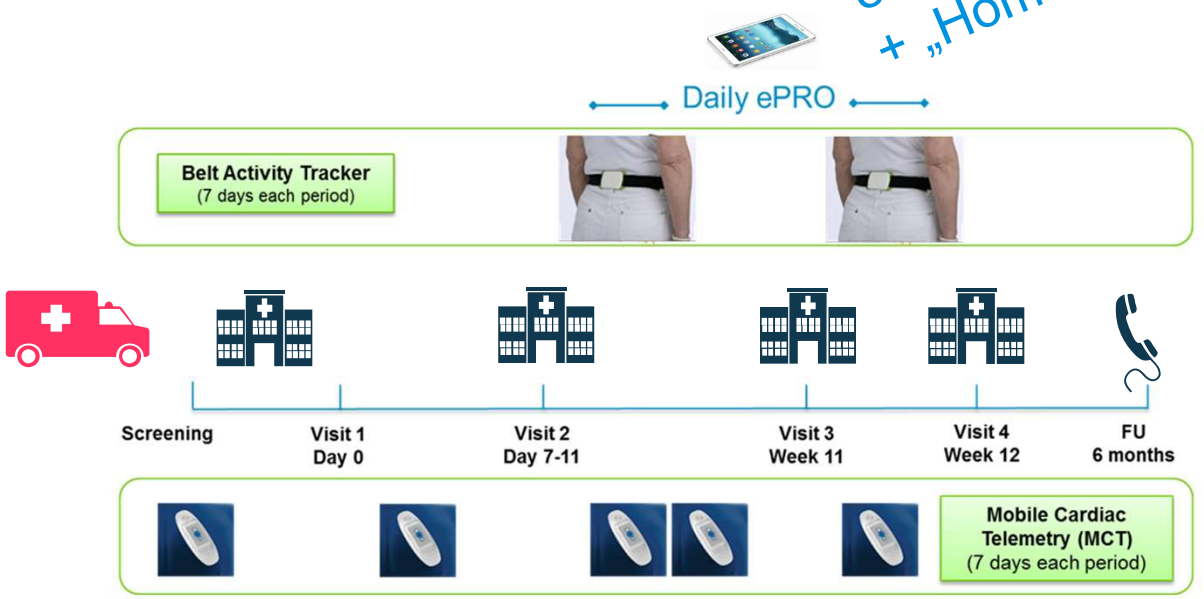
REALIsM-HF

Countries

- Germany
- Italy
- USA

Patients

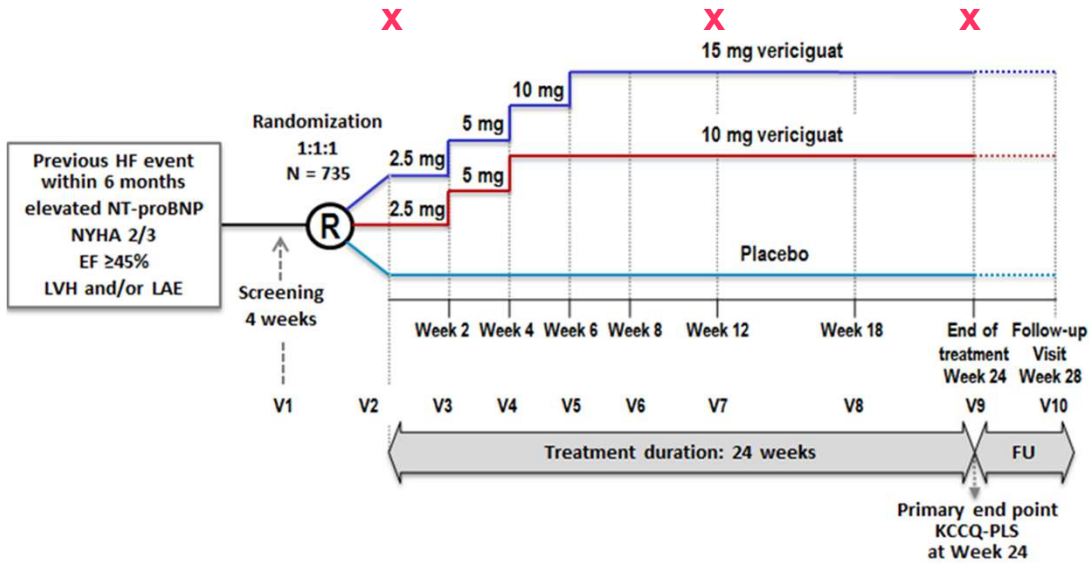
- N = 100



- Kramer F. et al 2020, Digit Biomark 2020;4:45–59
- ClinicalTrials.gov Identifier: NCT03507439

KCCQ - A primary Endpoint in Vericiguat Ph IIa Study

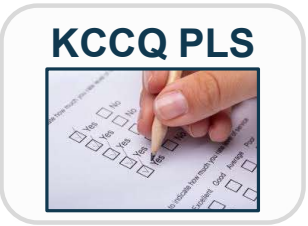
VITALITY Study: PRO, 6MWT and Accelerometer to assess Exercise Capacity



1° EP: change in **KCCQ PLS**,
2° EP: **change in the 6MWT**
from baseline to week 24, for 10 and 15 mg vericiguat arms compared to placebo.

x

+



Objective (6MWT, Accelerometer) **& Subjective** (PRO) **Measures**
complement each other to **assess Exercise Capacity**

EF, ejection fraction; FU, follow-up; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide, EF, ejection fraction; FU, follow-up; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; PLS, physical limitation score; V, Visit. KCCQ as the entire questionnaire is administered, not just the PLS domain.

“Off-the-Shelf” ePRO Applications

Example: Assessing Sleepiness in Patients with Sleep Disorders

Epworth Sleepiness Scale

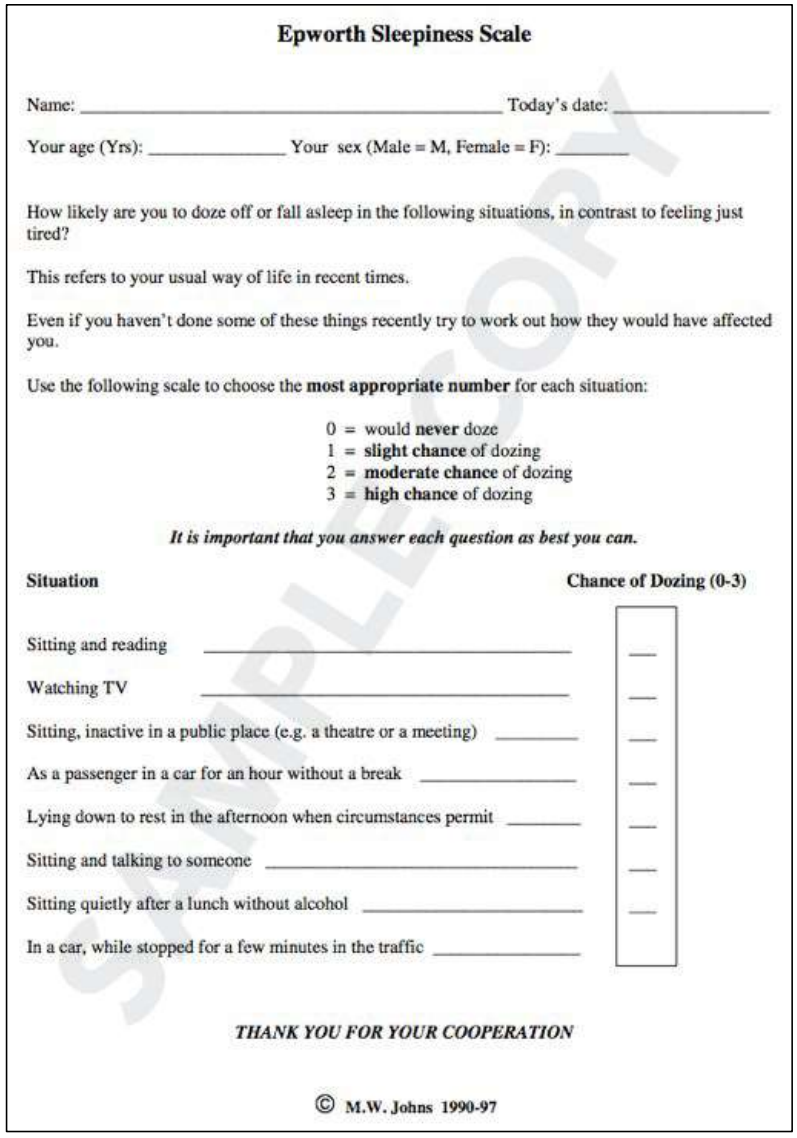
Number 1 through 8 on a scrap of paper.

The Epworth Sleepiness Scale (ESS)

- ESS for adults, assess the ‘daytime sleepiness’
- self-administered questionnaire with 8 questions; respondents are asked to rate, on a 4-point scale (0-3)

0-5 Lower Normal Daytime Sleepiness
6-10 Higher Normal Daytime Sleepiness
11-12 Mild Excessive Daytime Sleepiness
13-15 Moderate Excessive Daytime Sleepiness
16-24 Severe Excessive Daytime Sleepiness

- responsiveness of ESS scores to treatment effects has been demonstrated by their reduction after CPAP treatment for OSA (Standard Response Mean >0.8; *Chen et al, 2002; Hardinge et al, 1995*)
- ESS is subject to copyright, license is required to use the ESS



Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

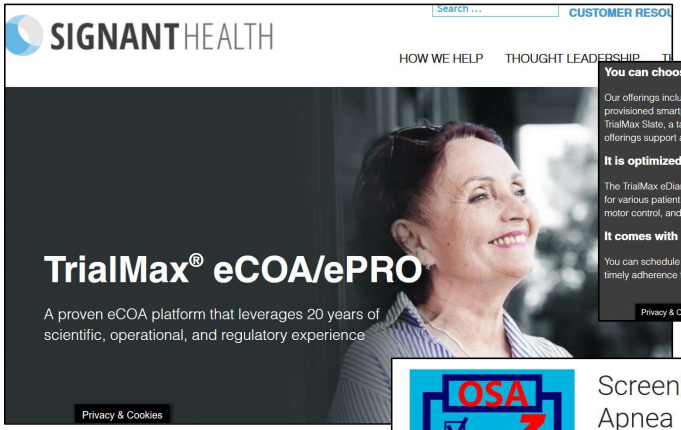
THANK YOU FOR YOUR COOPERATION

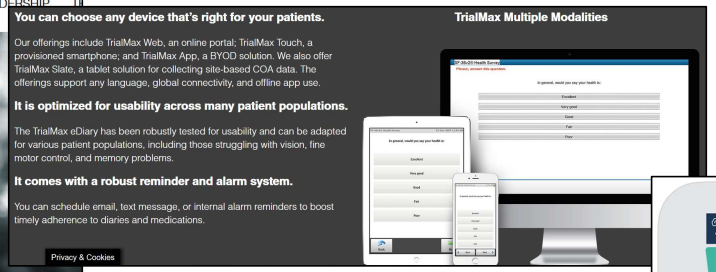
© M.W. Johns 1990-97

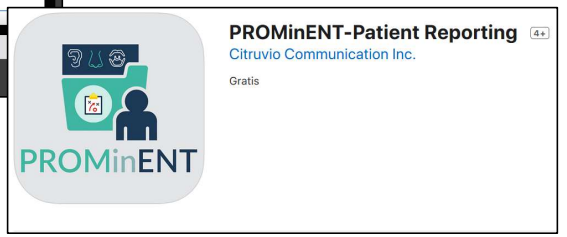
Introduce ESS App – Faster & More Convenient

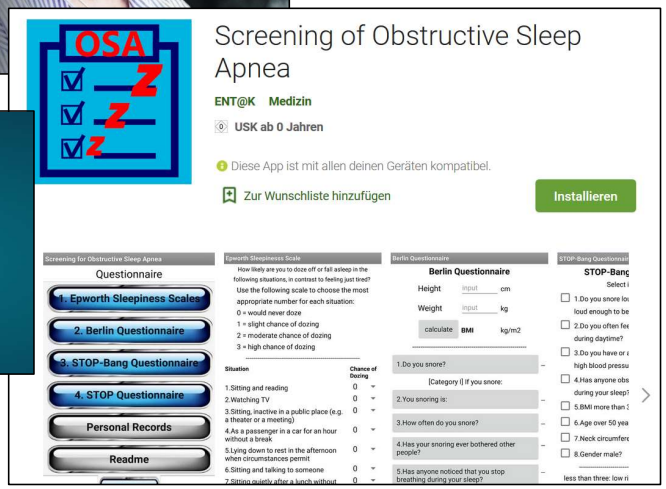
Digital solution for sequential ESS- questionnaires

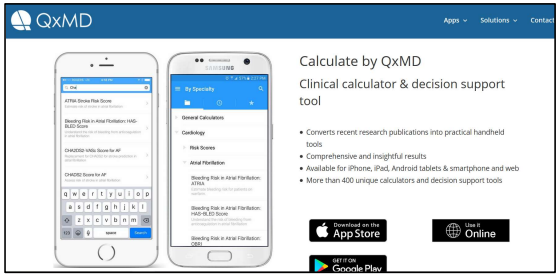
https://www.umotif.com/#platform
https://signanthealth.com/ecoa-epro/











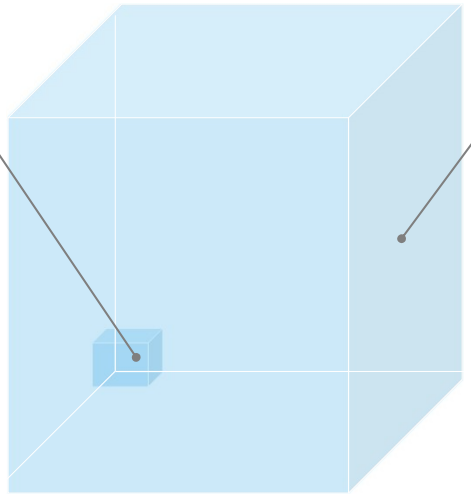
Data

Increasing Amount of Data being Collected in Clinical Studies

MAGELLAN Study

- Classical datasets
- Different time points
- ~ 8000 patients
- 52 countries

➢ **~ 2,6 Gigabyte**



REALIsM-HF

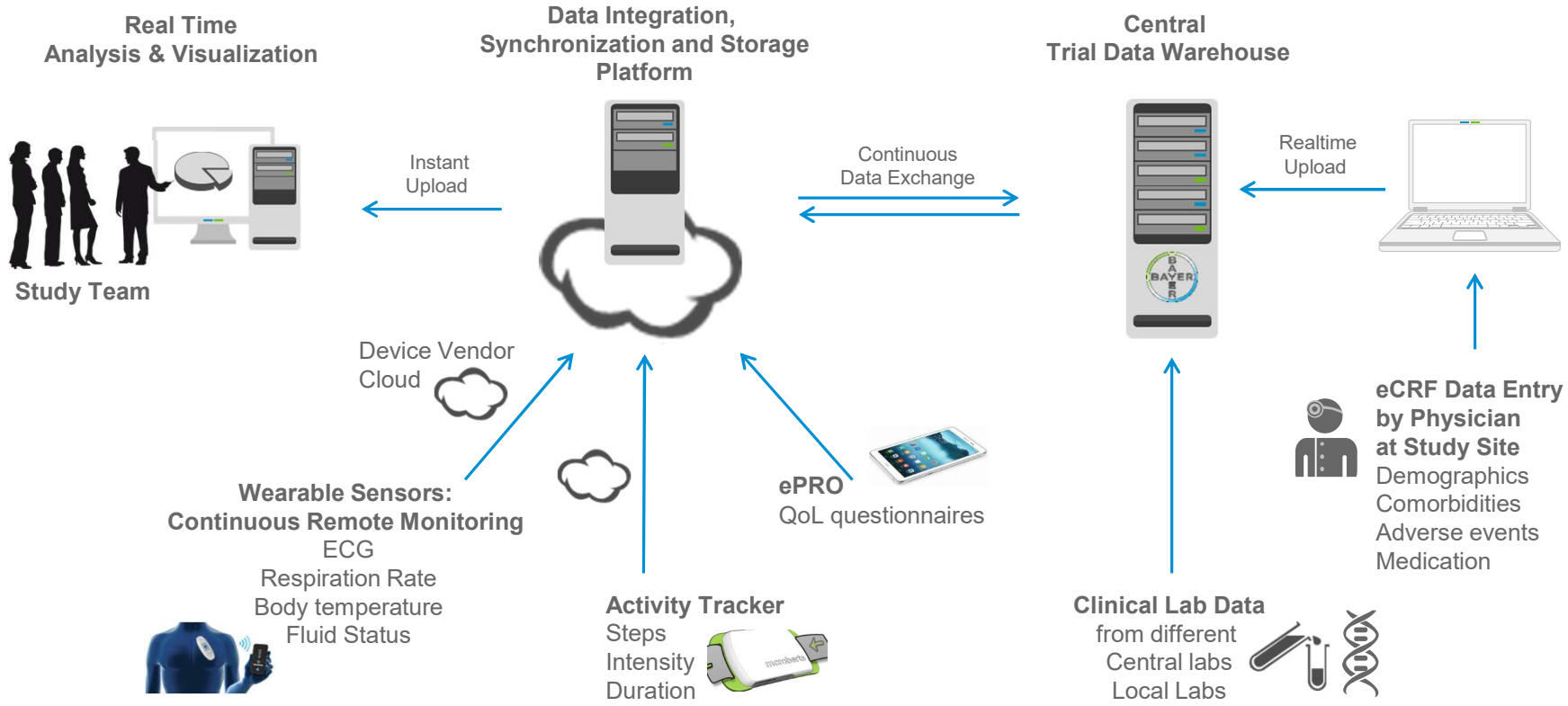
- 38 Variables / 16 parameters
- 5 Days x 5 weeks continuous monitoring
- ~ 11,5 Million records / day
- 100 Patients
- 1 Patient ~ 21 GB

➢ **~ 2,1 Terabyte (one device alone)** !

Figure developed together with Stephan Cichos, BAYER

The Challenges & How Cloud Technology Helped to Solve

Capturing, Integration, Storage, Analysis and Visualization of Data



Sarwar CMS…Kramer F…et al., 2018, Int J Cardiol.

Challenges

What Prevents Us from Using eHealth Applications More Widely in Clinical Trials?

Patient

- // Skills / Digital capabilities
- // Motivation
- // Compliance
- // Access to www

Device

- // Reliability
- // Validity
- // Clinical utility
- // Connectivity / Interfaces
- // Clinically meaningful changes

Data

- // Different sources
- // High volume
- // Different sampling rates
- // Different time zones
- // Synchronization, integration, analysis & visualization
- // Privacy & security

Assessment of **Feasibility** and the **Generation of a Data Base Layer** which allows the **Development of Standards** are essential next steps.

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MOBILISE-D

Connecting Digital Mobility Assessment to Clinical Outcomes for Regulatory and Clinical Endorsement

Five years project, 10 EFPIA Companies, 22 Universities, 2 Research Organizations, Public Bodies & Non-Profit Groups - funding of almost 50.000.000 €

Bring **digital mobility outcomes** (DMO) as a digital endpoint* to **health authority acceptance**.

(1) to **develop** a technically valid solution (**sensor**, **algorithms**, **data analytics**) for **real-world** digital mobility assessment,

(2) to **validate digital mobility outcomes in predicting clinical endpoints in** adults and pediatric patients with a variety of indications and disease stages.

(3) to **obtain key regulatory and health stakeholder approval** for digital mobility assessment

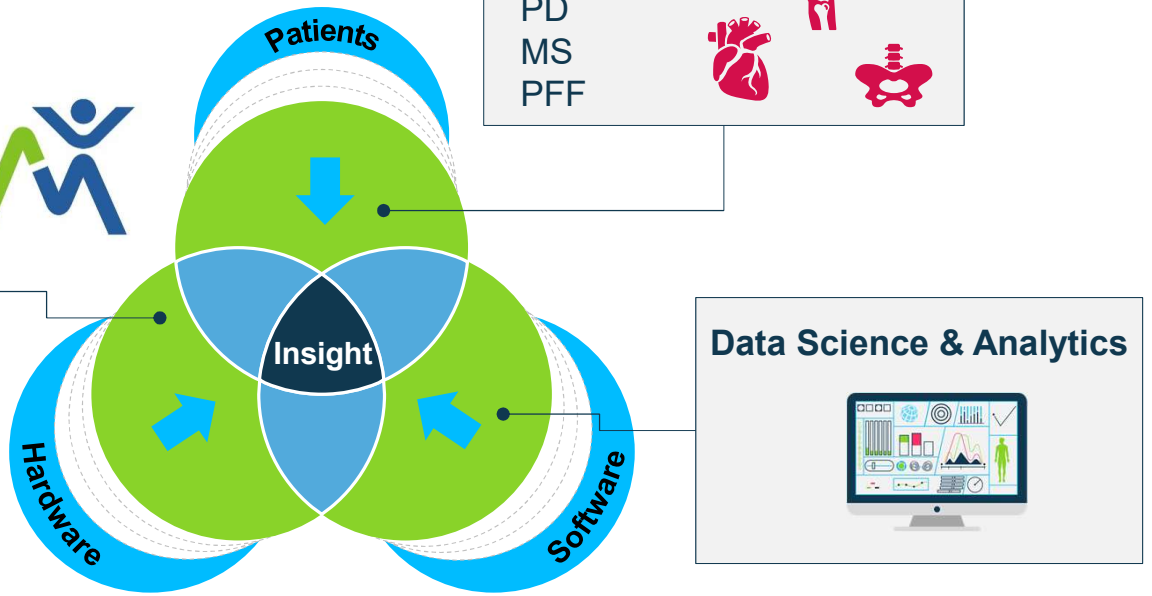
*primary / surrogate or key secondary endpoints in several indications

MOBILISE-D

Applied Technology & Indication Space

Wearable Sensors & eHealth Applications

OSPS
INDIP
3D Accelerometer
GNSS



Populations

COPD
CHF
PD
MS
PFF

Data Science & Analytics

// Complementing hardware and digital technologies **enable insight generation**

// Various patient populations covered

INDIP = INertial module with DIstance Sensors and Pressure insoles
GNSS = Global Navigation Satelite System; OSPS = Optoelectronic Stereo-Photogrammetric System

FDA`s View

Press Release April 27th 2018

- Pre-market **Digital Safety Program**

FDA Goes All Out With Digital Health Regulatory Paradigm Shift

2018-04-27

RF Today Posted 26 April 2018 | By Ana Mulero Digital health is taking the stage at the US Food and Drug Administration (FDA). From the launch of a premarket digital safety program and an internal data science incubator, to the release of drafted policies for multi-function device products and a working model for FDA's digital health Pre-Certification program, Commissioner Scott Gottlieb left audience members in a daze with a plethora of announcements at the Health Datapalooza conference Thursday. Harnessing the potential of digital health tools can lead to "making medical care truly patient-centric" and to reduce healthcare costs and risks to patients, Gottlieb argued. FDA's Internal Digital Health Incubator in support of the agency's vision to advance digital health innovation, a ...

RF Today

Posted 26 April 2018 by Ana Mulero

Digital health is taking the stage at the US Food and Drug Administration (FDA).

- Internal **Data Science Incubator**

- **Draft Policies** for multi function device products

- **Digital Health Pre-Certification** Program

FDA Development of Patient-Focused Drug Development Guidance*

FDA is developing four methodological patient-focused drug development (PFDD) guidance documents over a **period of 5 years (2017-2022**) and will be addressing methodologies, standards, and technologies

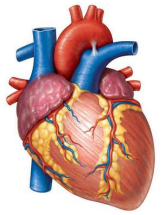
- to collect, analyze, submit COA and **patient experience data**
- to **inform medical product development and regulatory decision making**.

In support, the FDA has been hosting **public workshops**[1] to gather input from the wider community of **patients**, **patient advocates**, academic **researchers**, expert **practitioners**, **drug developers**, and other stakeholders.

* Note: FDA guidance documents do not establish legally enforceable responsibilities. Instead, guidance describes the FDA's current thinking on a topic and should be viewed as a recommendation

[1] https://www.fda.gov/drugs/development-approval-process-drugs/public-workshop-patient-focused-drug-development-guidance-4-incorporating-clinical-outcome

Relevance of (e)PRO as Approvable Endpoint in Heart Failure Drug Development



ENDPOINTS REFLECTING SYMPTOMS, FUNCTIONAL CAPACITY, AND QOL

Considering the aforementioned issues, there is a need for complementary endpoints to assess other more patient-centric outcomes reflecting daily symptom burden in HF. Both functional capacity, measured objectively, and QoL scales, which are often subjective but may be captured by validated instruments, offer such opportunities.

….from an expert consensus document based on **FDA-hosted workshop** on new clinical endpoints….

Butler J, ….Kramer F… et al. Exploring New Endpoints for Patients With Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016;9(11):e003358.

Einfluß der Digitaliserung auf Qualität & Effizienz der Versorgung

Vision & Evidenz

Effizienzpotentiale durch eHealth: Studie im Auftrag des Bundesverbands Gesundheits-IT – bvitg e.V. und der CompuGroup Medical SE

Von: Dr. Rainer Bernnat, Marcus Bauer, Holger Schmidt, Dr. Nicolai Bieber, Nick Heusser, Ralf Schönfeld

27.04.2017

1. Die Potentiale von eHealth bleiben aktuell noch weitgehend ungenutzt

2. Eine gesamthaft umgesetzte eHealth-Lösung führt zu einer signifikanten Verbesserung der medizinischen und operativen Exzellenz

3. Das (monetäre) Effizienzpotential durch eHealth im deutschen Gesundheitswesen beträgt nach Extrapolation der Studiengrundlage ca. 39 Mrd. Euro

Impact of eHealth on Quality & Efficiency in Healthcare

Vision & Evidence

70 % of Physicians use m/eHealth for therapy [1]

80 % of citizens use ≥ 1 digital Health solution / App [2]

318 572 Health-Apps became available in 2017 [3]

Worldwide Spendings of 49 Mrd US$ for digital Health Solutions in 2020 [4]

Top 20 leading digital health companies Have **not yet demonstrated** substantial **impact on disease burden or cost** in US health care system.


RESEARCH ARTICLE HEALTH INFORMATION TECHNOLOGY

HEALTH AFFAIRS > VOL. 38, NO. 1: SUBSTANCE USE, PAYMENT & MORE

Top-Funded Digital Health Companies And Their Impact On High-Burden, High-Cost Conditions

Kyan Safavi[1], Simon C. Mathews[2], David W. Bates[3], E. Ray Dorsey[4], and Adam B. Cohen[5]

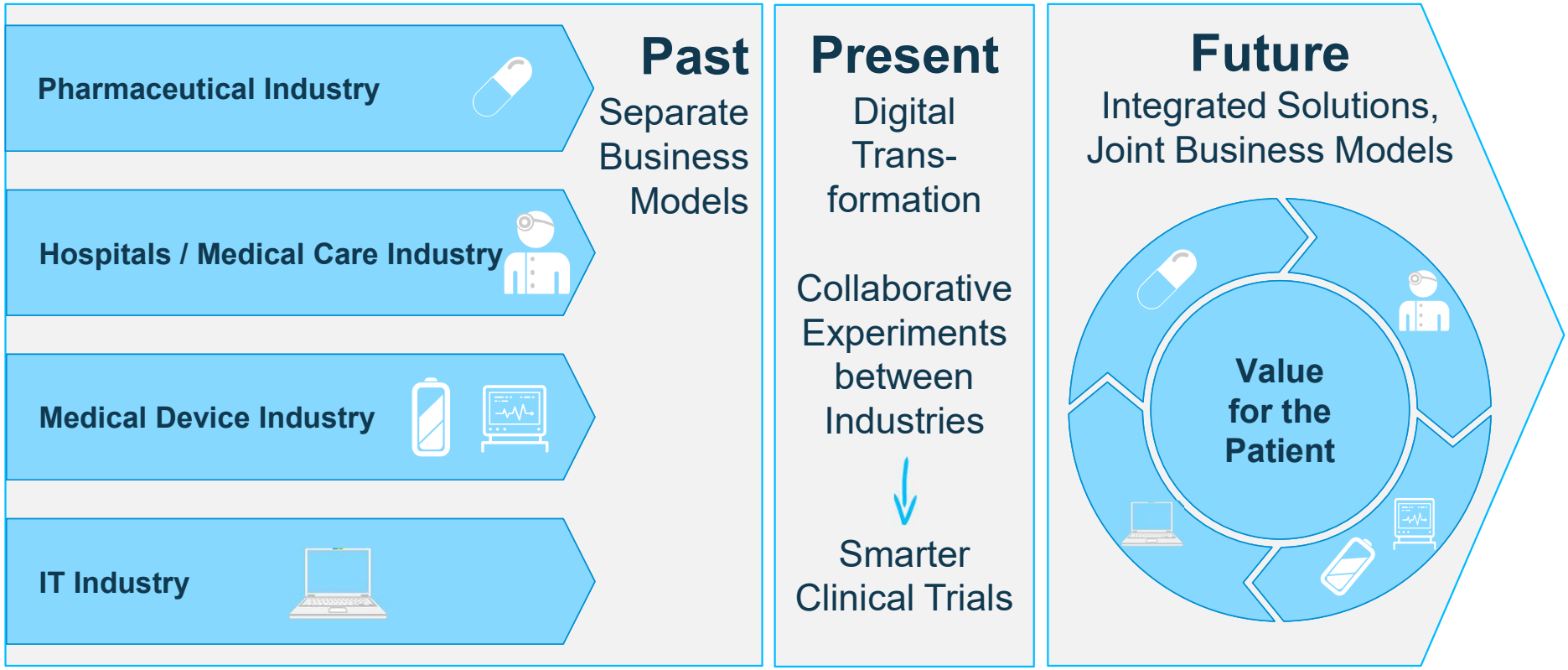
AFFILIATIONS

PUBLISHED: JANUARY 2019 Full Access https://doi.org/10.1377/hlthaff.2018.05081

[1, 2] *Poushter J., Pew Research Center, 2nd Feb 2016; HIMSS Analytics, Dec 9th 2014;*
[3] *IQVIA Commercial GmbH, Report 2018*
[4] *Health S, 22nd Sept 2015*

The Future of Drug Development & Health Care

Value-based Integrated Health Solutions to Enable Personalized Therapies



Kramer F. et al 2020, Digit Biomark 2020;4:45–59

Summary

- Emerging digital technologies induces **paradigm shifts** in drug development.
- Cardiovascular indications e.g. **Heart Failure seem to particularly benefit** from emerging technologies.
- **Activity tracking, remote continuous cardiac monitoring and ePRO** are attractive read outs for **clinical studies** and **routine patient management**.
- **Health authorities reacted to the quickly** changing environment.
- Multiple studies already performed or ongoing to **qualify eHealth application in patients**.
- **Objective and subjective measurements** should be combined in order to capture benefits of (drug) therapies
- Significant **challenges** with regard to **data storage and handling** on industry site and **digital capabilities** on the patient/physician site are to be overcome.
- **New care and disease management business** models are being developed in **cooperation between established and emerging players** in the health care arena
- Positive **impact of eHealth/mHealth on quality and efficiency of health care** is still to be clearly demonstrated.

Thank You !

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Scientific Publications:

Mobile health applications in cardiovascular research.

Sarwar CMS, Vaduganathan M, Anker SD, Coiro S, Papadimitriou L, Saltz J, Schoenfeld ER, Clark RL, Dinh W, Kramer F, Gheorghiade M, Fonarow GC, Butler J. Int J Cardiol. 2018 Oct 15;269:265-271. doi: 10.1016/j.ijcard.2018.06.039. Epub 2018 Jun 12. PMID: 29921516

Exploring New Endpoints for Patients With Heart Failure With Preserved Ejection Fraction.

Butler J, Hamo CE, Udelson JE, Pitt B, Yancy C, Shah SJ, Desvigne-Nickens P, Bernstein HS, Clark RL, Depre C, Dinh W, Hamer A, Kay-Mugford P, Kramer F, Lefkowitz M, Lewis K, Maya J, Maybaum S, Patel MJ, Pollack PS, Roessig L, Rotman S, Salsali A, Sims JJ, Senni M, Rosano G, Dunnmon P, Stockbridge N, Anker SD, Zile MR, Gheorghiade M. Circ Heart Fail. 2016 Nov;9(11):e003358. doi: 10.1161/CIRCHEARTFAILURE.116.003358. PMID: 27756791

Real-Life Multimarker Monitoring in Patients with Heart Failure: Continuous Remote Monitoring of Mobility and Patient-Reported Outcomes as Digital End Points in Future Heart-Failure Trials.

Kramer F, Butler J, Shah SJ, Jung C, Nodari S, Rosenkranz S, Senni M, Bamber L, Cichos S, Dori C, Karakoyun T, Köhler GJ, Patel K, Piraino P, Viethen T, Chennuru P, Paydar A, Sims J, Clark R, van Lummel R, Müller A, Gwaltney C, Smajlovic S, Düngen HD, Dinh W. Digit Biomark. 2020 Jun 30;4(2):45-59. doi: 10.1159/000507696. eCollection 2020 May-Aug. PMID: 33083685

BEST (**Biomarkers**, **EndpointS**, and other Tools) Resource.

FDA-NIH Biomarker Working Group. Silver Spring (MD): Food and Drug Administration (US); 2016–. PMID: 27010052

Selection of Wearable Device and ePRO Vendors:

https://www.mcroberts.nl/products/movemonitor/

https://www.physiq.com/

https://www.umotif.com/#platform

https://signanthealth.com/ecoa-epro

FDA Workshop Documents:

https://www.fda.gov/drugs/development-approval-process-drugs/public-workshop-

patient-focused-drug-development-guidance-4-incorporating-clinical-outcome