PhUSE SDE Utrecht

How Digital Devices and Apps can empower the digital transformation of your clinical studies

Welcome

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Douglas dos Santos

Toeresin Karakoyun

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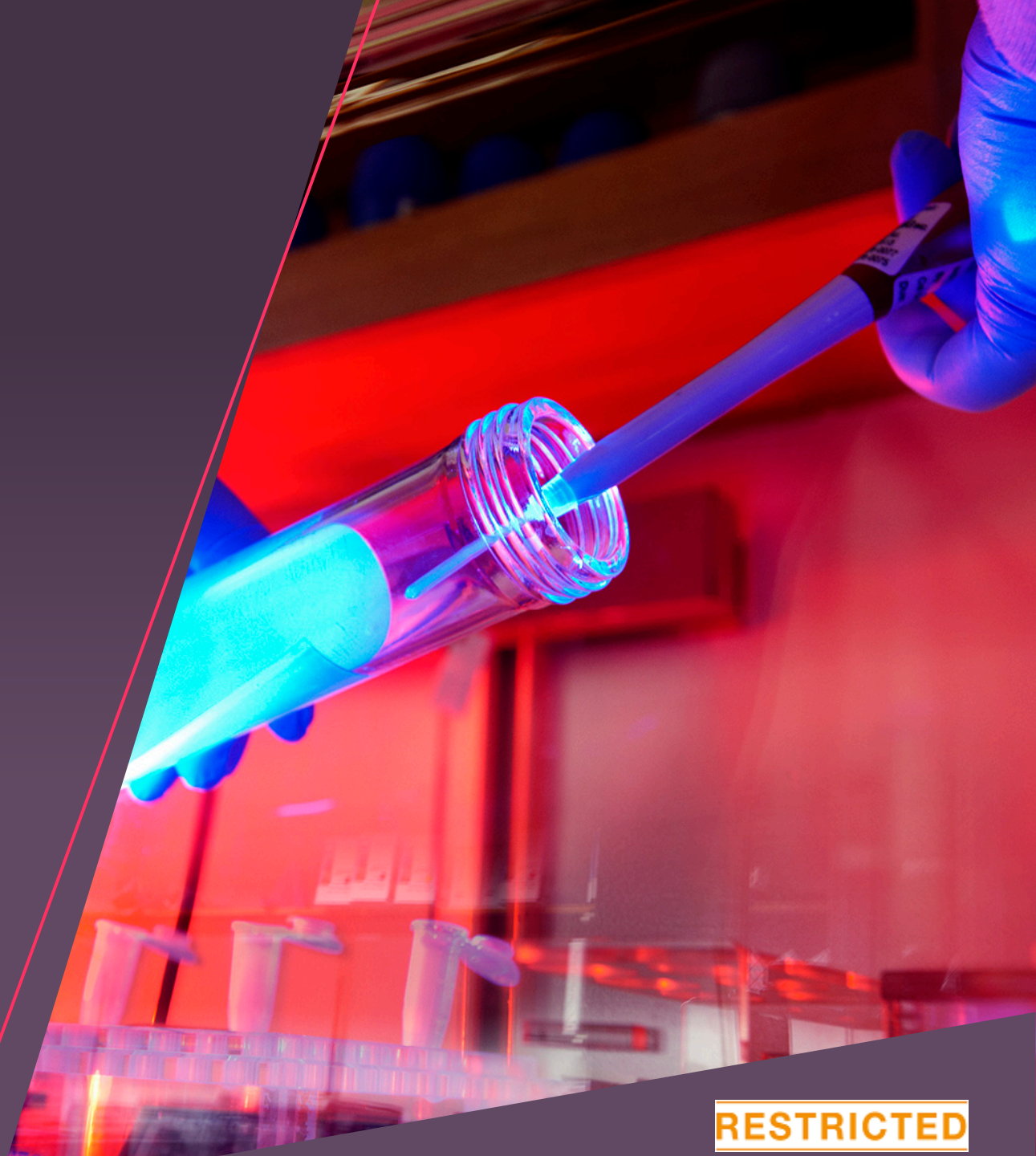
Agenda:

- Objectives & Motivation
- Reference Studies
- Challenges & Opportunities
- Soft Landing

Motivation

Why Bayer have engaged into this road?



Digital tech can both increase the efficiency of the existing site-based trial process, and allow for new ways of capturing clinical data from patients

Impact of digital technology on clinical trial process

A "Doing things better"

More efficient clinical research (site-based)

- ✓ Trial design and setup driven by data, and early 360° stakeholder input leads to **better trial setup and planning**, thereby leading to **increased overall cost efficiency**, e.g. by reducing number of amendments

- ✓ **Improving patient recruitment efficiency** by data-driven site selection and in-silico feasibility checks

- ✓ **More efficient trial execution** through improved investigator information provision and training, and improved patient trial adherence through convenient mobile information provision and tailored reminders

B "Doing better things"

FOCUS OF THIS PRESENTATION

New ways of capturing data (at the patient)

- ✓ **Real-time and continuous data capture** through medical-grade wearables resulting in improved accuracy, and **clinical utility of data**

- ✓ **Improved pattern identification** and trial result interpretation with artificial intelligence allows for identification of **novel "digital biomarkers"**, i.e. signals in the data that predict clinical outcome

- ✓ **Remote data capturing** allows to monitor patients in the convenience of their homes, leading to **improved logistics, or even "virtual trials"**

A mix of both forms is obviously possible (e.g. existing ePRO measurements, or limited use of wearables in mainly site-based trials)

Wearable Technology is Driving Changing

- Digital Health and wearable technologies are booming
  - Sensors are being packed in watches, Band-Aids, clothing and contact lenses
  - They will be embedded in smart pills that we swallow

SMART PHONES

Already monitor our activity levels, lifestyles and habits.

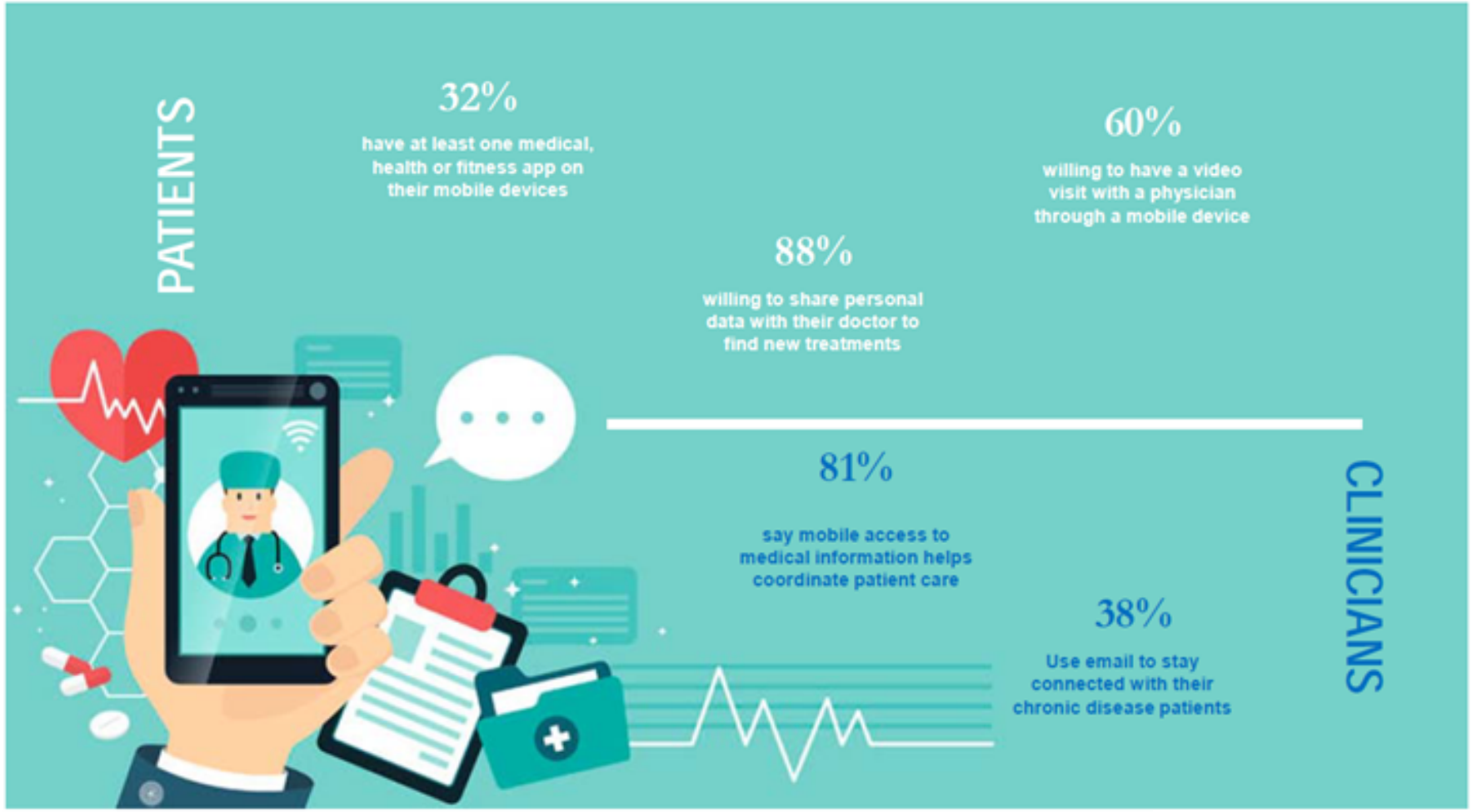
They know where we go, how quickly we move and when we sleep.

Some smartphones apps already try to judge our emotions and health based on this information

PATIENT'S LIVES ARE BEING CHANGED

Wearable Technology is Driving Changing

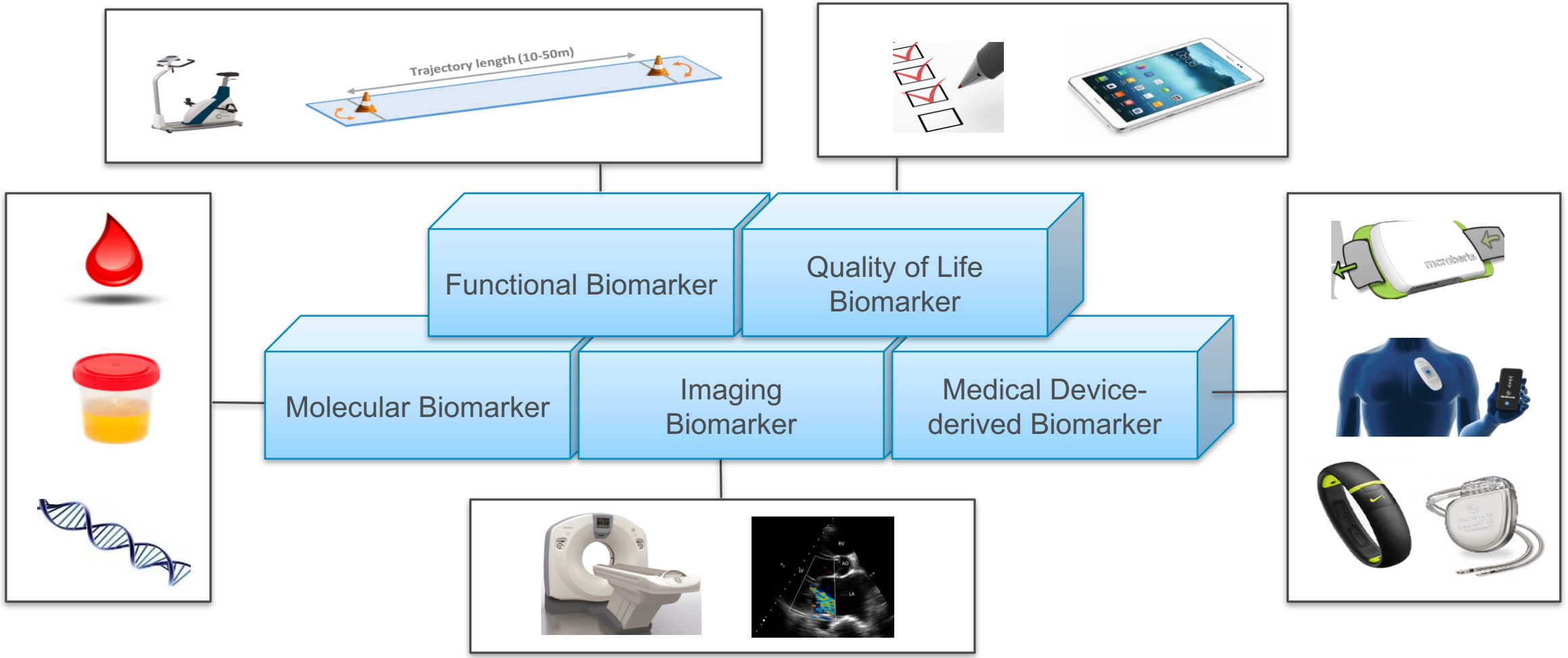
Connected Care – More mobile, more accessed, more connected.



Source: PWC – Top Health Industry Trends and Issues of 2016

What is a Digital Clinical Trial

Digital Biomarker



F. Kramer at 7th Annual World CDx Congress Europe, London, UK, March 2017
F. Kramer et al.; Heart Fail Rev. 2017 May;22(3):263-277.

Apps4Patients

Study objectives changed overtime to reflect evolving needs

Original objectives	➢ Determine the user acceptance of a smartphone app and an actigraphy device with a connected scale ➢ Determine the suitability of these instruments for inclusion in a clinical trial of patients with hemophilia planned for 2018
Final objectives	➢ Assess the usability and user acceptance of a smartphone app and an actigraphy device (with or without a wireless hub) with a connected scale. ➢ Determine the suitability of these instruments for inclusion in a clinical trial of patients with hemophilia planned for 2018 and the implications for study site implementation

Apps4Patients

Study design and eligibility criteria

STUDY DESIGN
OVERVIEW

- Single-arm pilot study (3 phases)
- IRB approved Pro00021564
- n=20 participants recruited from the general population via convenience sampling
- 3-month study duration with 4 in-person visits and 1 phone visit
- Participants instructed to use SureSource Engage and connected devices

ELIGIBILITY CRITERIA
FOR STUDY POPULATION

- Aged 18-63 years
- Participated in a concluded clinical trial during the past 2 years
- Uses a compatible Apple iOS or Samsung Android (S5 or higher) smart phone
- Willing to follow study procedures for 3 months
- Able to read, write, and speak in English

Apps4Patients

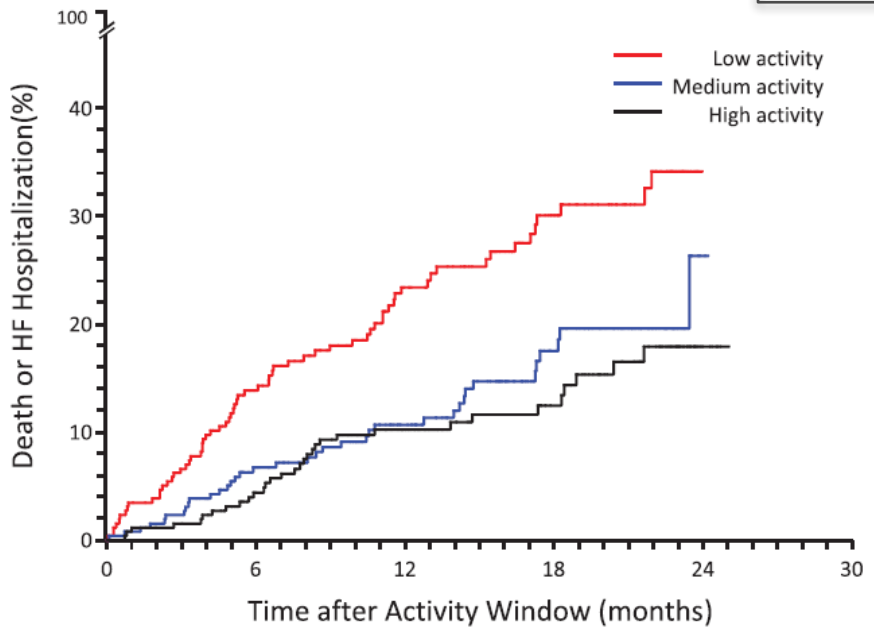
Devices Used

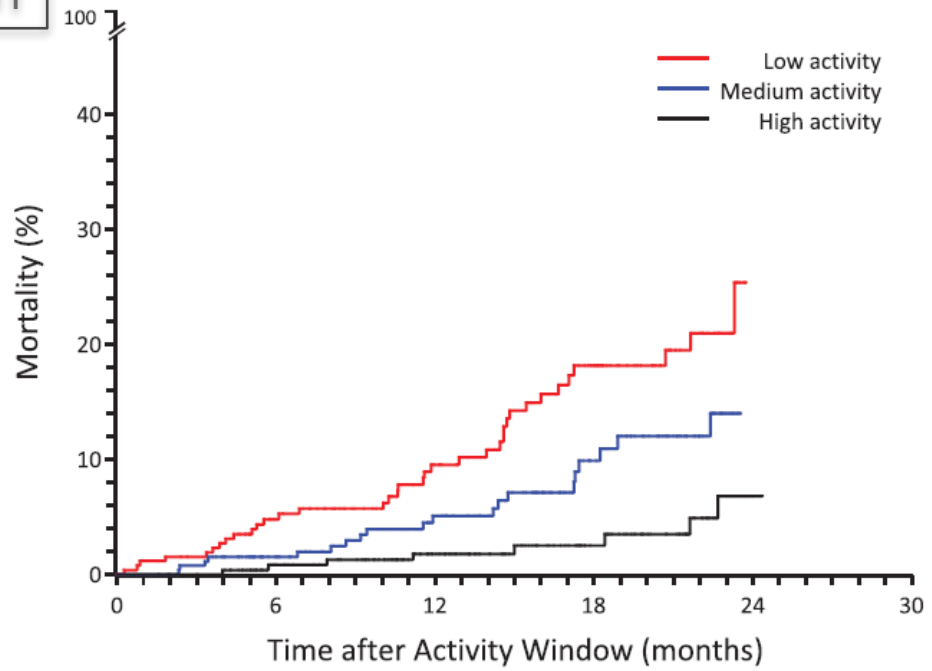
SureSource Engage by Clinical Ink	➢ Mobile application (Android and iOS device compatible) designed to improve experience of participants in a clinical trial. Participants were instructed to download and use a study-specific version of this application.
ActiGraph GRT9X Link	➢ The ActiGraph Link is a small wristwatch like device that measures indicators of the wearer's activity and sleep patterns. ➢ Participants will put on the ActiGraph Link and wear it for 8 weeks in total - 4 weeks during Phase I and 4 weeks during Phase II. ➢ During Phase I, participants were instructed not to remove the ActiGraph Link until Visit 2. During Phase II, participants were instructed not to remove the ActiGraph Link until Visit 4. Participants were instructed to remove device only for charging as needed, as well as showering/bathing/swimming.
A&D Medical Precision Health Scale	➢ Participants were instructed to take their weight weekly using this Bluetooth-connected scale.
CentrePoint Data Hub	➢ In Phase II, half of participants were instructed to use the CentrePoint Data Hub from ActiGraph, which transmits data captured by the ActiGraph GT9X Link devices to the CentrePoint cloud software platform.

Realism HF

Real Life Multimarker Monitoring in Patients with Heart Failure

N=781





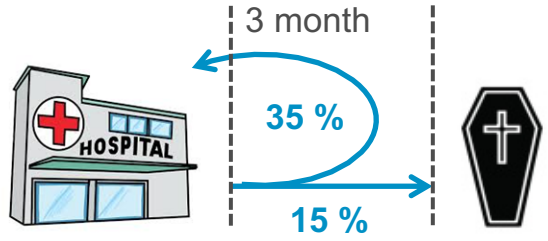
Physical Activity Predicts Patient Outcome in Chronic Heart Failure

Realism HF

Real Life Multimarker Monitoring in Patients with Heart Failure

Challenge

- 50% of heart failure (HF) = HFpEF
- High unmet medical need and low success in drug R&D
- Exercise intolerance is the cardinal symptom of HFpEF [1]
- Complementary endpoints to hospitalization / death targeting patient centric outcomes to be considered for drug approval [2]



BAYER`s Actions:

Hosted Workshop Nov `15[2] Nov `16

complement „traditional“ endpoints“

- Physical activity
- PRO

\+ Partner

Quali-fication

REALIsM-HF Registry

- Feasibility and validation
- Real life & real time data

Wearable Devices and PRO provide Real Life Patient Centric Endpoints

- ➢ Enables development in indications where other companies failed with traditional approach
- ➢ Precision medicine: high-definition view of our patients vs. “one size fits all trial & error medicine”

PRO = Patient Reported Outcome
HFpEF = Heart failure with preserved ejection fraction

[1]Upadhya *et al.*, Journal of Geriatric Cardiology 2015
[2]FDA workshop Nov 2015, publication in press

Realism HF

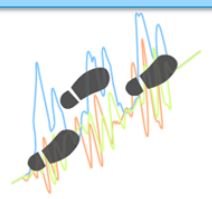
Real Life Multimarker Monitoring in Patients with Heart Failure

MoveMonitor

Types of activity
Incl. sleeping patterns

Transition between type of activity

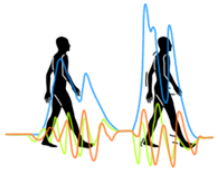
STEPS



Movement duration

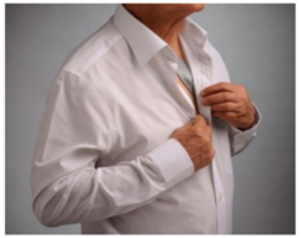
Movement frequency

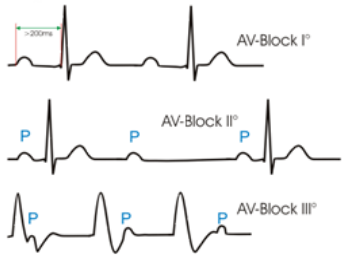
Movement intensity



Heart failure patch

Safety:
ECG, Afib

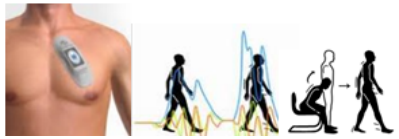




Multimarker Monitoring (24/7)

- ECG
- Physical activity
- Fluid status
- Heart rate variability
- Respiratory rate
- Posture

Efficacy
Response to therapy



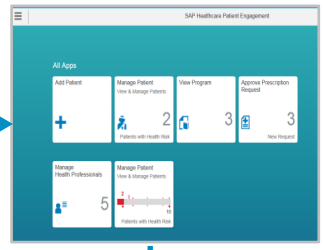
Digital device based biomarkers reflects longitudinal changes over time under real life conditions complementing traditional spot-check assessments

Realism HF

Architecture

Legacy data flow

KCCQ,
Daily,
weekly
questionaire data



Health Engagement Platform (HEP)

Researcher's app (Fiori App)

- enables the site to onboard / offboard subjects (via a portal)
- site can control the progress of the study

HR, HR-variability, AF burden, Arrhythmia, Respiratory rate, Transcutaneous thoracic Impedance (fluid status), Posture, Physical activity (duration and intensity)

Physical activity,
Energy expenditure,
Sleep movements

Connected Health Platform (CHP)

Medical Research Insights

Transfer of Sensor- & QS Data

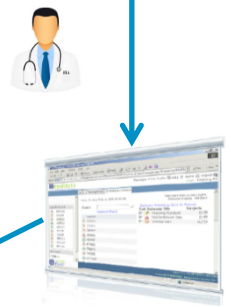
Transfer clinical data (Data Model 1) into CHP to connect with „SAP Medical Research Insights"

- Mapping to SDTM+ and ADaM
- Generating tables, listings & figures

SWAN

LSH

Site captures data



Download RAVE eCRF data

eCRF data entry by site
(e.g. Demographics, AEs, MHs, Visit data)

Data transfer

External lab data

Molecular Biomarker

NTproBNP, GDF15, hs-TNT, IGFBP7, hs-Copeptin, sST2, Gal3

Challenges & Opportunities

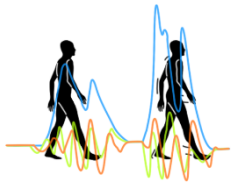
Challenges & Opportunities

”RealismHF as example”

It is hypothesized, that subjective items derived from ePRO in combination with an (objective) device based activity monitoring, captures all relevant dimensions of physical activity in patients with HFpEF, will help test efficacy of HF drug candidates and may even serve as surrogate EP for drug approval.

1. Physical activity

- Type of activity
- Transitions between type of activity
- Steps
- Movement duration
- Movement frequency
- Movement intensity



2. Energy Expenditure

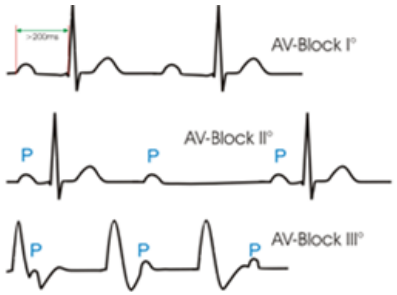
- Basal metabolic rate (BMR)
- Diet Induced Thermo Genesis (DIT)
- Activity-Related Energy Expenditure (AEE)
- Total Energy Expenditure (TEE)
- Physical Activity Ratio (PAR)
- Physical Activity Level (PAL)

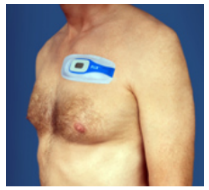
3. Sleep Movements

- Going Out of Bed
- Night's Rest Detection
- Postures
- Movement Time
- Movement Intensity
- Transitions

4. ECG parameter:

- Derived parameters like heart rate, HRV, AF burden, arrhythmias etc.
- Respiratory rate
- Transcutaneous thoracic impedance = fFuid status
- Physical activity (duration and intensity), Posture





Challenges & Opportunities

How to choose the right device / interpret different data dimensions?"

….and which endpoints should be analyzed regarding the research question of the trial?

	Aggregated data device 1			Raw data device 2	
Variable	**Details**	**Unit**	**Sampling (processed)**	**Unit**	**Sampling**
duration of use	total duration	hhmmss	1 week, 1 day		
activity duration	if > mG threshold	sec	5 min	acceleration	~30 Hz
activity intensity	max, mean	%	5 min	on x-, y-, z-axis	
posture daily	mean	degrees	5 min	qualitative assessment	~1 Hz
respiration rate	min, mean, max	breaths/min	15 min	breaths/min	0.25 Hz
fluid status	min, mean, max	ohms	15 min	?	0.25 Hz
HR	min, mean, max	beats/min	1 day, 1 hour, 5 min	beats/min	0.25 Hz
HR variability	SDANN	ms	1 day		
steps				cumulative count	~1 Hz
body temperature				celsius degree	0.25 Hz

Sampled on Hertz-scale

Challenges & Opportunities

”Challenges of aggregrations & correlations”

Current data structure

Date & Time	HR (raw)
18NOV2016 07:00:03.885	84
18NOV2016 07:00:07.944	84
18NOV2016 07:00:12.008	81
18NOV2016 07:00:16.071	81
18NOV2016 07:00:20.135	83
18NOV2016 07:00:24.190	85
18NOV2016 07:00:28.253	89
18NOV2016 07:00:32.317	85
18NOV2016 07:00:36.374	85
18NOV2016 07:00:40.436	85
18NOV2016 07:00:44.499	83

Possible target data structure

Interval Start	Interval Stop	HR (mean)
18NOV2016 07:00	18NOV2016 07:05	83
18NOV2016 07:05	18NOV2016 07:10	81
18NOV2016 07:10	18NOV2016 07:15	85
18NOV2016 07:15	18NOV2016 07:20	82

- Who can aggregate the data according to given specifications?
- Probably need to consider noise filtering, etc. but how to reduce noise and variability and in what extend it will be accepted by regulatory authorities e.g. FDA?
- How to correlate activity data / events etc. with ECG sensor data, considering that measurement intervals are not the same, due to its devices „nature“?
- What about missing values (Null = no signal) ?

Challenges & Opportunities

”Re-thinking Data Privacy”

- ✓ EPRO Device lock (time to lock screen, re-identification process)
- ✓ What data will be transmitted? (Geolocation, IP ?)
- ✓ Retention time of data?
- ✓ Will you require an email-address to onboard a patient in your mobile application?
- ✓ Where will the data be stored? China, USA, Germany? Any regulatory / legal requirements to be followed?

Challenges & Opportunities

Our four dimensions

Patient Engagement

- Appropriate Training
- Usability & User Acceptance to Devices
- Long time to enroll patients
- Communication via App is key to increase engagement

Data

- Find and interpret rich data sources.
- Manage large amounts of data despite hardware, software, bandwidth constraints
- Merge data sources
- Ensure consistency of data sets.
- Create visualization to understand the data
- build mathematical models using the data
- present and communicate the data insights

Technology

- Solution Architecture vs. Enterprise Architecture
- Device Management (Installation of app on devices)
- BYOD or Provisioning
- Cloud Assessment
- App – in-house development or outsourcing
- Contract

Legal / Ethical

- EPRO Device lock (time to lock screen, re-identification process)
- What data will be transmitted?
- Retention time of data?
- Will you require an e-mail address to onboard patient in your mobile application?
- Germany? Any Regulatory /legal requirement to be followed?

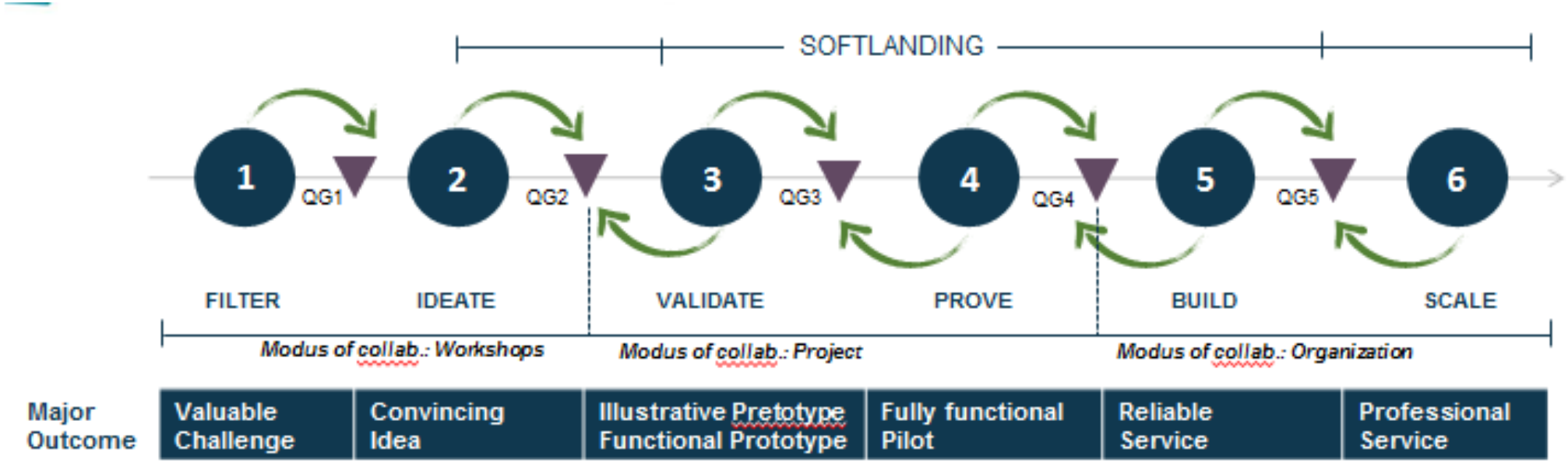
Softlanding

Ideas are Cheap

Landing them softly is a skill

Developing Stages

Terminology needs to be aligned



Conclusions

Conclusion

Paradigm Shift

Wearable

Parameters / Findings

- ECG
- Activity
- Posture
- Impedance
- HR Variability
- AF-Burden
- Respiration Rate
- Body Temp.

Monitoring Center

QC & Alerts
24 hrs / 365 days

Site / Sponsor

Realtime

- Safety
- Efficacy
- Monitoring

Remote continuous monitoring of vital signs, activity and cardiac function allows **almost real-time monitoring of safety and efficacy** in clinical studies.

Conclusion


CLOTHES? WITH ALL THIS WEARABLE TECHNOLOGY I DON'T HAVE ROOM FOR CLOTHES!!!
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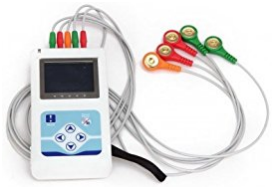
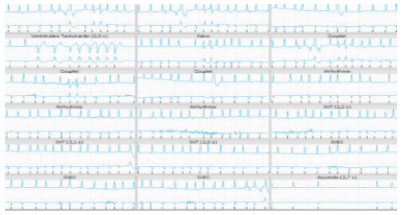
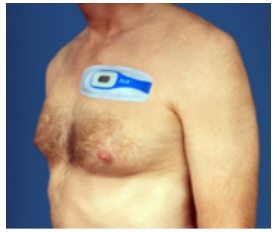
What is a digital clinical trial?

”Paradigm shift”

Traditional assessments versus new digital ways capturing data







What is a digital clinical trial?

”Paradigm shift”

Better Profile
Drug Candidates

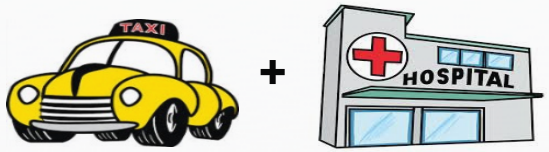
Intermittant

Continuous

Monitoring

Reduce Patient`s Burden

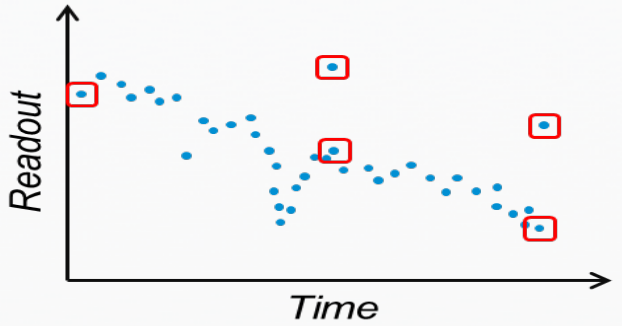
In-Hospital



Remote

Monitoring

Reduce Costs
Save Time



Reliably Capture Disease Course

Devices will induce **Paradigm Shift** and enable **Highly Innovative Trial Designs**

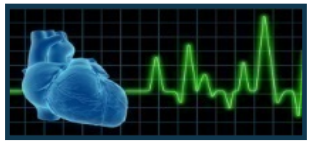
What is a digital clinical trial?

"Example from RealismHF: ECG Patch"

Wearable

Parameters / Findings

- ECG
- Activity
- Posture
- Impedance
- HR Variability
- AF-Burden
- Respiration Rate
- Body Temp.



Monitoring Center

QC & Alerts
24 hrs / 365 days

Site / Sponsor

Realtime

- Safety
- Efficacy
- Monitoring

Remote continuous monitoring of vital signs, activity and cardiac function allows **almost real-time monitoring of safety and efficacy** in clinical studies.

Digital clinical trial buzzwords

"IoT – Internet of things"

- IoT enable healthcare professionals to monitor patients more effectively and use the data captured from the devices to assess any adverse events.
- IoT deliver insights from patients in between visits to clinical trial sites, while reducing costs along the way.
- IoT provide flexible opportunities for patients to engage with clinicians and vice versa, with a goal of better self-care.

IoT can:

+ be cost efficient

+ reduce Errors

+ improve Outcomes of Treatment

+ improve Disease Management

+ inhance Patient Experience