PROF DR FREIMUT SCHLIESS

Digital Tools for Narrowing the Gap between Clinical Research and Clinical Care

Freimut Schliess,[a] Cindy Dopierala,[b] Thibault Parmentier,[b] Stéphanie de Marco,[b] Ulrich Froriep,[c] Malte Jacobsen,[d] Katharina Schütt,[d] Constance Stegbauer,[e] Anna Hentschel,[e] Julia Hoxha,[f] Francois Recorbet,[g] Björn Broge,[e] Joachim Szecsenyi,[e] Marc Lemaire,[b] Dirk Müller-Wieland,[d] Nikolaus Marx,[d] Philippe Cinquin,[h] Charles Clemens Ruling,[i] Leona Plum-Mörschel,[j] Sascha Heckermann,[a] Lutz Heinemann,[a] Tim Heise[a]

[a]Profil GmbH, [b]SentinHealth SAS, [c]Fraunhofer ITEM, [d]RWTH Aachen, [e]aQua GmbH, [f]Zana Technologies GmbH, [g]PrYv S.A., [h]Université Grenoble Alpes, [i]Grenoble Ecole de Management, [j]Profil Mainz GmbH & Co. KG

4th International QI Forum • June 2020
a pre-ISQua conference

4TH INTERNATIONAL QI FORUM HEIDELBERG

Digitalization & Quality Improvement:
Challenges for Better Health Outcomes

@evaplanHealth #QIForum2020

profil
ANSWERS FOR DIABETES

eit Health

EIT Health is supported by the EIT, a body of the European Union

Digital Tools for Narrowing the Gap between Clinical Research & Clinical Care

Prof. Dr. Freimut Schliess

Director Science & Innovation
Profil Institut für Stoffwechselforschung GmbH (www.profil.com)
Neuss · Germany

4th International QI Forum · 11-12 June 2020 · Heidelberg · Germany · @evaplanHealth #QIForum2020

www.profil.com

www.profil.com

- >400 employees
- Huge recruitment capabilities
- 2 inhouse CRUs >80 test beds
- Data Management & Statistics
- Regulatory Affairs

Profil is a full service CRO performing early phase clinical trials with a strong focus on obesity, (pre)diabetes, and diabetes complications

- Pharmacology
- GMP-certified pharmacy
- Medical Technology
- Cardiovascular Research
- Metabolic ward
- Medical device development

www.profil.com

clamp.art

- Inhouse development and **proprietary technology** of Profil
- CE Mark certified **class IIb** medical device
- **Central remote monitoring** of clinical experiments
- **Parallel & quantitative assessment** of
  - Insulin (analogues) time-action profiles
  - Insulin sensitivity
  - Beta cell function
  - Endogenous glucose production
  - CGM systems

Heise T. et al. 2016, **Diabetes Obes. Metab.** 18(19):962-972
Benesch C. et al. 2015, **J. Diabetes Sci. Technol.** 9(4):297-800.

profil
ANSWERS FOR DIABETES

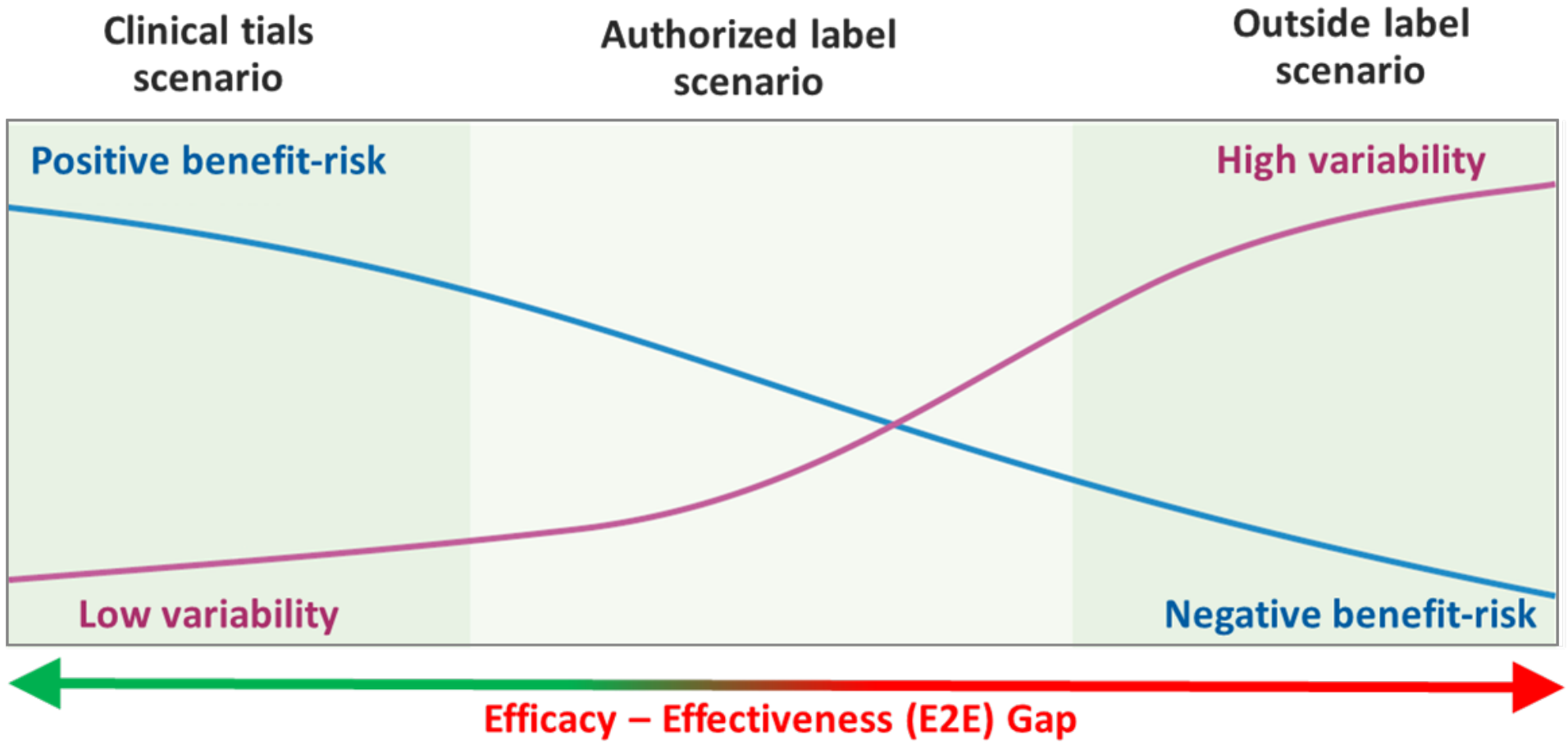
Agenda

- The efficacy-to-effectiveness (E2E) gap
- Lack of data problem in clinical research and clinical care
- Implementing digital tools for narrowing the E2E gap: it's all about collaboration
  - EIT Health public-private-partnership
  - Example: CLOSE
  - Example: RealWorld4Clinic
  - Example: iPDM-GO
- Concluding remarks

The efficacy-to-effectiveness (E2E) gap

- The efficacy-to-effectiveness (E2E) gap
- Lack of data problem in clinical research and clinical care
- Implementing digital tools for narrowing the E2E gap: it's all about collaboration
  - EIT Health public-private-partnership
  - Example: CLOSE
  - Example: RealWorld4Clinic
  - Example: iPDM-GO
- Concluding remarks

The efficacy-to-effectiveness (E2E) gap



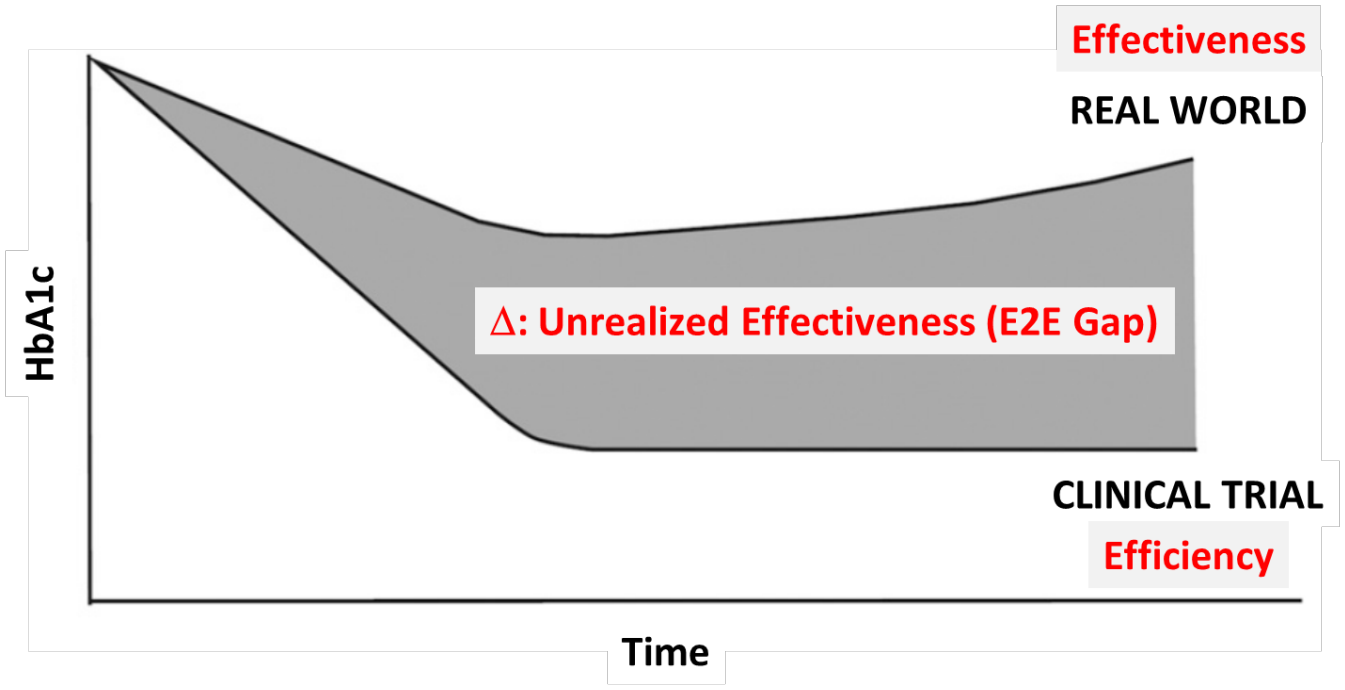
Selker, H.P., Eichler, H.G. et al., **Clin. Pharmacol. Ther.** 105(4):867-866, 2019
Eichler, H.G. et al. **Nat. Rev. Drug Discov.** 10(7):495-506, 2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

profil
ANSWERS FOR DIABETES

The efficacy-to-effectiveness (E2E) gap

Glycemic control quality in diabetes



Real-World Treatment Effect Modifiers

50% **Physicians**

- Lack of time
- Reactive care
- Generalizing guidelines

30% **Patients**

- Low health literacy
- Frailty, co-morbid conditions
- Polypharmacy

20% **System**

- Fragmentation of healthcare
- Fee for service
- No disease registry

- Edelman, S.V. & Polonski, W.H. 2017, **Diabetes Care** 40:1425-1432
- Eichler, H.G. et al. 2011, **Nat. Rev. Dug Disov.** 10:495-506
- O'Connor, P.J. et al. 2005, **Advancves in Patient Safety,** Rockville

profil
ANSWERS FOR DIABETES

Real-world data for better decision making

- The efficacy-to-effectiveness (E2E) gap
- Lack of data problem in clinical research and clinical care
- Implementing digital tools for narrowing the E2E gap: it's all about collaboration
  - Example: CLOSE
  - Example: RealWorld4Clinic
  - Example: iPDM-GO
- Concluding remarks

We have a lack of data problem

Clinical research

low predictive value of clinical trials

Average Costs: 1.5B €

Average Time: 15 years

Success rate: 1 in 10

Failure rate: 50 % in phase III

Post-marketing withdrawal: 462

- Liu, C.Y et al. A novel approach to drug development in heart failure: towards personalized medicine. Can. J. Cardiol. 30(3):288-295
- Selker, H.P., Eichler, H.G. et al. Efficacy and Effectiveness too trials: clinical trial designs to generate evidence on efficacy and on effectiveness in wide practice, Clin. Pharmacol. Ther. 105(4):857-888, 2019
- Lo, C. Conting the costs of failure in drug development. Pharmaceutical Technology. June 19, 2017
- European Commission & OECD: Health at a glance report. November 22, 2018
- Onakpoya, I.J et al. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Medicine 14:10, 2016

profil
ANSWERS FOR DIABETES

Real-world data for better decision making

Clinical research

earlier prediction of late phase & real-world outcomes

- Continuous gathering and **AI-powered exploitation of real-world data** on
  - Safety & tolerability
  - Pharmacodynamic efficiency
  - Patient-reported outcomes
- **Clinical CRO**
  - Data Management & Statistics integrated, fully compliant **Data Sciences Services**

- https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

profil
ANSWERS FOR DIABETES

We have a lack of data problem

Clinical care	**reactive crisis management**

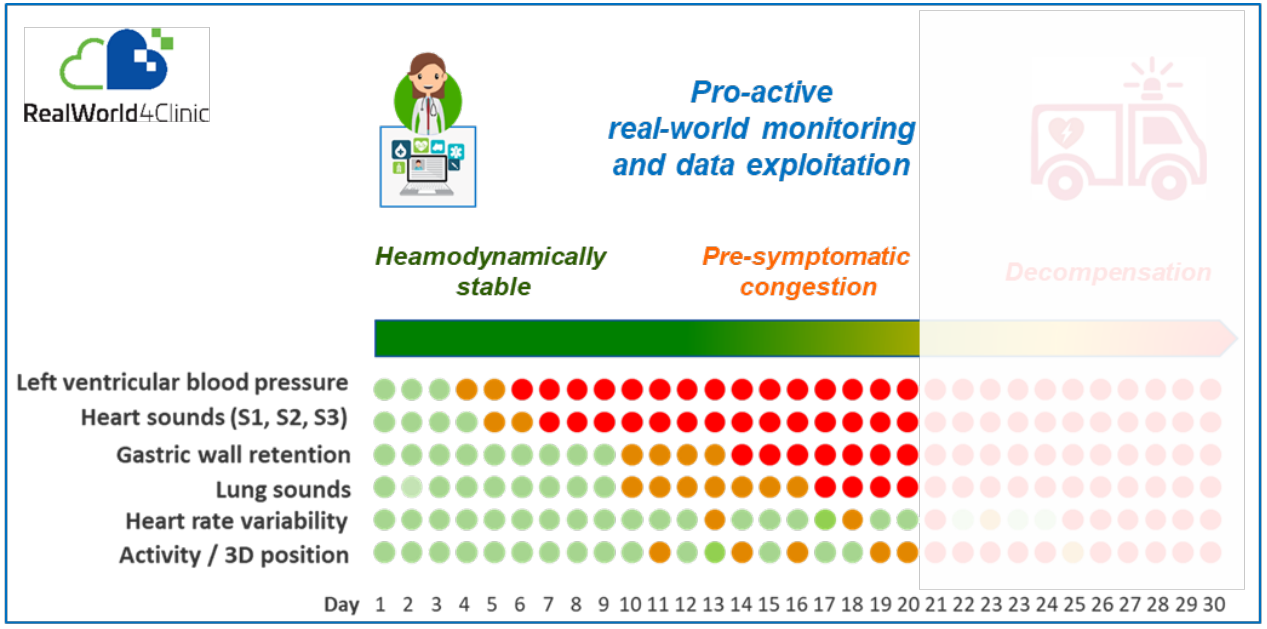
- Emergency hospitalization in Heart Failure **46 Bio €** (US & EU)
- Within 5 years up to **50%** of people with diabetes hospitalized for Heart Failure decompensation **die**

- Liu, C.Y et al. A novel approach to drug development in heart failure: towards personalized medicine. Can. J. Cardiol. 30(3):288-295
- European Society of Cardiology (Auriccio, A. et al., Eur. J. Heart Failure 12(12):1363-1371, 2010)
- CDC Centers of Disease Control and Prevention, May 16, 2019
- Ofstad, et al. 2013; Heart Fail. Rev. 23(3):303-323.
- Maggioni, A.P. et al. Epidemiology of heart failure in Europe. Heart Fail. Clin. 11(4):625-535, 2015
- European Commission & OECD: Health at a glance report. November 22, 2018

profil
ANSWERS FOR DIABETES

Real-world data for better decision making

Clinical care **proactive crisis prevention**



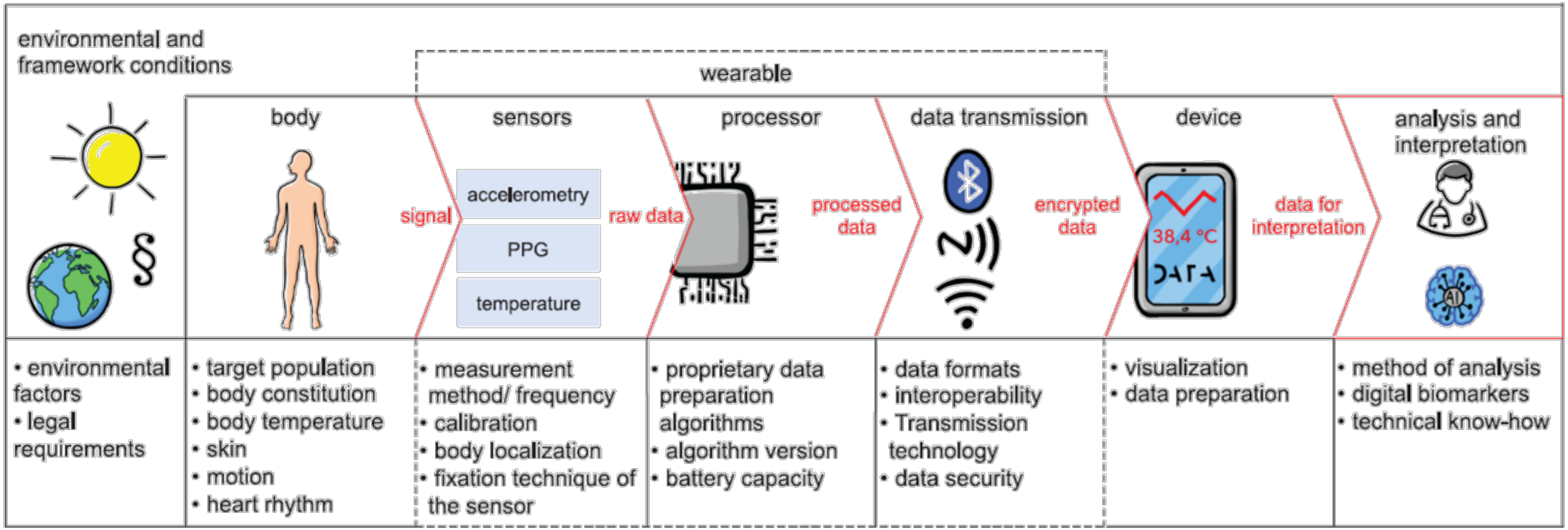
- Gathering and **AI-powered exploitation of real-world data** in **tele-cardiology** on
  - Cardio-respiratory health
  - Locomotor activity
  - Patient-reported outcomes
- **Heart failure patient journey**
  - Less outpatient visits
  - Fewer days in the hospital

- https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

profil
ANSWERS FOR DIABETES

Wearables in clinical research & clinical care

Non-invasive monitoring of vital signs with wearables



- Jacobsen, M. et al. **J. Diabetes Sci. Technol.** 2020 Feb 17;1932296820904947. doi: 10.1177/1932296820904947. Online ahead of print
- Affini Dicenzo, T. & Schliess, F. **Open Acess Government** 2020, https://www.openaccessgovernment.org/clinical-trials-and-clinical-care/85894/

profil
ANSWERS FOR DIABETES

Wearables in clinical research & clinical care

STATE OF THE ART

Clin. Pharmacol. Ther. 104(1):42-52, 2018

Wearable Devices in Clinical Trials: Hype and Hypothesis

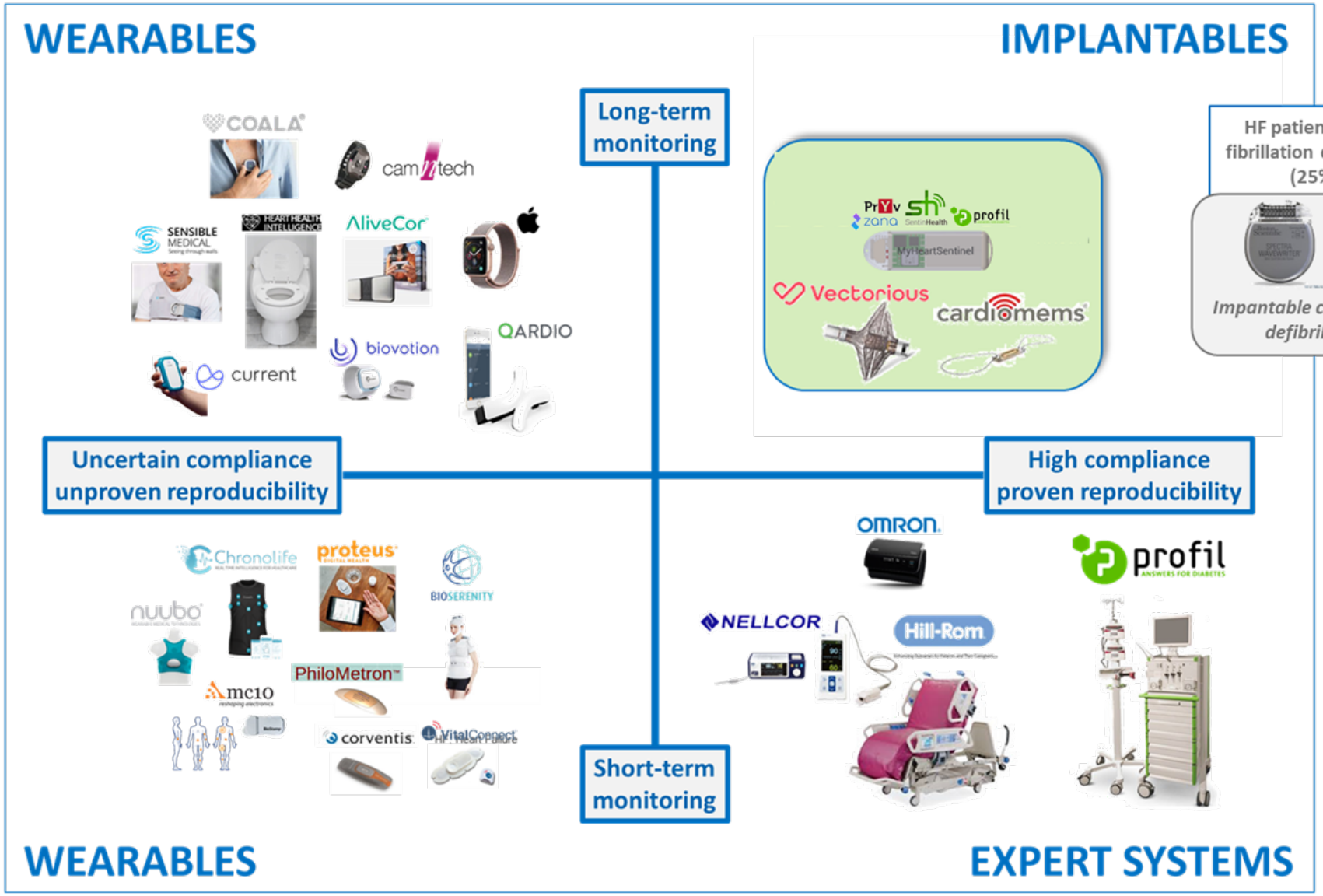
Elena S. Izmailova[1], John A. Wagner[1] and Eric D. Perakslis[1]

The development of innovative wearable technologies has raised great interest in new means of data collection in healthcare and biopharmaceutical research and development. Multiple applications for wearables have been identified in a number of therapeutic areas; however, researchers face many challenges in the clinic, including scientific methodology as well as regulatory, legal, and operational hurdles. To facilitate further evaluation and adoption of these technologies, we highlight methodological and logistical considerations for implementation in clinical trials, including key elements of analytical and clinical validation in the specific context of use (COU). Additionally, we provide an assessment of the maturity of the field and successful examples of recent clinical experiments.

- Mixed levels of
  - clinical & analytical **validation** for use in pivotal clinical trials and chronic care – **fitness for purpose, context of use**
  - patient/clinical trial volunteer **adherence** to wearing the device

profil
ANSWERS FOR DIABETES

Wearables in clinical research & clinical care



profil
ANSWERS FOR DIABETES

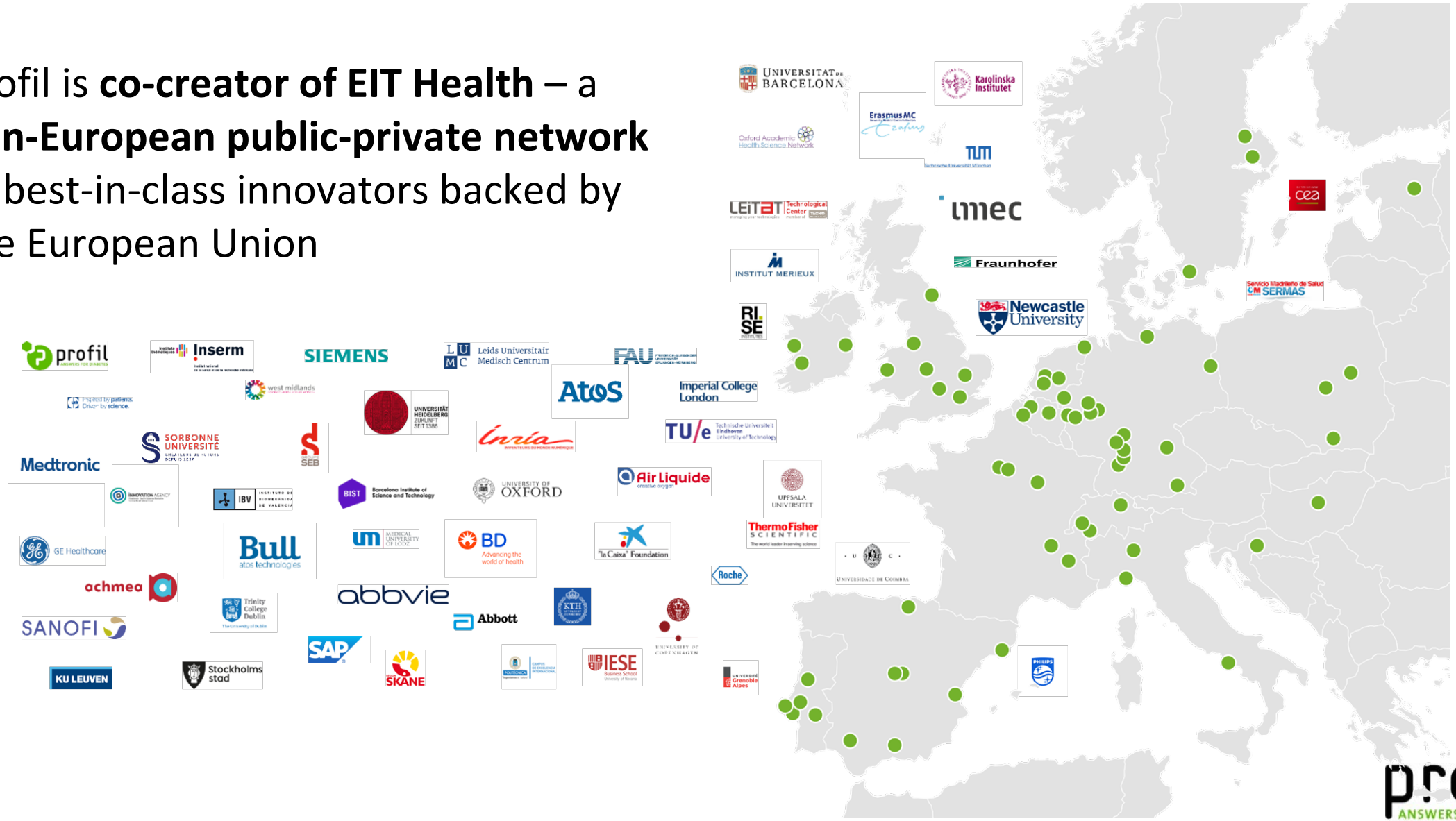
Agenda

- The efficacy-to-effectiveness (E2E) gap
- Lack of data problem in clinical research and clinical care
- Implementing digital tools for narrowing the E2E gap: it's all about collaboration
  - EIT Health public-private partnership
  - Example: CLOSE
  - Example: RealWorld4Clinic
  - Example: iPDM-GO
- Concluding remarks

EIT Health KIC

EIT Health is supported by the EIT, a body of the European Union

- Profil is **co-creator of EIT Health** – a **pan-European public-private network** of best-in-class innovators backed by the European Union



profil
ANSWERS FOR DIABETES

EIT Health KIC

EIT Health is supported by the EIT, a body of the European Union

- EIT Health partners collaborate across borders to deliver **new solutions** that can enable European citizens to live longer healthier lives

- EIT Health focus areas
  - **Bringing care home**
  - Reforming care pathways
  - Healthcare transformation
  - **Harnessing real-world data**
  - Health in the workplace
  - Fostering healthier lives

EIT Health KIC

- **Identifying unmet clinical and economic needs within complex healthcare systems**

EIT Health KIC

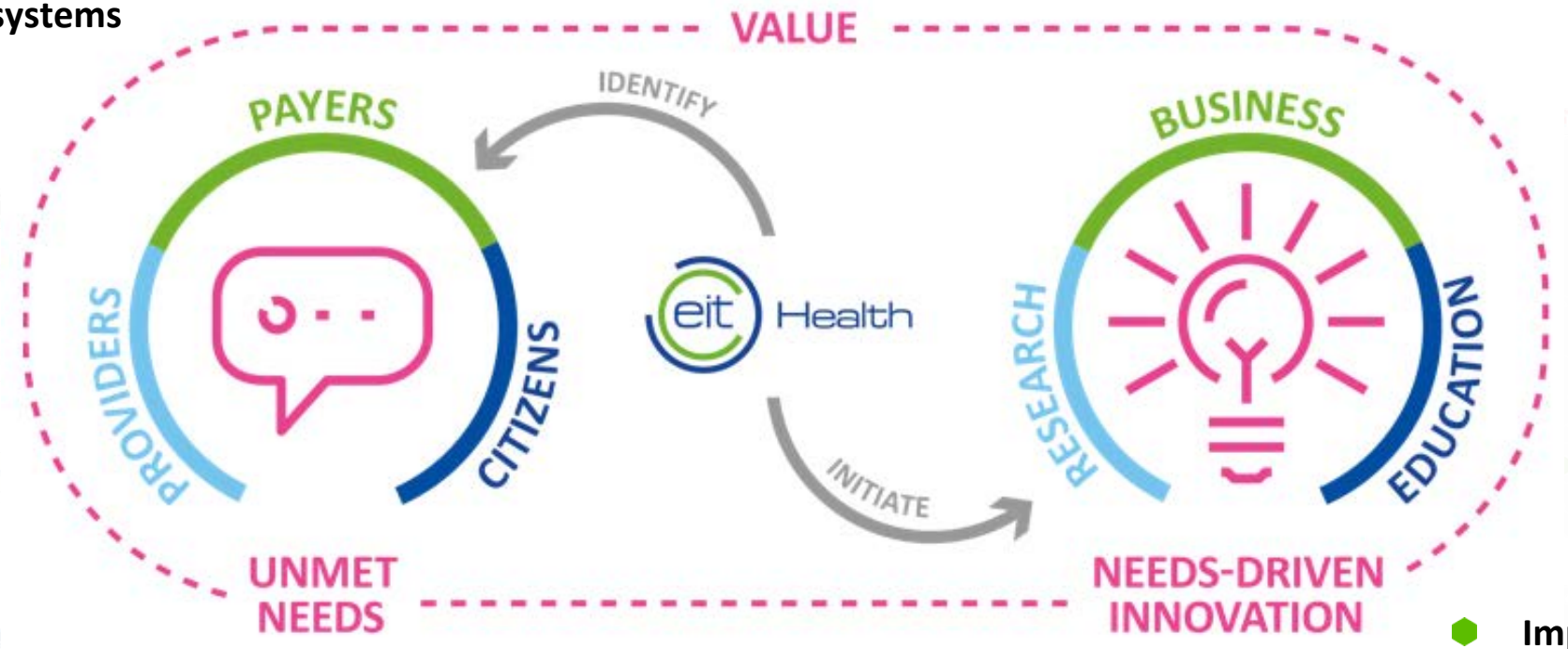
- **Identifying unmet clinical and economic needs within complex healthcare systems**

- **Implementing innovation initiatives integrating R&D, business creation & education**

EIT Health KIC

- Identifying unmet clinical and economic needs within complex healthcare systems

- Value creation by addressing the needs of markets and societies



- Implementing innovation initiatives integrating R&D, business creation & education

Example: CLOSE

Automated glucose control at home for people with chronic disease

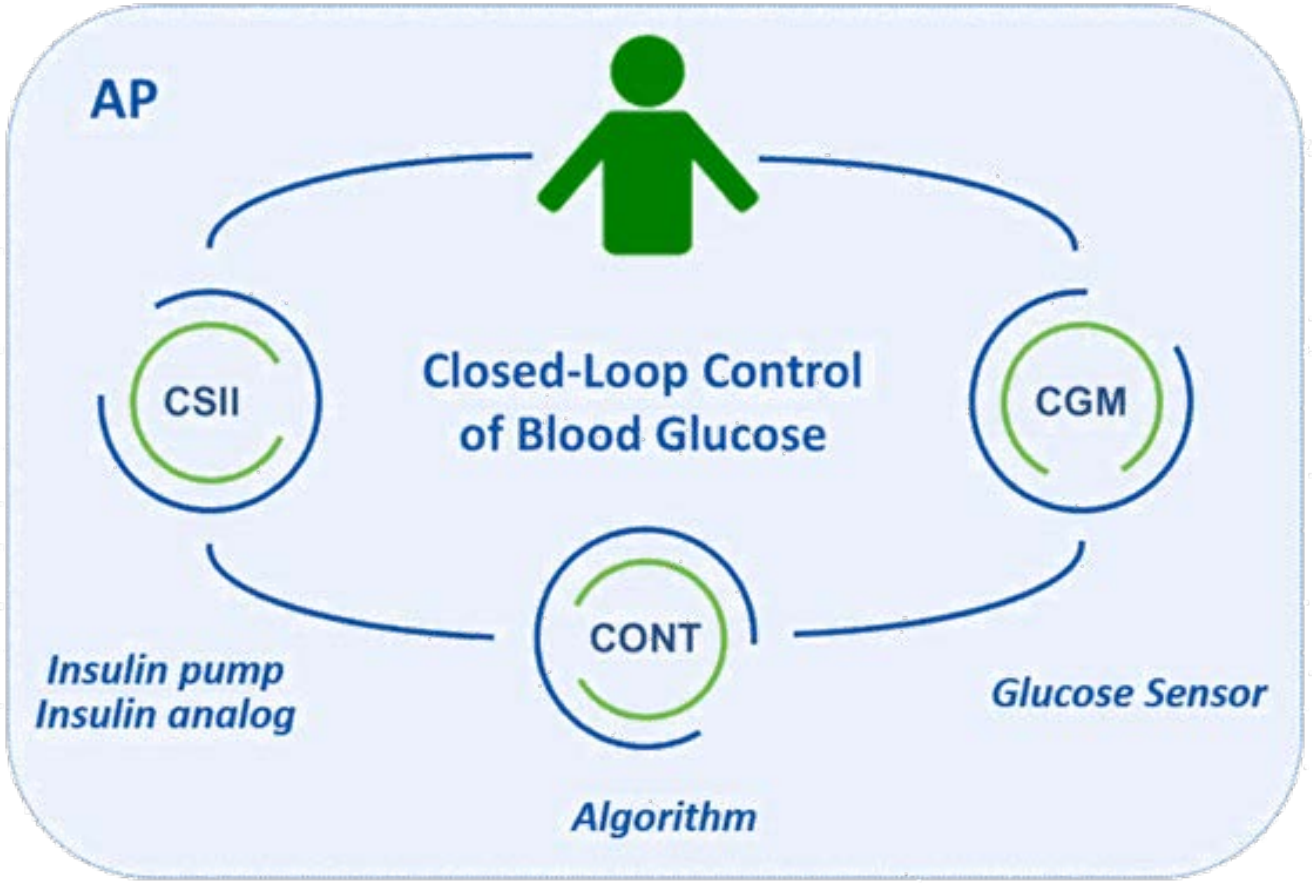
Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

Example: CLOSE

EIT Health is supported by the EIT, a body of the European Union

Air Liquide HEALTHCARE
SANOFI
profil ANSWERS FOR DIABETES
aQua ZUKUNFT DURCH QUALITÄT
IESE Business School University of Navarra
KU LEUVEN
MEDICAL UNIVERSITY OF LODZ
EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH

Automated glucose control at home for people with chronic disease



Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

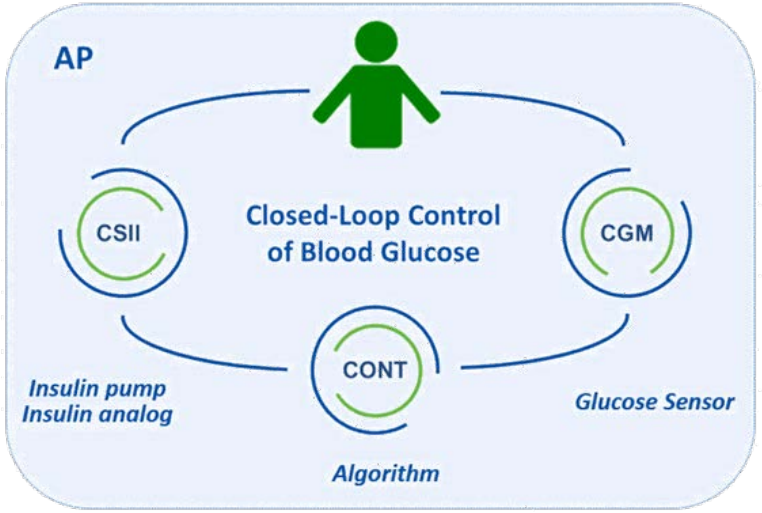
profil ANSWERS FOR DIABETES

Example: CLOSE

EIT Health is supported by the EIT, a body of the European Union

Air Liquide HEALTHCARE
SANOFI
profil ANSWERS FOR DIABETES
aQua ZUKUNFT DURCH QUALITÄT
IESE Business School University of Navarra
KU LEUVEN
MEDICAL UNIVERSITY OF LODZ
EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH

Automated glucose control at home for people with chronic disease



Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

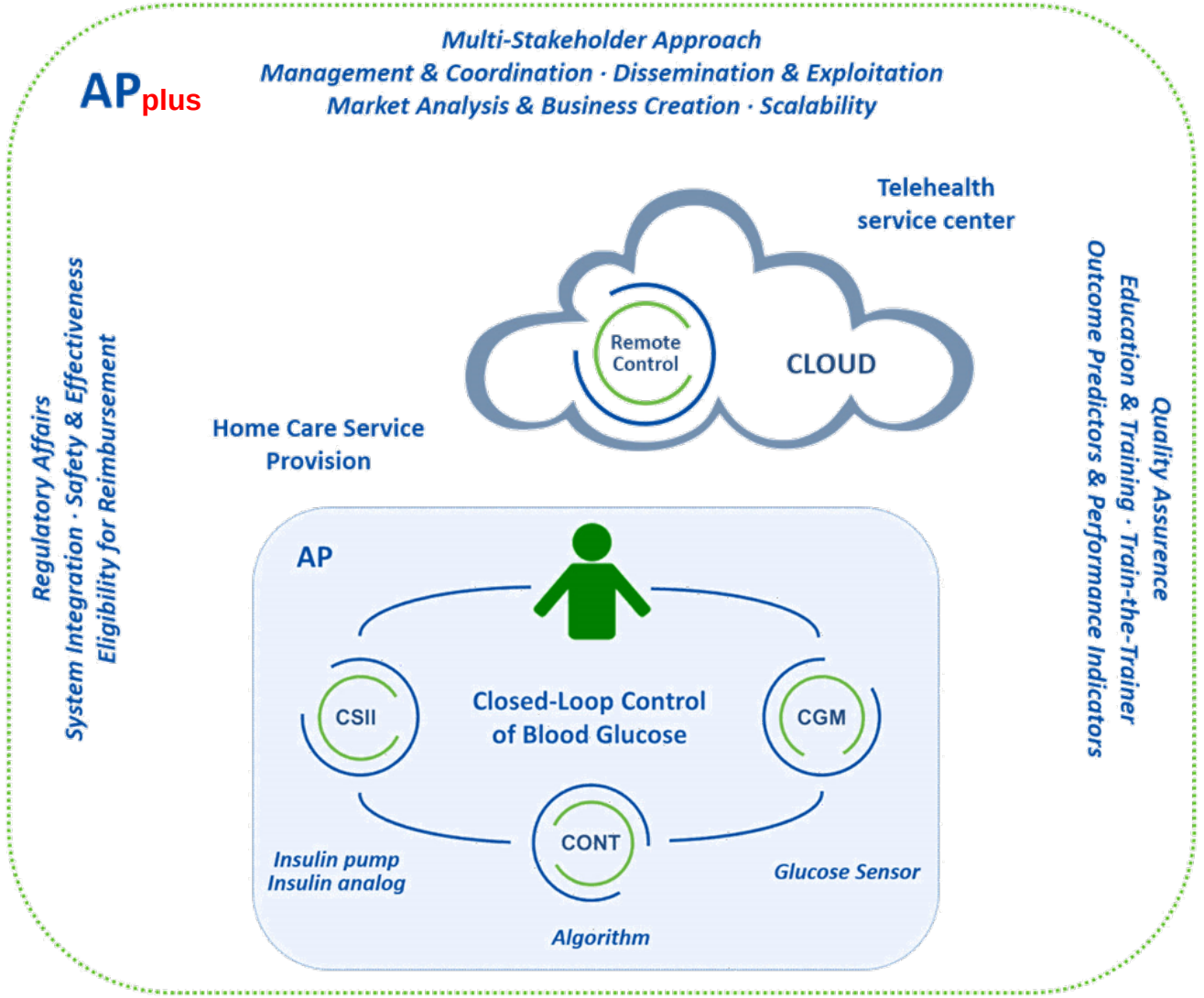
profil ANSWERS FOR DIABETES

Example: CLOSE

EIT Health is supported by the EIT, a body of the European Union

Air Liquide HEALTHCARE · SANOFI · profil ANSWERS FOR DIABETES · aQua ZUKUNFT DURCH QUALITÄT · IESE Business School University of Navarra · KU LEUVEN · MEDICAL UNIVERSITY OF LODZ · EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH

Automated glucose control at home for people with chronic disease



Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

profil ANSWERS FOR DIABETES

Example: CLOSE

Automated glucose control at home for people with chronic disease

- Needs orientation: APplus **co-created** at the heart of a **French homecare service provision** eco-system
- Innovation meets **key strategic interests** of Air Liquide and Profil
- **Real-world clinical validation in homecare** currently running[1]
- Perspective
  - Medium-term: scaling up French paradigm towards **APplus portfolios** matching the diversity of persons with type 2 diabetes
  - Longer-term: transition towards **interconnected health and social care**

Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

[1]NCT04233229

Example: CLOSE

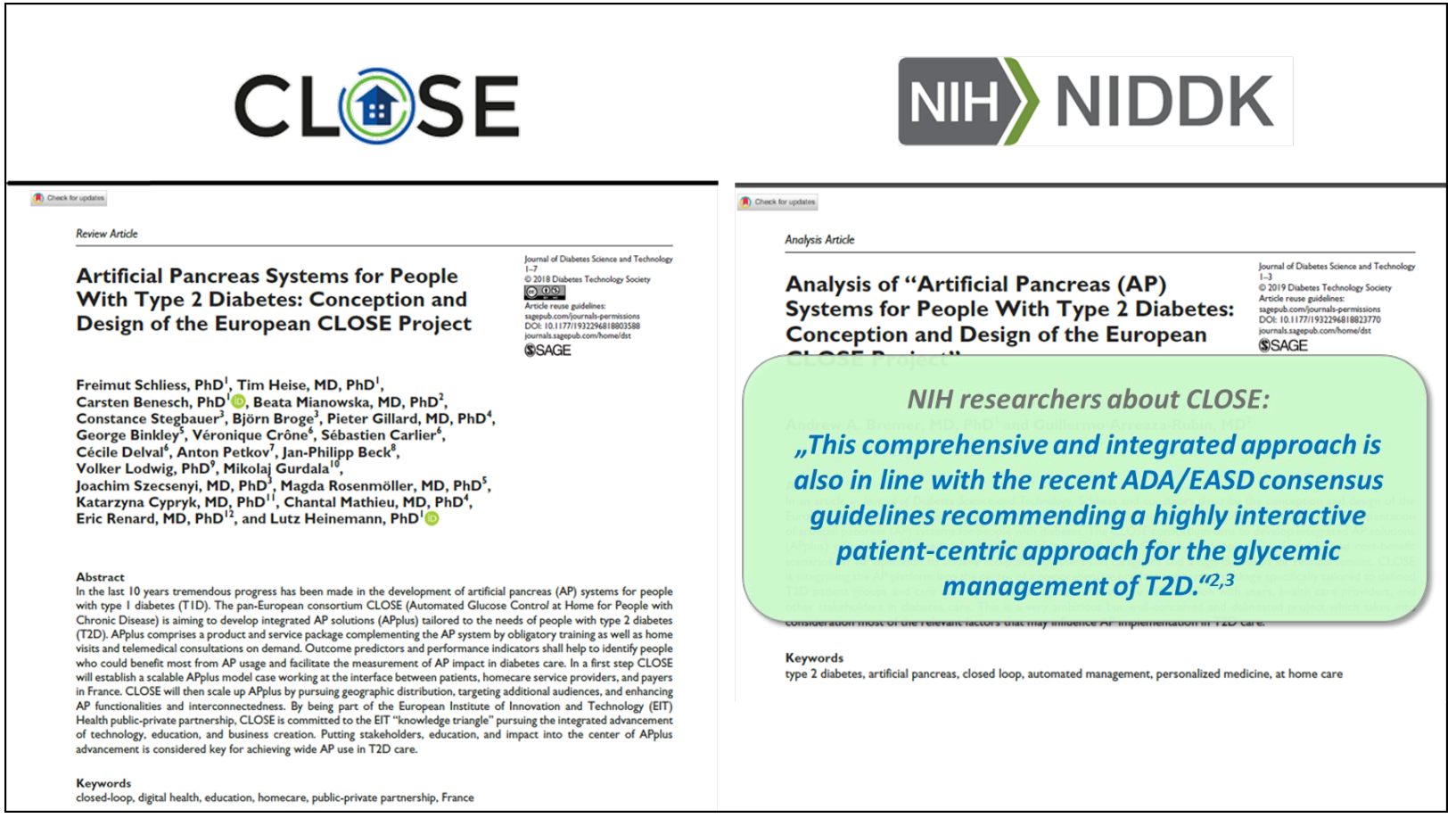
EIT Health is supported by the EIT, a body of the European Union

Air Liquide HEALTHCARE · SANOFI · profil ANSWERS FOR DIABETES · aQua ZUKUNFT DURCH QUALITÄT · IESE Business School University of Navarra · KU LEUVEN · MEDICAL UNIVERSITY OF LODZ · EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH

Automated glucose control at home for people with chronic disease

CLOSE

NIH NIDDK



Review Article

Artificial Pancreas Systems for People With Type 2 Diabetes: Conception and Design of the European CLOSE Project

Journal of Diabetes Science and Technology 1–7 © 2018 Diabetes Technology Society

Freimut Schliess, PhD[1], Tim Heise, MD, PhD[1], Carsten Benesch, PhD[1], Beata Mianowska, MD, PhD[2], Constance Stegbauer[3], Björn Broge[3], Pieter Gillard, MD, PhD[4], George Binkley[5], Véronique Crône[6], Sébastien Carlier[6], Cécile Delval[6], Anton Petkov[7], Jan-Philipp Beck[8], Volker Lodwig, PhD[9], Mikolaj Gurdala[10], Joachim Szecsenyi, MD, PhD[3], Magda Rosenmöller, MD, PhD[5], Katarzyna Cypryk, MD, PhD[11], Chantal Mathieu, MD, PhD[4], Eric Renard, MD, PhD[12], and Lutz Heinemann, PhD[1]

Abstract
In the last 10 years tremendous progress has been made in the development of artificial pancreas (AP) systems for people with type 1 diabetes (T1D). The pan-European consortium CLOSE (Automated Glucose Control at Home for People with Chronic Disease) is aiming to develop integrated AP solutions (APplus) tailored to the needs of people with type 2 diabetes (T2D). APplus comprises a product and service package complementing the AP system by obligatory training as well as home visits and telemedical consultations on demand. Outcome predictors and performance indicators shall help to identify people who could benefit most from AP usage and facilitate the measurement of AP impact in diabetes care. In a first step CLOSE will establish a scalable APplus model case working at the interface between patients, homecare service providers, and payers in France. CLOSE will then scale up APplus by pursuing geographic distribution, targeting additional audiences, and enhancing AP functionalities and interconnectedness. By being part of the European Institute of Innovation and Technology (EIT) Health public-private partnership, CLOSE is committed to the EIT "knowledge triangle" pursuing the integrated advancement of technology, education, and business creation. Putting stakeholders, education, and impact into the center of APplus advancement is considered key for achieving wide AP use in T2D care.

Keywords
closed-loop, digital health, education, homecare, public-private partnership, France

Analysis Article

Analysis of "Artificial Pancreas (AP) Systems for People With Type 2 Diabetes: Conception and Design of the European

Journal of Diabetes Science and Technology 1–3 © 2019 Diabetes Technology Society

NIH researchers about CLOSE:
„This comprehensive and integrated approach is also in line with the recent ADA/EASD consensus guidelines recommending a highly interactive patient-centric approach for the glycemic management of T2D."[2,3]

Keywords
type 2 diabetes, artificial pancreas, closed loop, automated management, personalized medicine, at home care

Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019
https://eit-health.de/en/close/

Bremer, A.A. & Arreaza-Rubín, G., **J. Diabetes Sci. Technol.** 13(2):268-270, 2019

profil ANSWERS FOR DIABETES

Example: RealWorld4Clinic

EIT Health is supported by the EIT, a body of the European Union

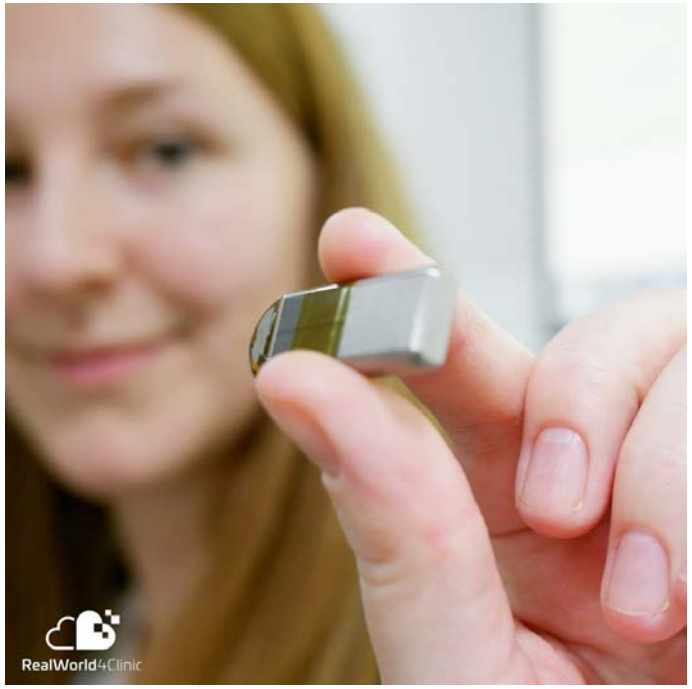
RealWorld4Clinic Kickoff · 10-11 February 2020 · Grenoble, France

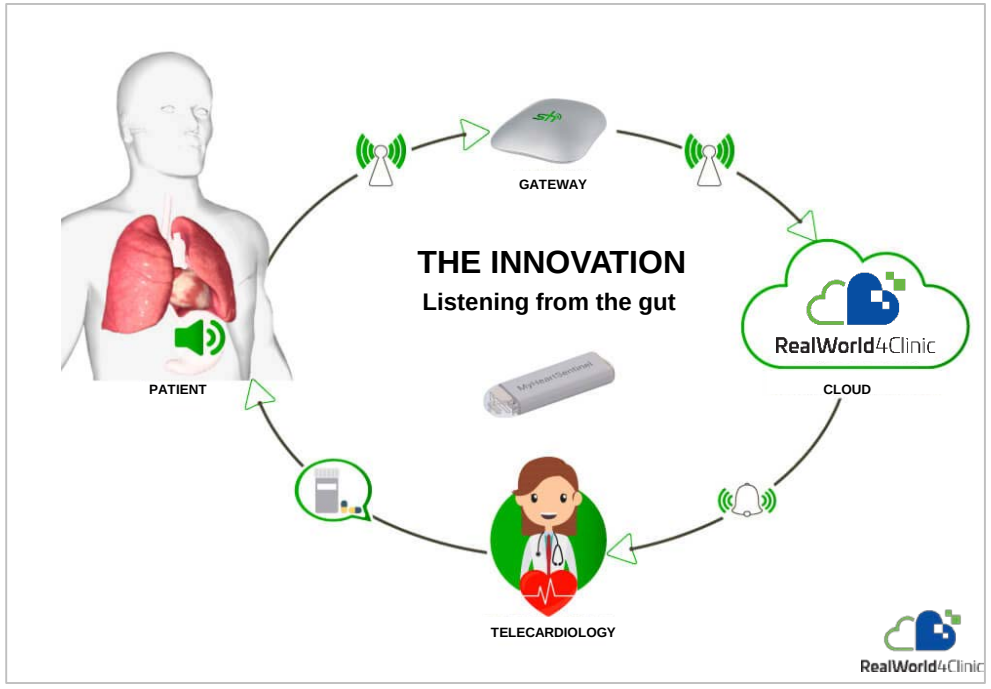
***Real-World* Cardio-Respiratory Health Monitoring *for Clinic*al Contract Research & Tele-Cardiology**

https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

Example: RealWorld4Clinic

EIT Health is supported by the EIT, a body of the European Union





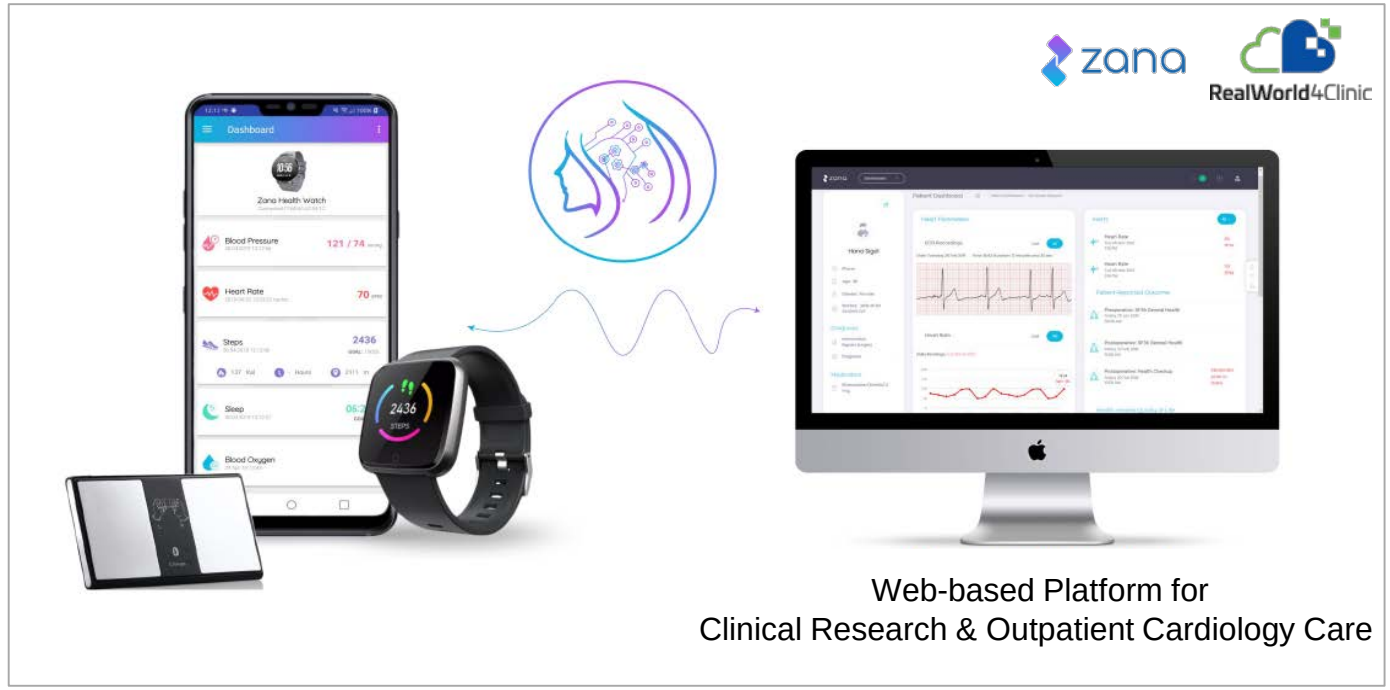
***Real-World* Cardio-Respiratory Health Monitoring *for Clinic*al Contract Research & Tele-Cardiology**

https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

- Developing a **class III medical sensor** anchored to the fundus of the stomach in immediate proximity to the heart, the lung and the gastric tract to access **multiple parameters**
- Ultimate ambition: making **real-world monitoring** of cardio-respiratory health a **Standard** in **out-patient cardiology care**

Example: RealWorld4Clinic

EIT Health is supported by the EIT, a body of the European Union



Web-based Platform for
Clinical Research & Outpatient Cardiology Care

***Real-World* Cardio-Respiratory Health Monitoring *for Clinic*al Contract Research & Tele-Cardiology**

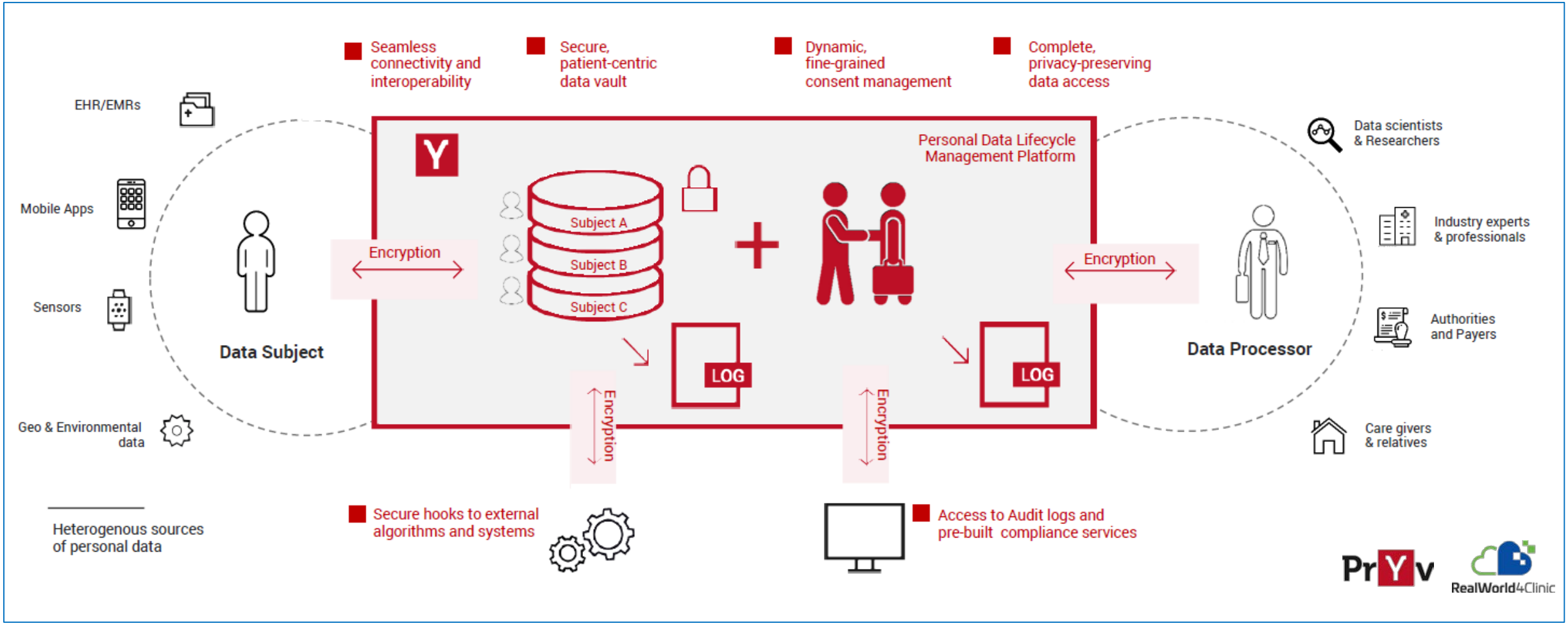
https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

- **Smartphone-based communication platform**
  - Patient reported outcomes **(PROMs)** assessment
  - Web-based **data presentation dashboards** tailored to clinical research and outpatient cardiology care

Example: RealWorld4Clinic

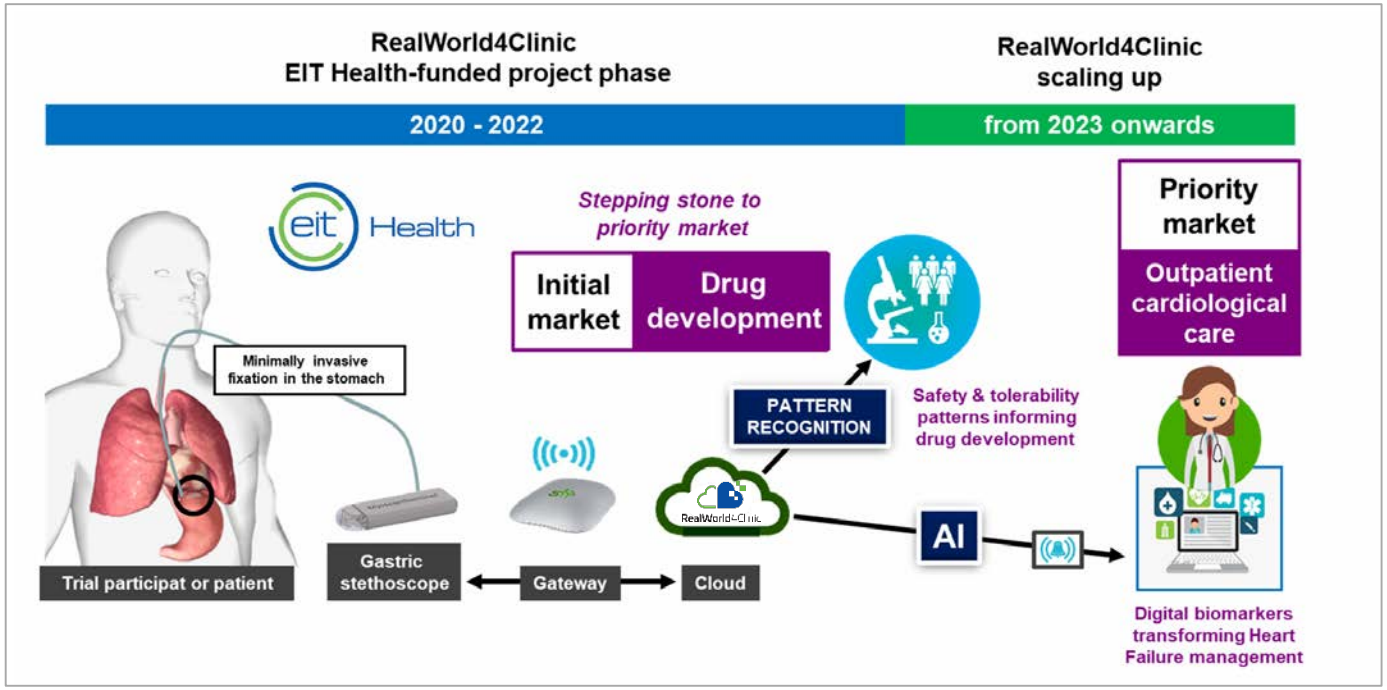
EIT Health is supported by the EIT, a body of the European Union

Personal data lifecycle management platform



Example: RealWorld4Clinic

EIT Health is supported by the EIT, a body of the European Union



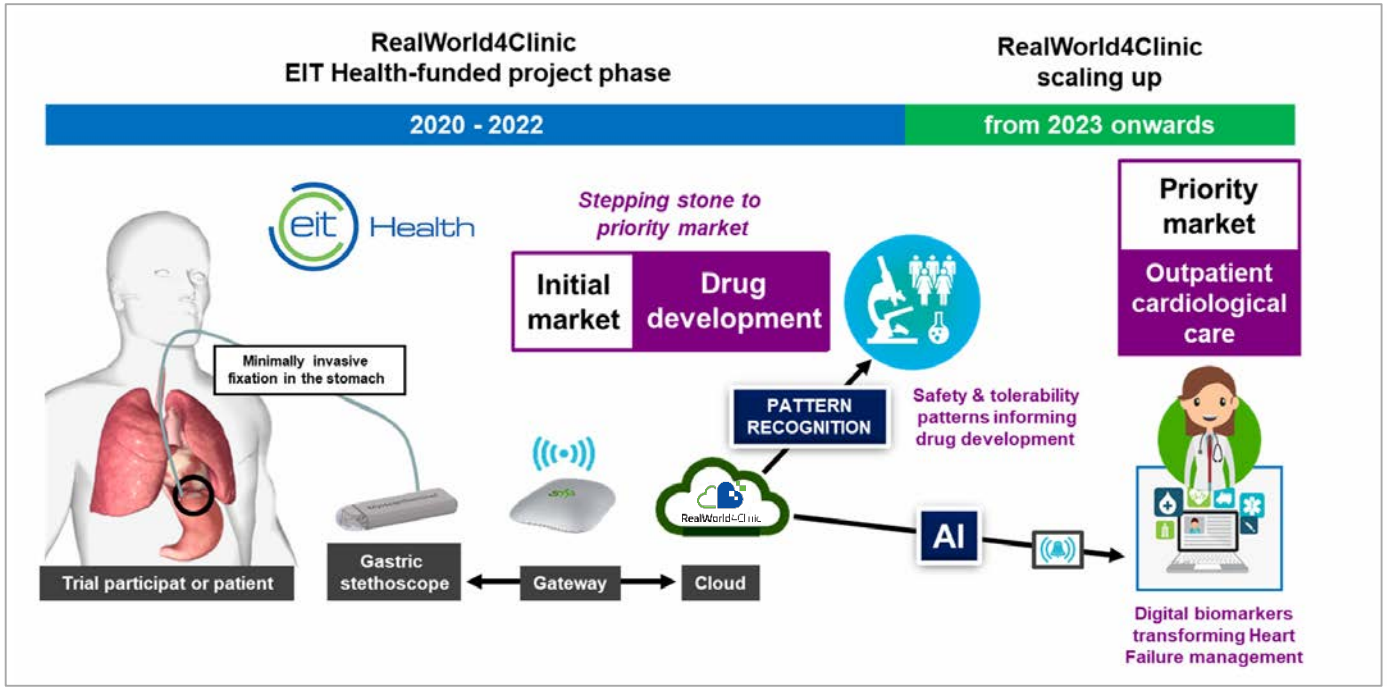
Real-World Cardio-Respiratory Health Monitoring _for Clinic_al Contract Research & Tele-Cardiology

https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

- Stepping stone approach to market launch: **drug development**
  - secured application environment, clear commercial case
  - generation of user experience
  - demonstration of regulatory and legal compliance
  - generation of evidence, peer-reviewed publications

Example: RealWorld4Clinic

EIT Health is supported by the EIT, a body of the European Union



Real-World Cardio-Respiratory Health Monitoring _for Clinic_al Contract Research & Tele-Cardiology

https://www.openaccessgovernment.org/realworld4clinic-clinical-research/81957/

- Stepping stone approach to market launch: **cardiology**
  - Instruments for outcome prediction (payers) and performance measurement (outpatient cardiology care)
  - Proactive tackling of ethical, legal and social issues
  - Performance-related remuneration model

Example:

iPDM-GO
Integrated Personalised
Diabetes Management
Goes Europe

EIT Health is supported by the EIT, a body of the European Union

***I*ntegrated *P*ersonalized *D*iabetes *M*anagement *Go*es Europe**

https://www.openaccessgovernment.org/ipdm-diabetes-and-patient-care/75520/ · https://eit-health.de/en/ipdm-go/

Example:

iPDM-GO
Integrated Personalised Diabetes Management Goes Europe

EIT Health is supported by the EIT, a body of the European Union

- iPDM: structured and iterative six-step process cycle
  - Education & training
  - Structured blood glucose assessment
  - documentation of glucose profiles
  - data analysis
  - data-based treatment adaption
  - treatment efficacy assessment
- ProValue study program demonstrated real-world effectiveness of iPDM

***I*ntegrated *P*ersonalized *D*iabetes *M*anagement *Go*es Europe**

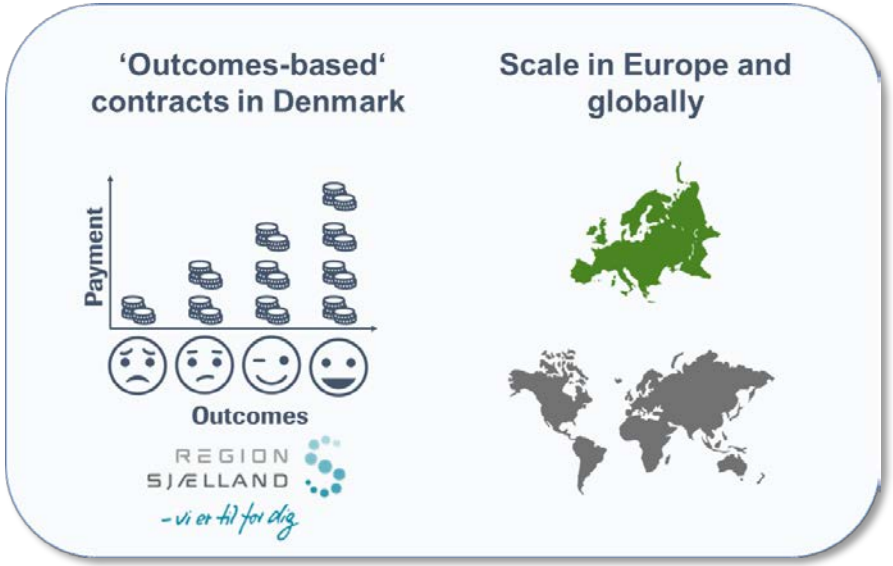
https://www.openaccessgovernment.org/ipdm-diabetes-and-patient-care/75520/ · https://eit-health.de/en/ipdm-go/

- Ceriello, A. et al. **Diabetes Res. Clin. Pract.** 98(1):5-10, 2012
- Kulzer, B. et al. **J. Diabetes Sci. Technol.** 10(3):772-781, 2016
- Kulzer, B. et al. **Diabetes Res. Clin. Pract.** 114:200-212, 2018
- Heinemann, L. et al. **J. Diabetes Sci. Technol.** 14(2):240-249, 2020

Example:

iPDM-GO
Integrated Personalised Diabetes Management Goes Europe

EIT Health is supported by the EIT, a body of the European Union



***I*ntegrated *P*ersonalized *D*iabetes *M*anagement *Go*es Europe**

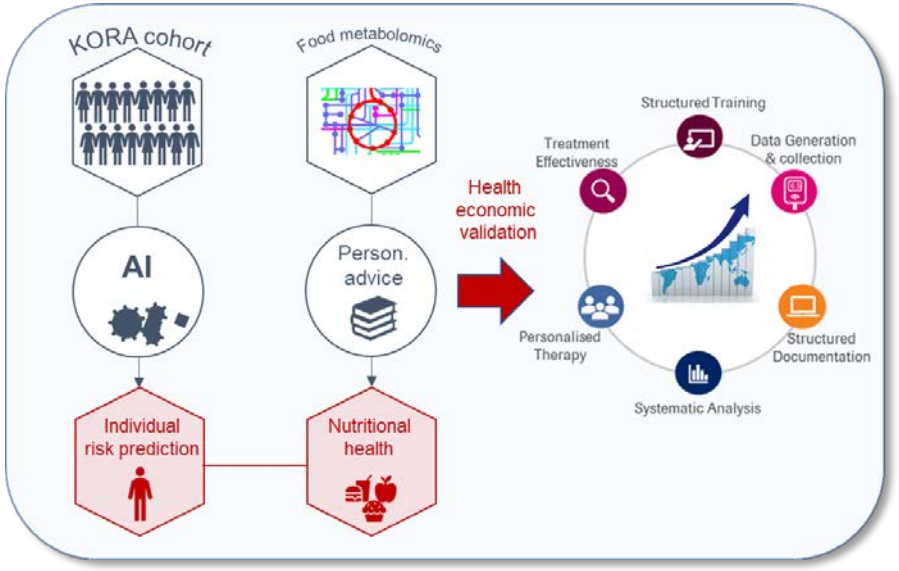
https://www.openaccessgovernment.org/ipdm-diabetes-and-patient-care/75520/ · https://eit-health.de/en/ipdm-go/

- Implementation in a Danish community setting for **value-based healthcare**
- Enhancement with a **digital patient assessment** tool
- **Upscaling:** geography, patient population, data types

Example:

iPDM-GO
Integrated Personalised Diabetes Management Goes Europe

EIT Health is supported by the EIT, a body of the European Union



***I*ntegrated *P*ersonalized *D*iabetes *M*anagement *Go*es Europe**

- Research in iPDM **enhancement, implementation** and **scalability**
  - connects the **AI-powered analysis of big population** data with **health economic modelling** for enhancing iPDM patient assessment, treatment personalization and cost effectiveness.

https://www.openaccessgovernment.org/ipdm-diabetes-and-patient-care/75520/ · https://eit-health.de/en/ipdm-go/

http://blog.profil.com/blog/profil-joined-ipdm-go

Concluding remarks

- There is a gap between the **efficacy** of investigational drugs & devices in clinical trials and the **effectiveness** of the marketed products in real-world healthcare (E2E gap).
- **Wearables for medical use** need to be validated for a **specific purpose** in a precisely defined medical **context of use**, taking into account complex influencing factors.
- The E2E gap can be narrowed by integrating the **acquisition & exploitation of real-world data**
  - in **pivotal clinical research** for a better quality of decision making based on a more reliable prediction of late-phase and real-world outcomes
  - in **chronic care** to create room for a pro-active prevention from disease aggravation, frailty & comorbid conditions, dependency and hospital admissions.

profil
ANSWERS FOR DIABETES

Concluding remarks

- **Collaboration** e.g. in the framework of the EIT Health public-private partnership helps to
  - follow a **co-creation** approach and early engagement with relevant **stakeholders** from all over Europe
  - tackle **cross-border barriers** to digital health implementation and early address the **ethical, legal and social** issues e.g. related to the acquisition and AI-powered exploitation of health data
  - shorten **time-to-market** and secure **scalability** in terms of geography, functional enhancement, and value-based healthcare

profil
ANSWERS FOR DIABETES

Thank you very much!

profil
ANSWERS FOR DIABETES