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

START-UPS MEET CRO

Clinical Trialing
Digital Health Technologies

Freimut Schliess, Tatiana Affini Dicenzo

Profil Institut für Stoffwechselforschung GmbH (www.profil.com)
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EIT Health Germany – START-UPS MEET HEALTHCARE PROVIDER (SMHCP) 2021 · 13 October 2021

www.profil.com

www.profil.com

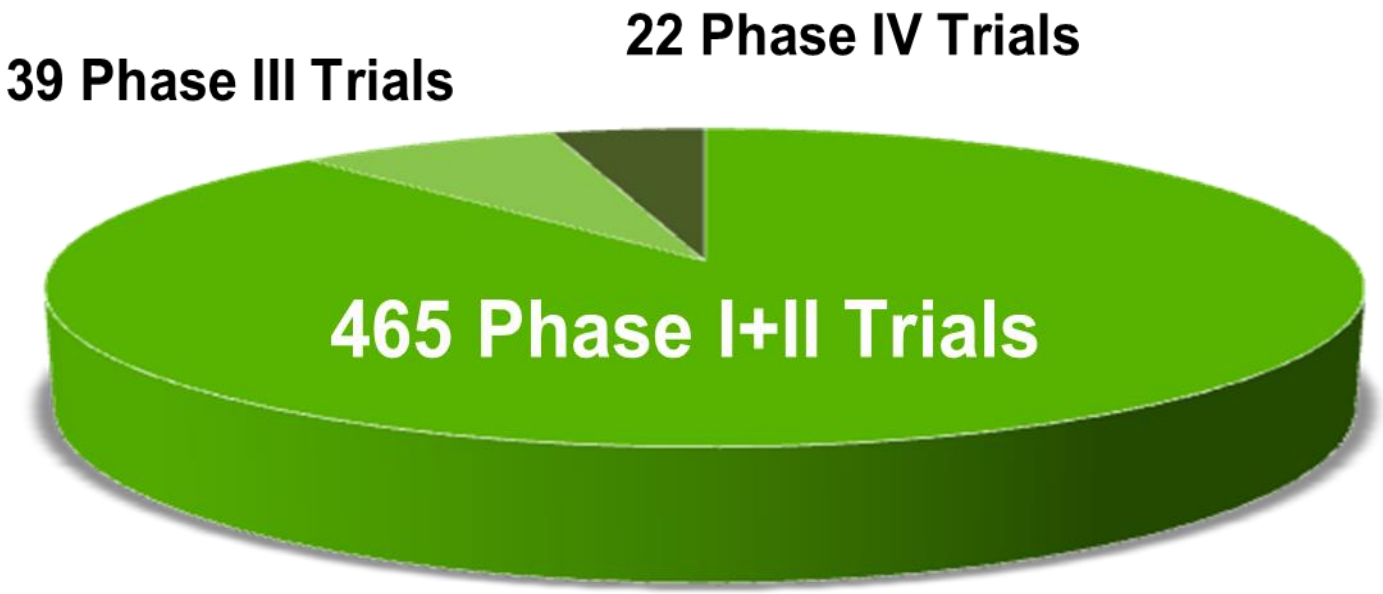
- >250 FTEs
- Huge recruitment capabilities
- 2 inhouse CRUs >80 test beds
- Data Management & Statistics
- Regulatory Affairs

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

Track record

> 500 in-house trials



15.10.2020

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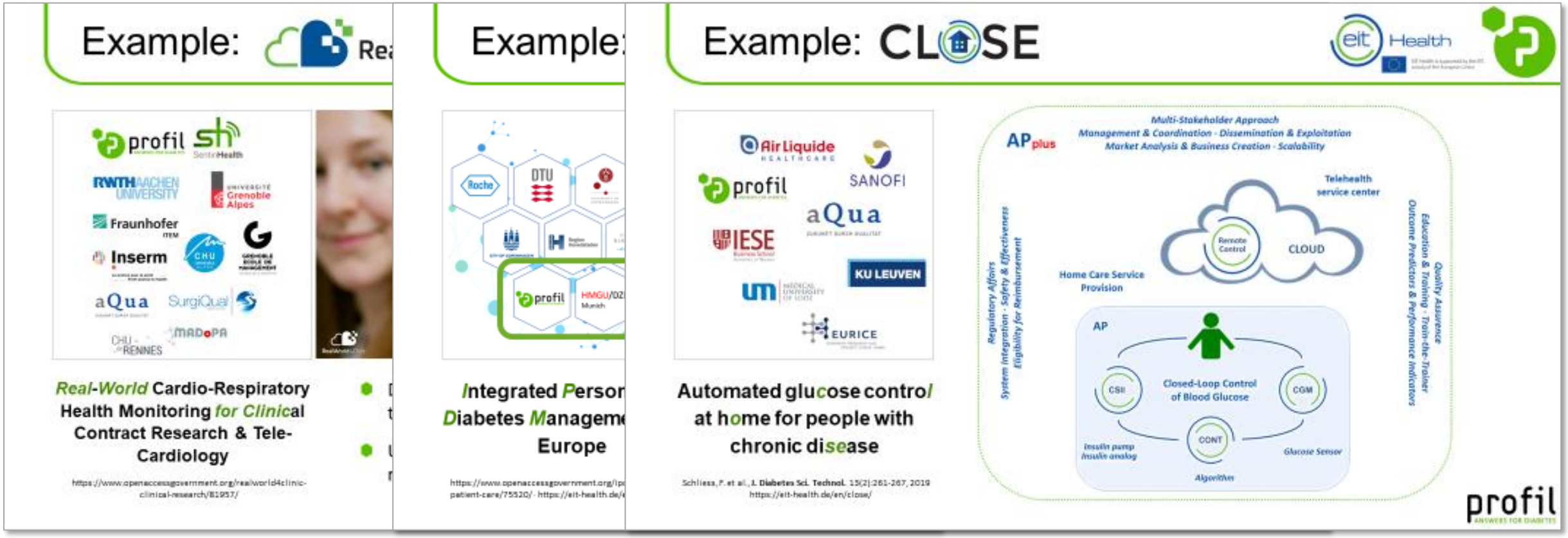
Part of EIT Health innovation portfolio



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Schliess, F. et al., **J. Diabetes Sci. Technol.** 13(2):261-267, 2019

https://eit-health.de/en/close/
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https://eit-health.de/en/ipdm-go/
https://eithealth.eu/project/ipdm-go/
https://eit-health.de/en/realworld4clinic/
https://eithealth.eu/project/realworld4clinic/
https://eithealth.eu/project/d4teens/
https://eithealth.eu/project/d4kids/

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Agenda

- Design approaches to trialing Digital Health Technologies
- Evidence frameworks for Digital Health Technologies
- Setting up your clinical trial program and selecting the right partners
- Q&A

Trial design

- Design approaches to trialing Digital Health Technologies
- Evidence frameworks for Digital Health Technologies
- Setting up your clinical trial program and selecting the right partners
- Q&A

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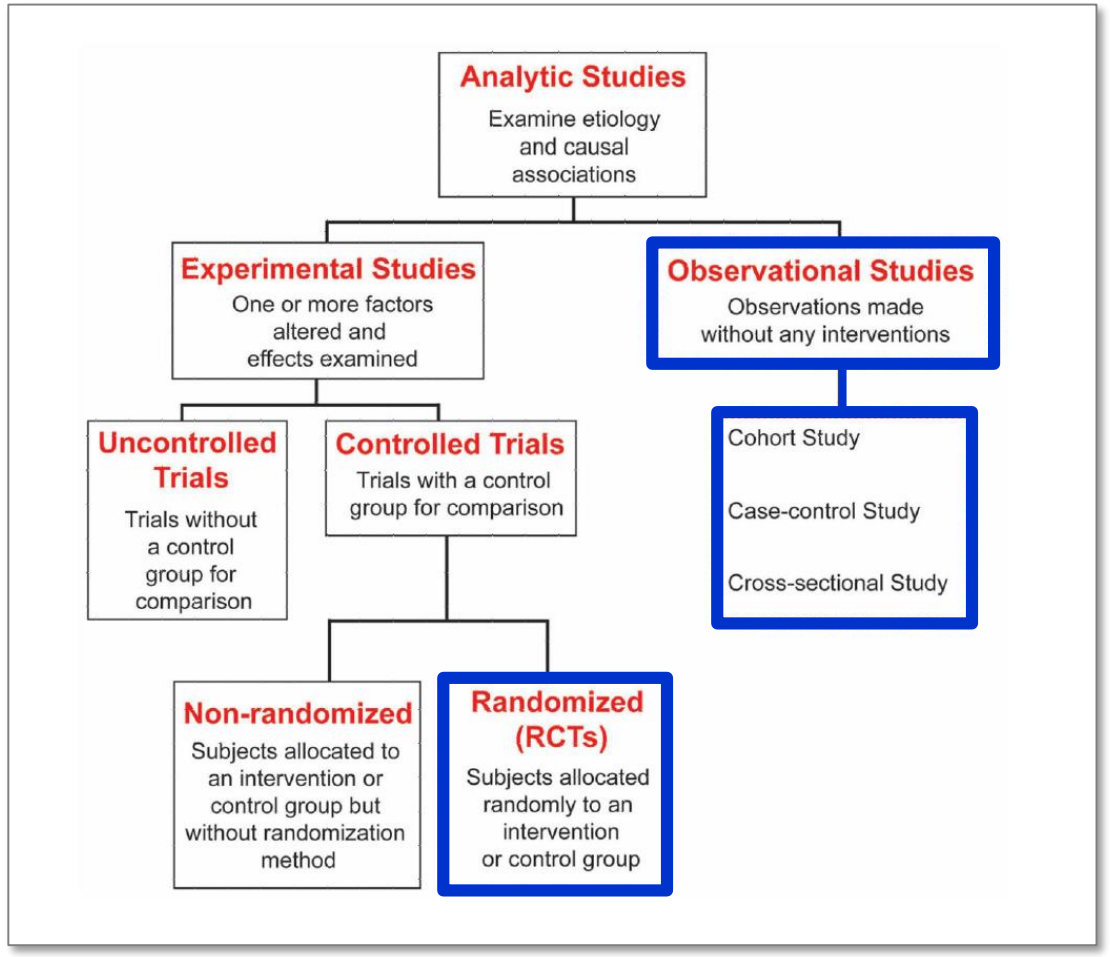
Clinical trial designs



- Randomised controlled clinical trials
- Observational trials
- Remote Decentralised Clinical Trials
- In-silico clinical trials

Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

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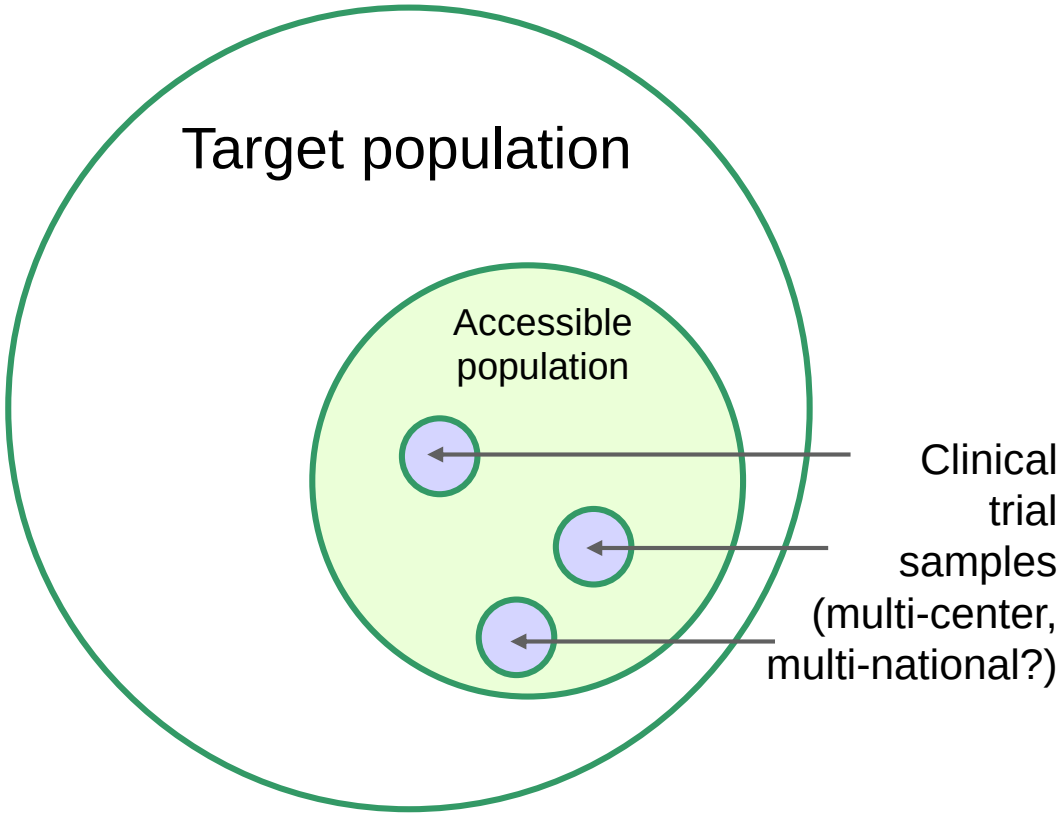
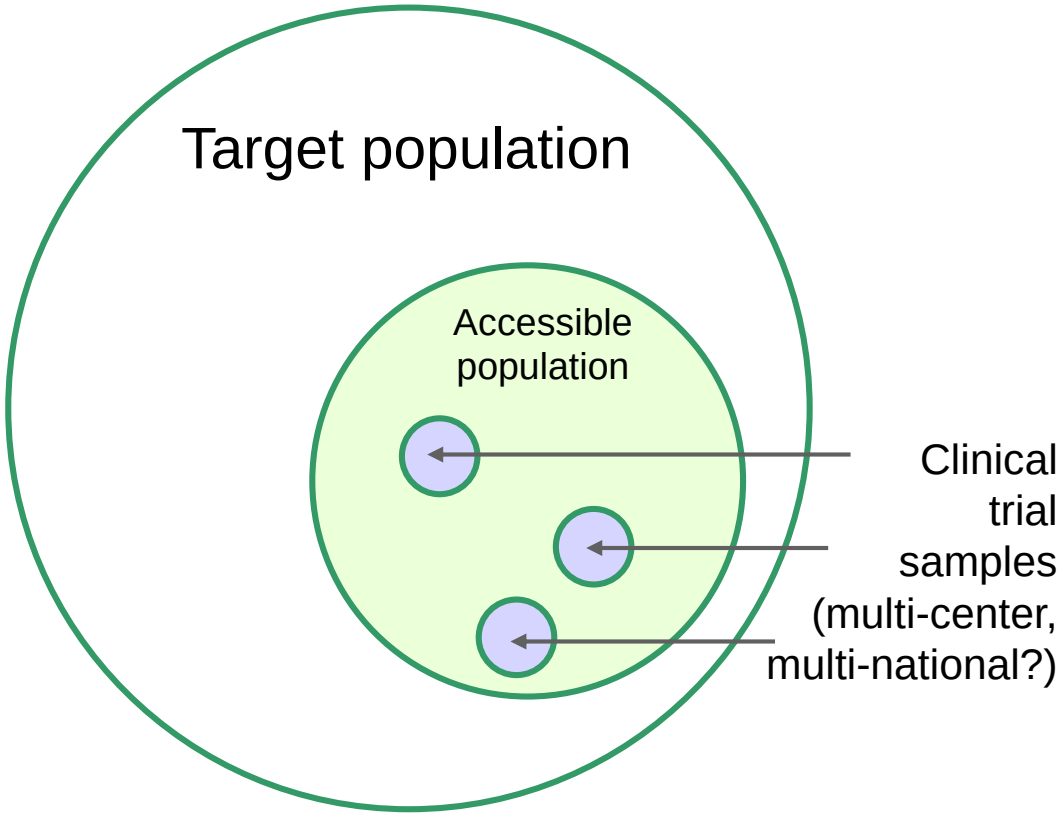
ANSWERS FOR DIABETES

Questions you should answer early on

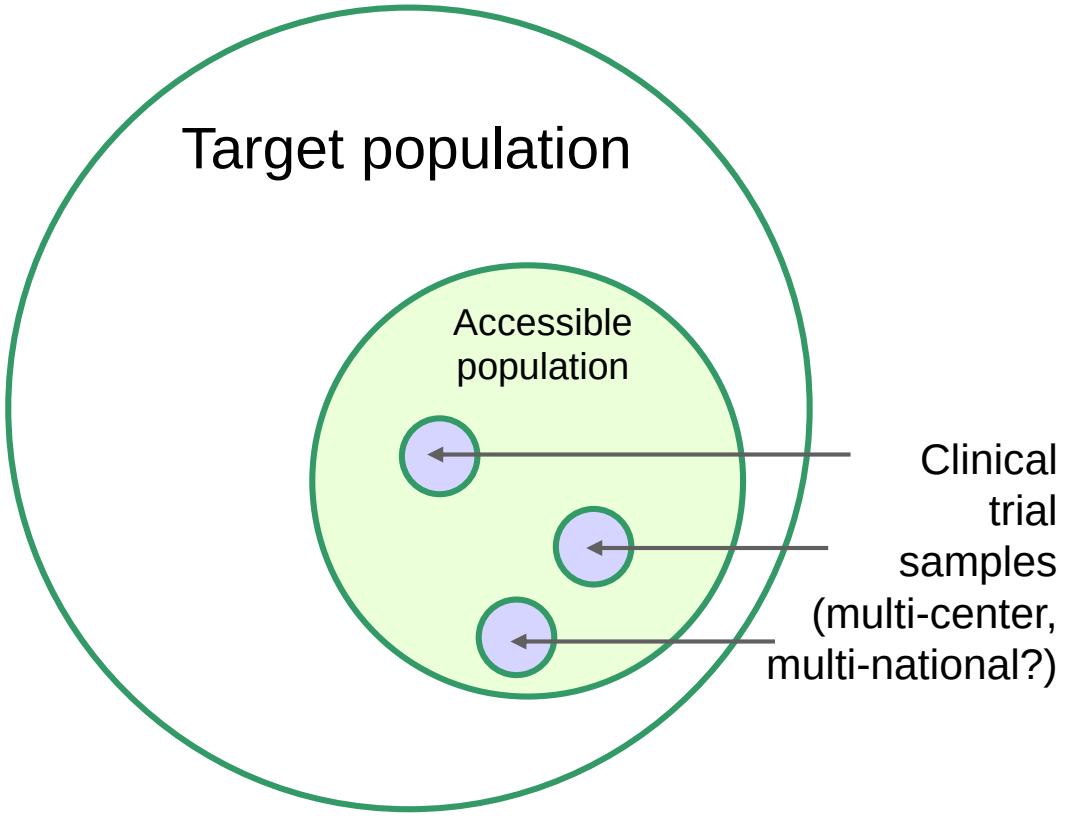


Questions you should answer early on



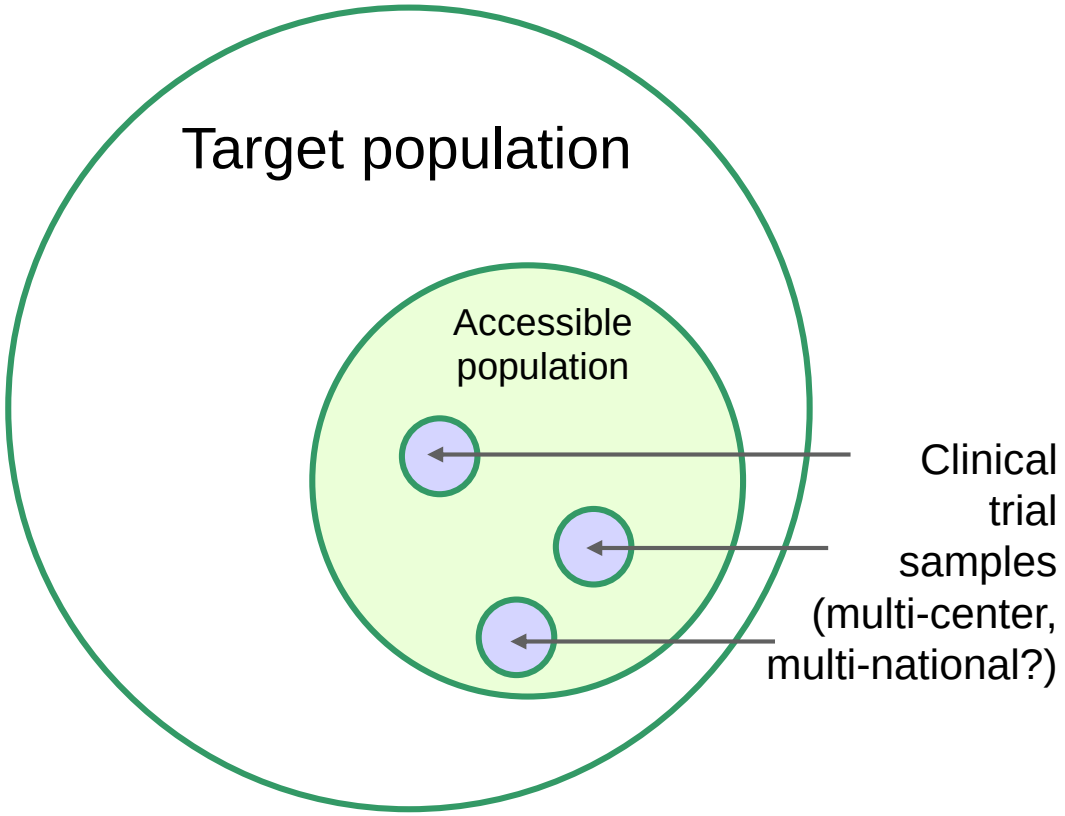
- Which **target population** you would like to address?
  - Representative clinical trial samples

Questions you should answer early on



- What is exactly the **research question** you would like to have answered?
  - Testable hypothesis (superiority, non-inferiority, equivalence as compared to a comparator treatment)

Questions you should answer early on



- What is exactly the **research question** you would like to have answered?
  - **Comparator** (baseline, no treatment, no treatment & placebo/mock device, current standard of care, current standard of care & placebo/mock device?)

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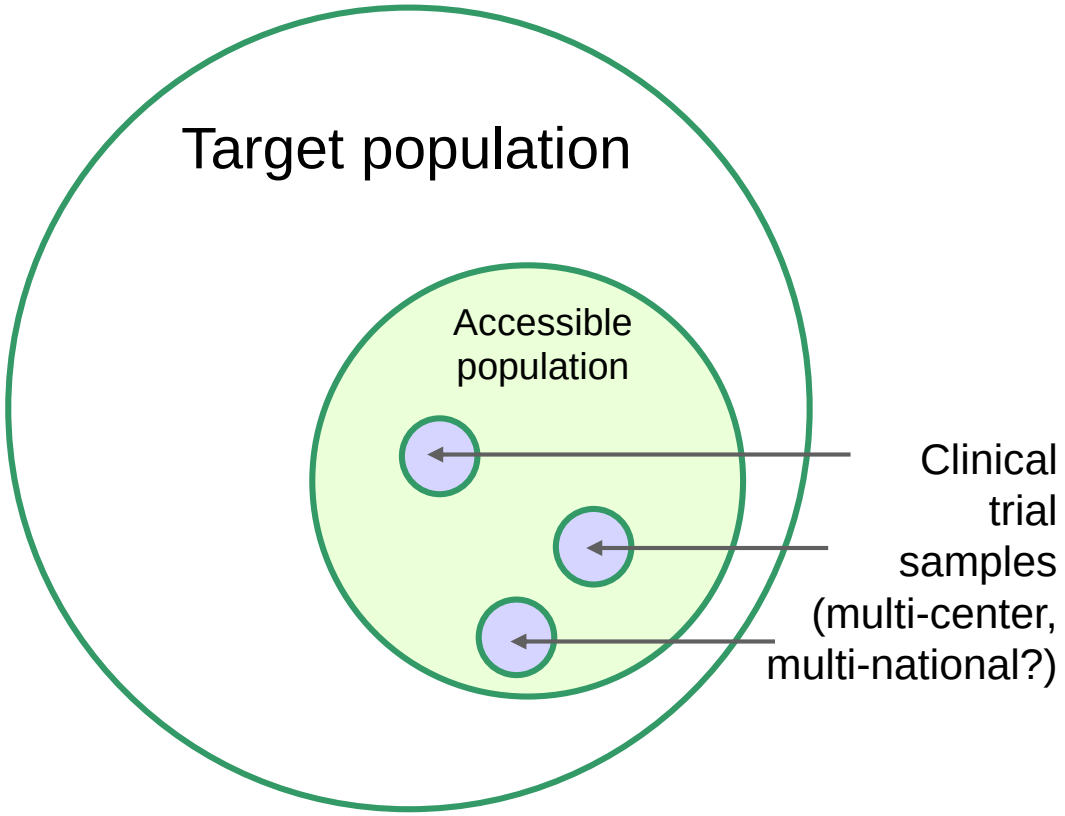
ANSWERS FOR DIABETES

Questions you should answer early on



- What is exactly the **research question** you would like to have answered?
  - **Trial endpoints** related to the state of health/disease progression (signs), quality of life, perception of symptoms, treatment adherence, treatment satisfaction
  - **Quantifiable** parameters (lab values, scores, digital biomarkers)
  - **Feasible assessment methods:** Lab analysis of blood, urine, or tissue samples; sensors/wearables for collection of real-world data, patient-reported outcomes, validated questionnaires (paper-based, digital, conversational AI)

Interventional & non-interventional trials

ISO 14155 – Definitions

Interventional & non-interventional trials

ISO 14155 – Definitions

- I.6.2 **Interventional clinical investigation** is a *pre- or post-market* clinical investigation where the *assignment of a subject to a particular medical device is* ***decided in advance by a Clinical Investigation Plan (CIP)*** ***or*** *diagnostic or monitoring procedures requested in the CIP are* ***in addition to those available as normal*** *clinical practice and burden* the subject. (*RCT* or *additional burden*)

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ANSWERS FOR DIABETES

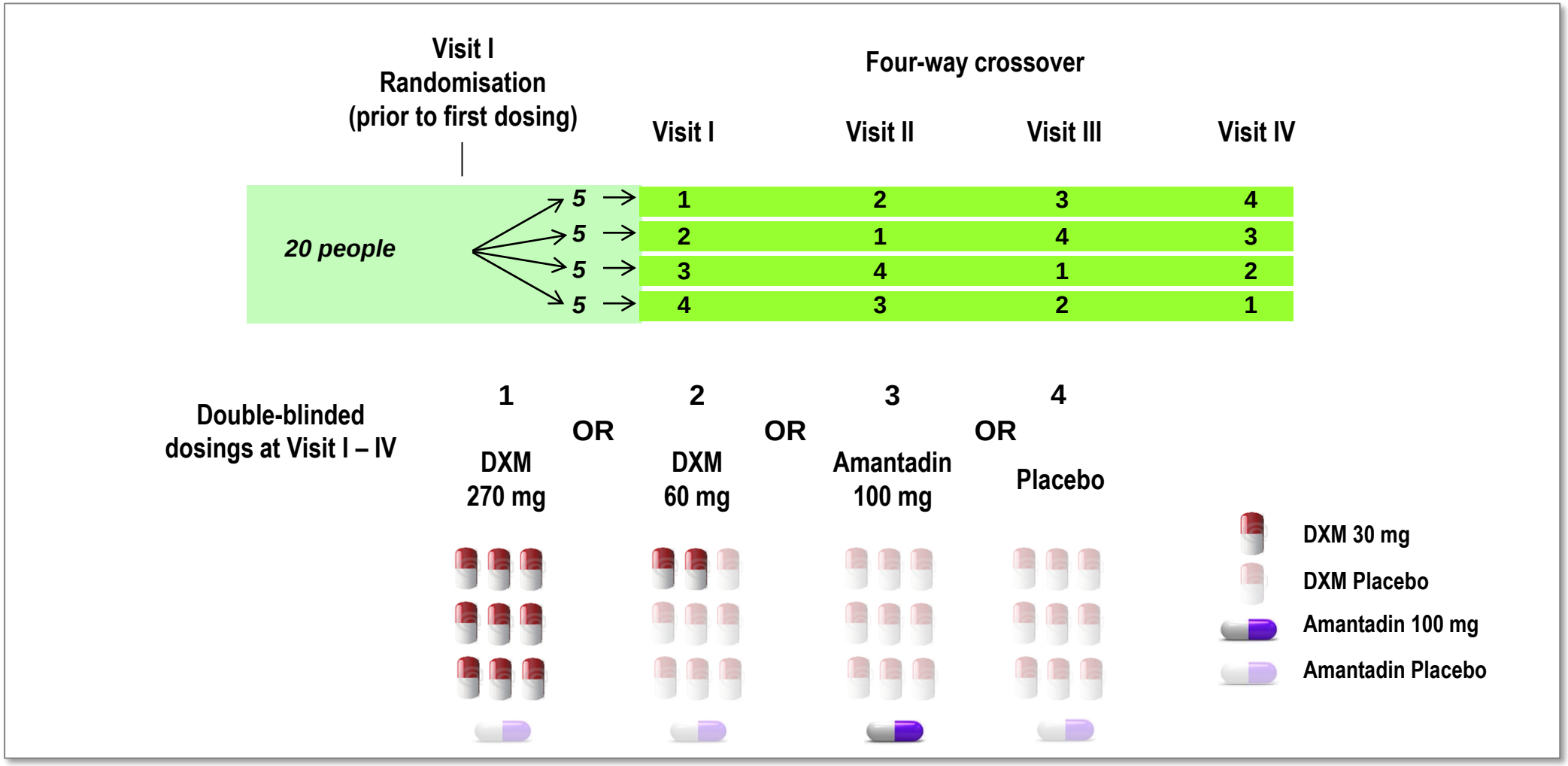
Interventional & non-interventional trials

ISO 14155 – Definitions

- I.6.3 **Non-interventional clinical investigation** *post-market* clinical investigation where the medical device is used in accordance with its approved labelling. *The assignment of a subject to a particular medical device is* ***not decided in advance by a CIP*** *but falls within current clinical practice.* The use of the medical device is clearly separated from the decision to include the subject in the clinical investigation. ***No additional*** *invasive or burdensome diagnostic or monitoring procedures* are applied to the subjects and *epidemiological methods* are used for the analysis of collected data.

- In general non-interventional trials are observational.

Randomised Controlled Trials



Marquard, J. et al., **Nat. Med.** 21(4):363-373, 2015
Marquard, J. et al., **Diabetes Obes. Metab.** 18(1):100-103, 2016

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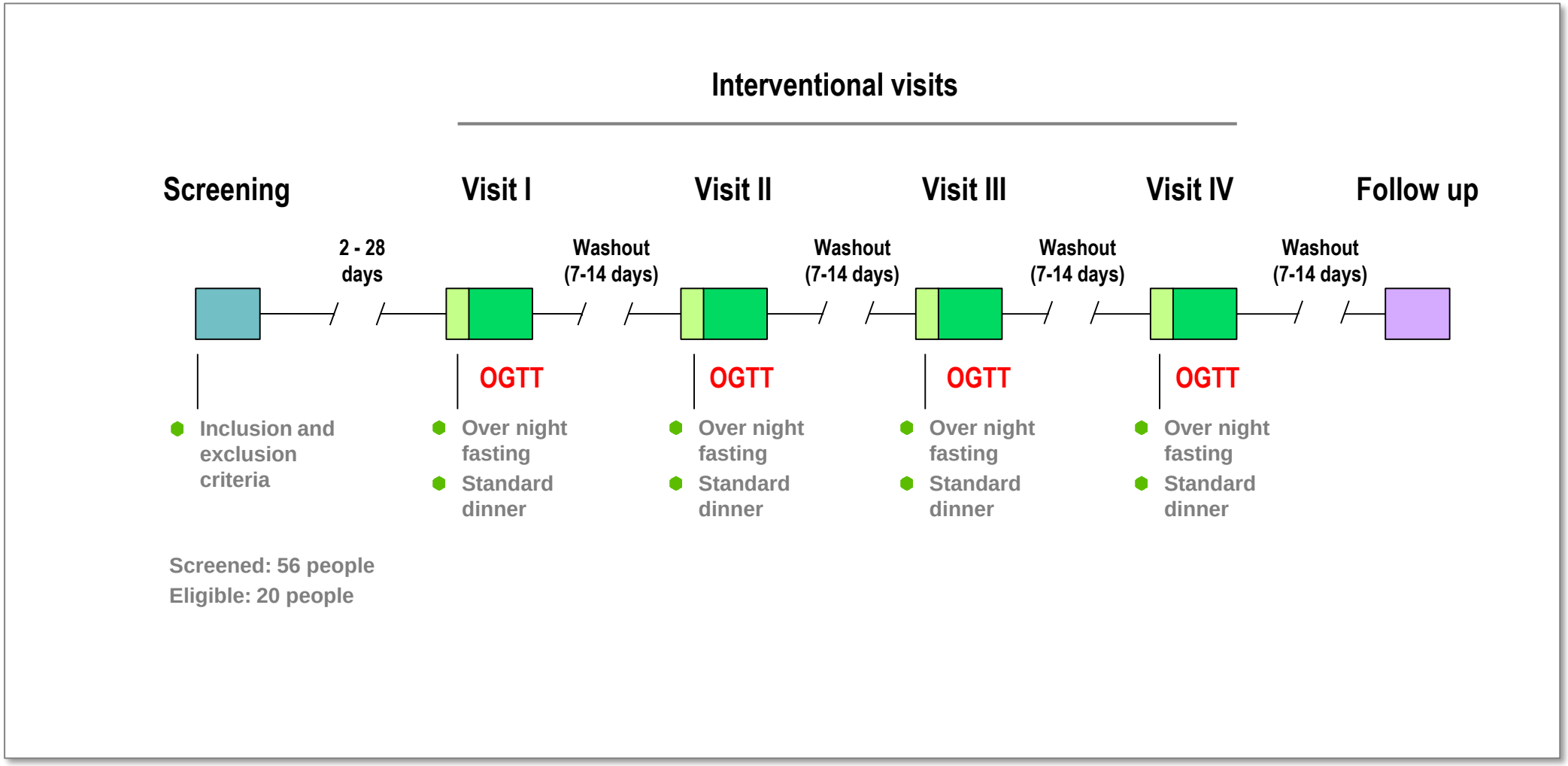
ANSWERS FOR DIABETES

Randomised Controlled Trials



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Marquard, J. et al., **Diabetes Obes. Metab.** 18(1):100-103, 2016

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Randomised Controlled Trials

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ANSWERS FOR DIABETES

CLINICAL STUDY PROTOCOL

EudraCT No.:	2011-002986-39
Study code:	DXM/AMT
Investigational Product(s):	Dextromethorphan, Amantadine
Title:	A phase IIa, double-blind, placebo-controlled, randomised, fourfold cross-over study to investigate the glucose lowering effects of dextromethorphan and amantadine in subjects with type 2 diabetes mellitus (T2DM) after an oral glucose tolerance test
Clinical Phase:	Phase IIa
Sponsor:	Profil Institut für Stoffwechselforschung GmbH Hellersbergstr. 9 41460 Neuss, Germany Phone: +49 (0) 2131 4018-157 Fax: +49 (0) 2131 4018-557
Principal Investigator:	Dr. med. Alin Stirban Profil Institut für Stoffwechselforschung GmbH Hellersbergstr. 9 41460 Neuss, Germany Phone: +49 (0) 2131 4018-486 Fax: +49 (0) 2131 4018-550
Status, Version, Date of Protocol:	Final 2.0 26.08.2011
Planned Study Period:	September 2011- January 2012
Author:	Dr. med. Alin Stirban, Director Endocrinology Profil Institut für Stoffwechselforschung GmbH

TABLE 1: ASSESSMENT SCHEDULE

		Assessment Period	
Visit	**Screening**	**Dosing Visits[1] 1-4,**	**Follow-up**
Study Day	**2-28 days prior to first dosing**	**7-14 days between dosing days**	**7-14 days after last dose**
Clinical site visit (outsubject)	X		X
Informed consent	X[2]		
Inclusion / exclusion criteria	X		
Withdrawal criteria		X	
Dosing day exclusion criteria		X	
Demographics & Medical history	X		
Concomitant medication	X	X	X
Physical examination (incl. height, weight, BMI)	X	X[3]	X
Vital signs	X	X	X
ECG	X	X	X
Pulse oximetry		X	
Safety laboratory	X		X
Breath alcohol	X	X	
HBsAg, HCV and HIV tests	X		
Fasting blood glucose & HbA1c	X		
Randomisation[4]		X	
Study drug administration		X	
PK sampling[5]		X	
PD sampling[6]		X	
OGTT [7]		X	
Blood glucose for safety (super GL)		X	
Adverse events (AEs)[8]		X	X

1 See TABLE 2: TIME SCHEDULE OGTT AT DOSING VISITS 1-4 for the timing of study procedures
2 Check of signed and dated informed consent. The actual signing must be performed prior to any trial related activities
3 Physical examination and weight only
4 Randomisation will be performed for eligible subjects prior to first dosing. Replacement subjects are allocated the same treatment sequence as the subject they are replacing;
5 PK blood sampling for DXM as defined in: TABLE 2: TIME SCHEDULE OGTT AT DOSING VISITS 1-4
6 PD blood sampling for blood glucose, serum insulin, catecholamines as defined in: TABLE 2: TIME SCHEDULE OGTT AT DOSING VISITS 1-4
7 A 75g OGTT will be started on each dosing day, 1 hour after dosing
8 Any AEs since the subject's last visit to the trial site (for first dosing visit: since signing of informed consent) and any AEs occurring during the study visit will be recorded

Marquard, J. et al., **Nat. Med.** 21(4):363-373, 2015
Marquard, J. et al., **Diabetes Obes. Metab.** 18(1):100-103, 2016

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Randomised Controlled Trials

LETTERS
https://doi.org/10.1038/s41591-020-1045-7
nature medicine

Check for updates

Insulin dose optimization using an automated artificial intelligence-based decision support system in youths with type 1 diabetes

Revital Nimri[1], Tadej Battelino[2], Lori M. Laffel[3], Robert H. Slover[4], Desmond Schatz[5], Stuart A. Weinzimer[6], Klemen Dovc[2], Thomas Danne[7], Moshe Phillip[1,8] ✉ and NextDREAM Consortium*

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel. [2]Department of Endocrinology, Diabetes and Metabolic Diseases, UMC-University Children's Hospital Ljubljana, and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [3]Joslin Diabetes Center, One Joslin Place, Harvard Medical School, Boston, MA, USA. [4]Barbara Davis Center for Childhood Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [5]Department of Pediatrics, College of Medicine, University of Florida, Gainesville, FL, USA. [6]Pediatric Endocrinology & Diabetes, Yale School of Medicine, New Haven, CT, USA. [7]Diabetes Center for Children and Adolescents, Children's Hospital AUF DER BULT, Hannover, Germany. [8]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. *A list of authors and their affiliations appears at the end of the paper. ✉e-mail: mosheph@tauex.tau.ac.il

Volume 26 Issue 9, September 2020

Guidelines for AI in clinical trials

The image on the cover illustrates the potential of artificial intelligence (AI) to enhance healthcare delivery. In this issue, new extensions of SPIRIT and CONSORT guidelines dedicated to randomized clinical trials involving AI delineate the reporting standards for these interventions, and Nimri and colleagues report the results of a randomized clinical trial evaluating the performance of an AI for optimizing insulin dosing in patients with type 1 diabetes.

comment

Check for updates

Welcoming new guidelines for AI clinical research

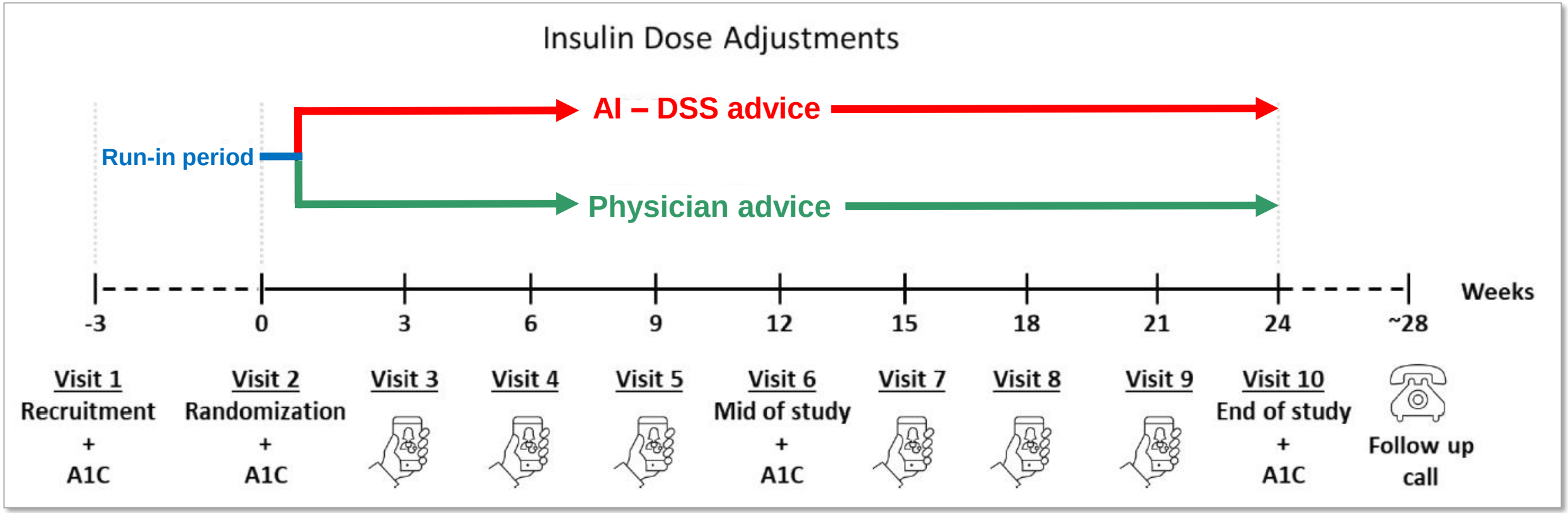
With only a limited number of clinical trials of artificial intelligence in medicine thus far, the first guidelines for protocols and reporting arrive at an opportune time. Better protocol design, along with consistent and complete data presentation, will greatly facilitate interpretation and validation of these trials, and will help the field to move forward.

Eric J. Topol

Liu, X., et al., **Nature Medicine** 26(9):1351-1363, 2020
Cruz Rivera, S., et al., **Nature Medicine** 26(9):1364-1374, 2020
Topol, E., **Nature Medicine** 26(9):1318-1320, 2020

- CONSORT-AI: **Con**solidated **S**tandards **o**f **Reporting** **T**rials – **A**rtificial **I**ntelligence
- SPIRIT-AI: **S**tandard **P**rotocol **I**tems: **R**ecommendations for **I**nterventional **T**rials – Artificial Intelligence

Randomised Controlled Trials



Nimri, R. et al., **Nature Medicine** 26(9):1380-1384, 2020

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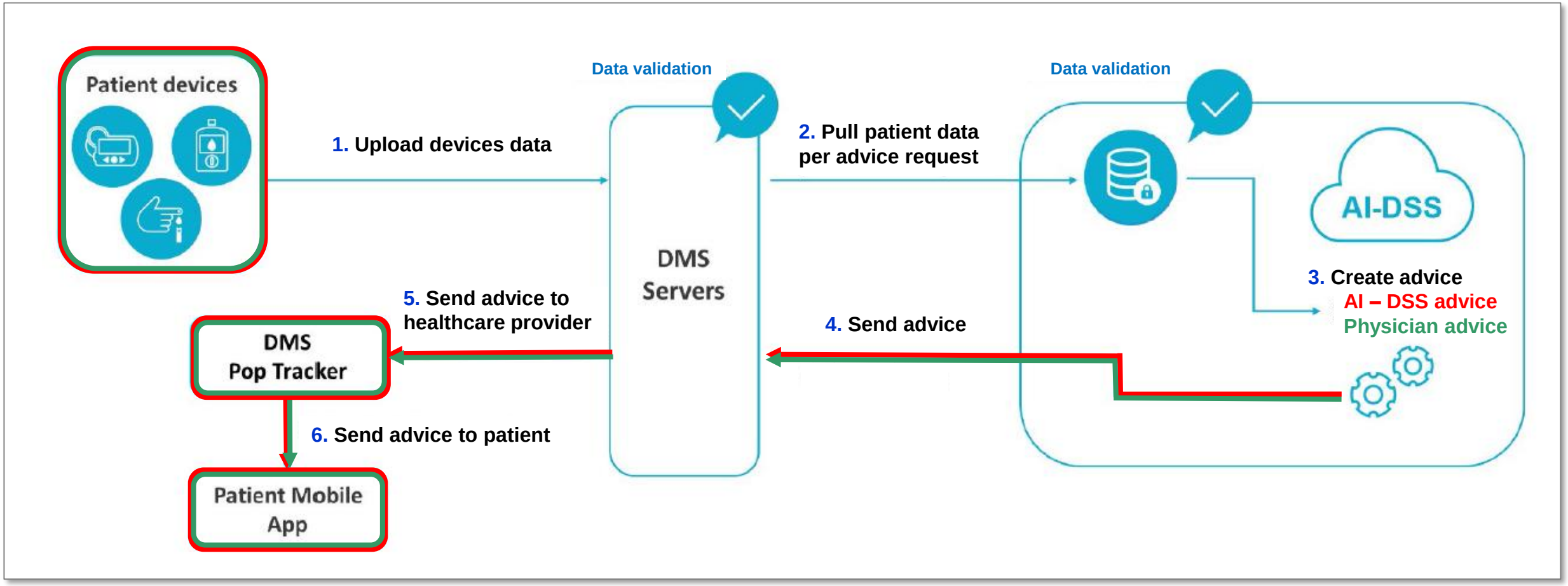
ANSWERS FOR DIABETES

Randomised Controlled Trials



Nimri, R. et al., **Nature Medicine** 26(9):1380-1384, 2020

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ANSWERS FOR DIABETES

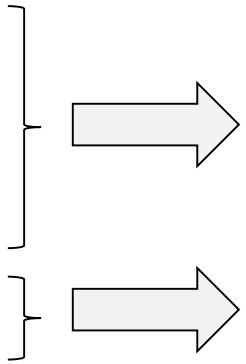
Randomised Controlled Trials

- The problem of confounding can be largely eliminated through randomisation
  - The process of **randomization** **balances all known and unknown (!) confounders,** thus creating groups with essentially **identical baseline** characteristics
  - That means: at the end of the trial any **between-group differences** can be largely **attributed to the intervention** under evaluation
- In pivotal clinical research key design requirements for a RCT include
  - A sufficiently large **sample size** **minimising the risk of random imbalances** and optimizing the chances to **detect clinically meaningful effects** of the intervention
  - **Intention-to-treat analysis:** all randomized participants are included in the statistical analysis and **analyzed according to the group they were originally assigned to,** regardless of what treatment (if any) they received
  - Almost **complete** **follow-up** of all randomly assigned participants

Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Gokhale, M. et al., **Diabetologia** 63(9):1694-1705, 2020

Randomised Controlled Trials

- Although considered gold standard RCTs may not always be possible
  - Adverse exposures
  - Rare outcomes
  - (Budget constraints)
  - Intervention already in wide use



- Observational trials
- Healthcare (outcomes) research

Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Gokhale, M. et al., **Diabetologia** 63(9):1694-1705, 2020

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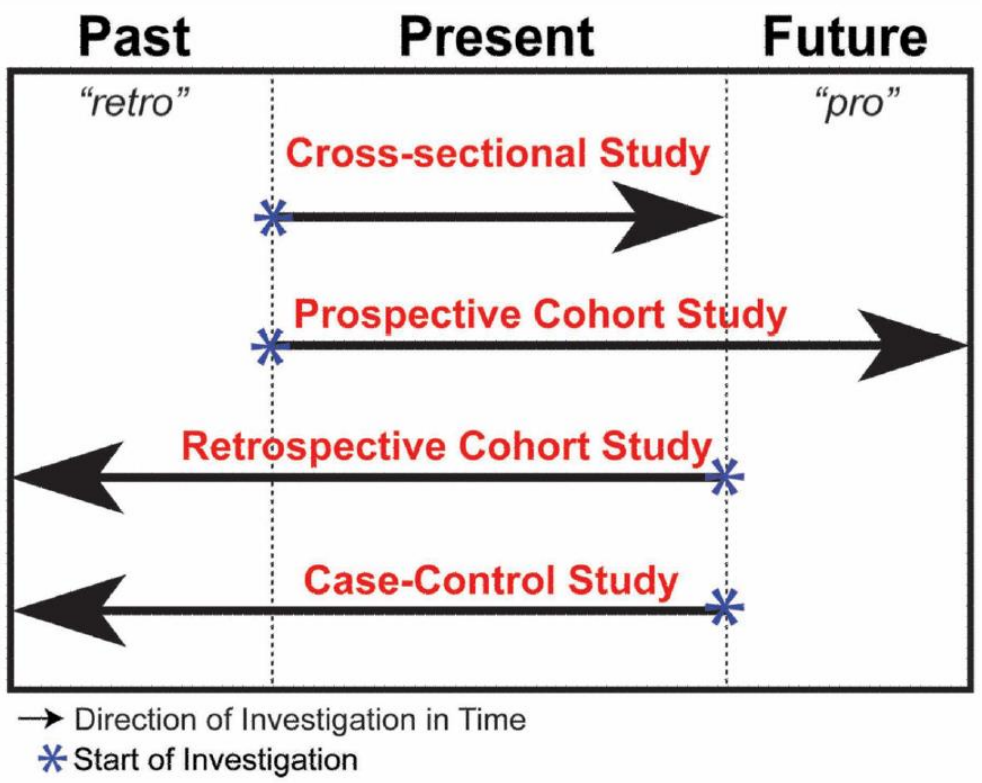
Observational trials



- Collecting observations from
  - A **cross-sectional** survey

Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

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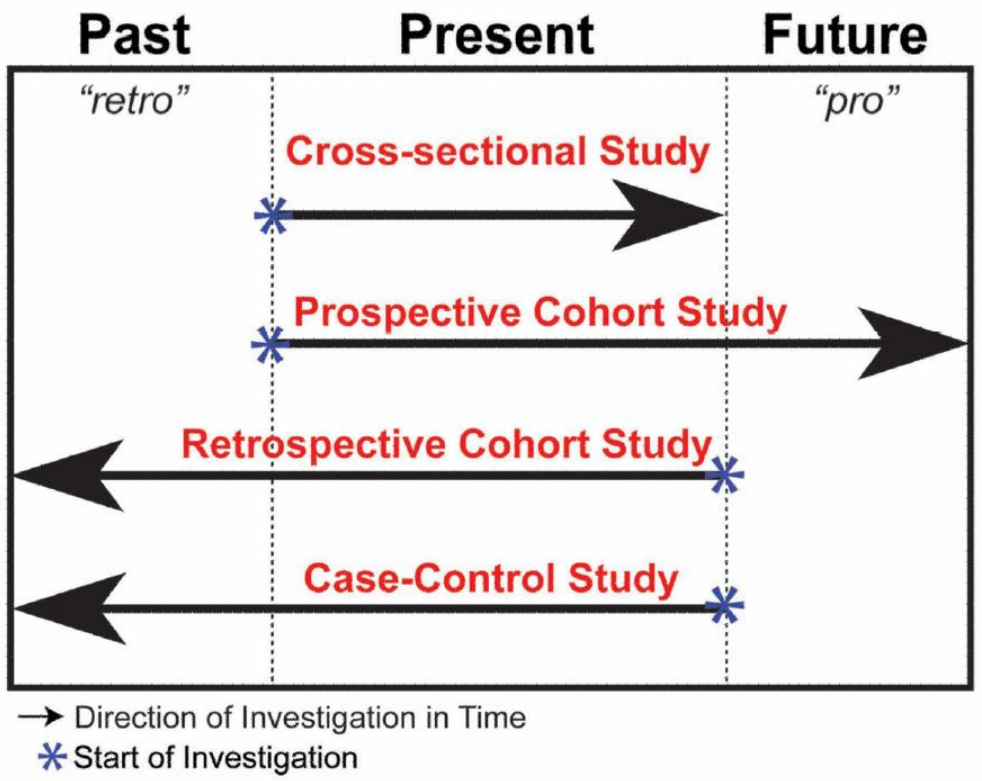
Observational trials



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- Collecting observations from
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  - **Prospective surveys** (e.g. collection of patient-reported outcome measures, digital biomarkers, behavioural data *via* an app)

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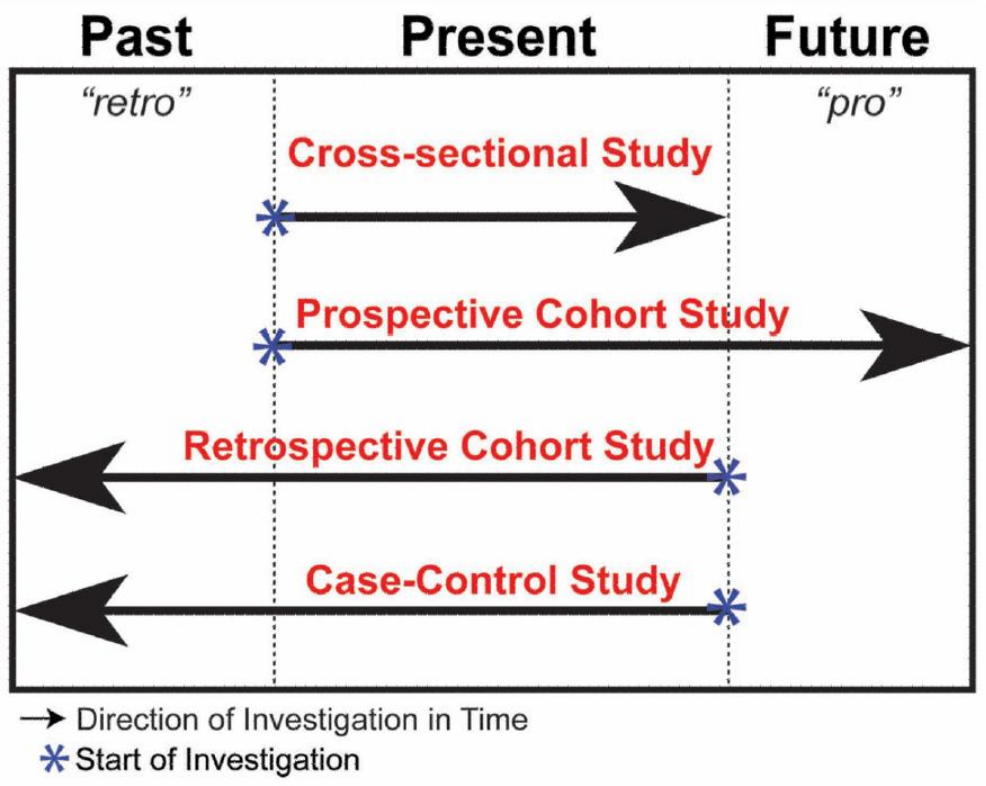
Observational trials



Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

- Collecting observations from
  - A **cross-sectional** survey
  - **Prospective surveys** (e.g. collection of patient-reported outcome measures, digital biomarkers, behavioural data *via* an app)
  - **Retrospective** analysis of registries, electronic health records, insurance claims

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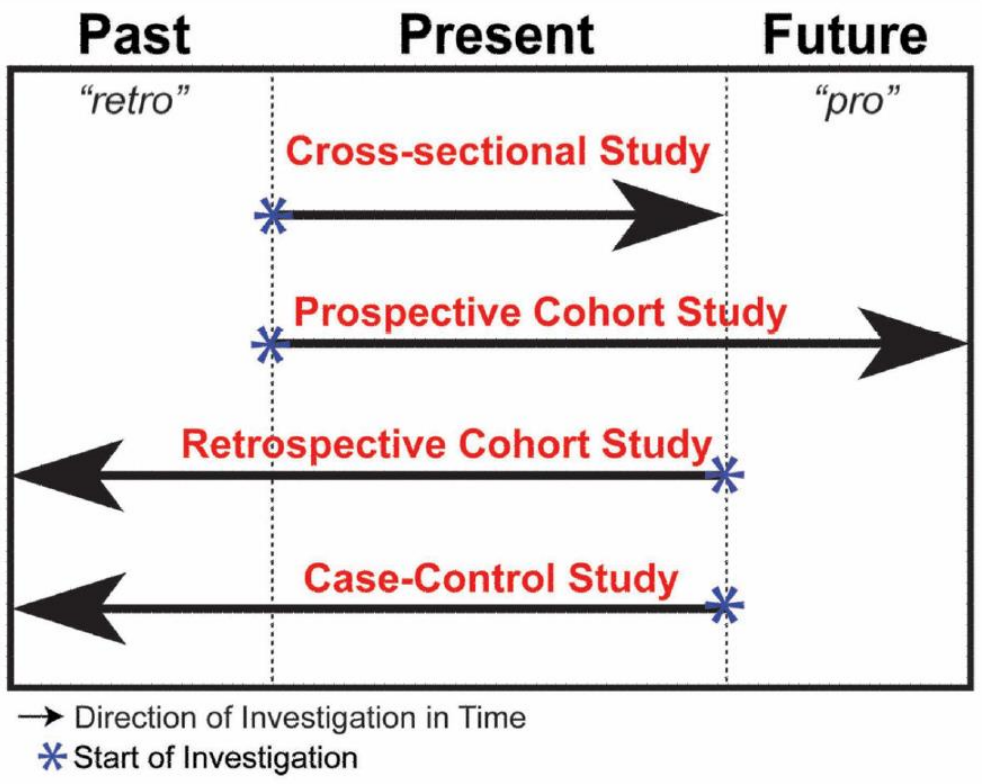
Observational trials



Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

- Collecting observations from
  - A **cross-sectional** survey
  - **Prospective surveys** (e.g. collection of patient-reported outcome measures, digital biomarkers, behavioural data *via* an app)
  - **Retrospective** analysis of registries, electronic health records, insurance claims
  - A **retrospective comparison of cases** with and without a specific outcome with regard to the exposure to defined factors of influence

Observational trials

- Drivers for the implementation of observational trials

Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

Observational trials

- Drivers for the implementation of observational trials
  - Demonstration of a positive healthcare effect in the full presence of **real-world treatment effect modifiers** which usually create a gap between the **efficacy** of an intervention seen in scientifically well controlled clinical trials and its **effectiveness** in the real-world (E2E gap).

Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

Observational trials

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  - Availability of easily collected huge amounts of **data** for common chronic diseases such as diabetes converges with an increasing availability of **data analysis tools** including those powered by AI

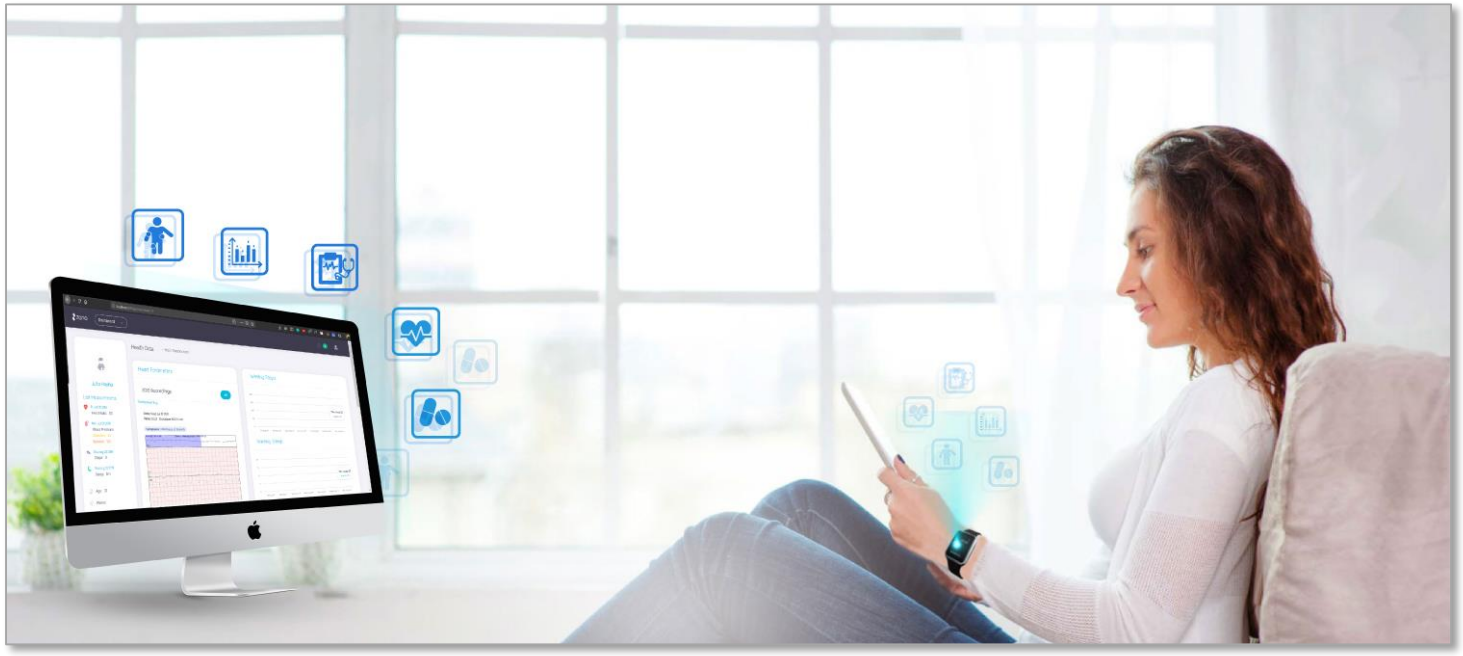
Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

Observational trials

- Drivers for the implementation of observational trials
  - Demonstration of a positive healthcare effect in the full presence of **real-world treatment effect modifiers** which usually create a gap between the **efficacy** of an intervention seen in scientifically well controlled clinical trials and its **effectiveness** in the real-world (E2E gap).
  - Availability of easily collected huge amounts of **data** for common chronic diseases such as diabetes converges with an increasing availability of **data analysis tools** including those powered by AI.
  - Retrospective observational trials can be implemented **fast and cost-effectively,** may require comparatively fewer subjects and allow for multiple risk factors to be assessed for one outcome.

Gerstein, H.C. et al., **Lancet** 393(10168):210-211, 2019
Song, J.W. & Chung, K.C. **Plast. Reconstr. Surg,** 126(6):2234-2242, 2010

Remote Decentralised Clinical Trials



- RDCT, also referred to as **virtual, web-based** or **hybrid** clinical trials.
- As many trial assessments as possible are carried out **in the participant's life settings,** without the need of visiting a medical facility.
- **Medical-grade wearables** applied to collect integrated information on digital endpoints based on a (multi) sensor-based acquisition of physiological and behavioural data

Schliess, F. Can Remote Decentralised Clinical Trials enhance clinical research? https://blog.profil.com/blog/can-randomised-decentralised-clinical-trials-enhance-clinical-research, 2021
Affini Dicenzo, T. & Schliess, F. Bridging the gap between clinical trials and clinical care. Are wearables fit for this purpose? https://www.openaccessgovernment.org/clinical-trials-and-clinical-care/85894/, 2020
Schliess, F. A vision on remote decentralised clinical trials. https://www.openaccessgovernment.org/a-vision-on-remote-decentralised-clinical-trials/88638/, 2020

RDCT opportunities

- **Democratize** the access to clinical trials by reaching population groups that would normally not have the possibility to enrol in a clinical study.
- More **diversity** and greater relevance to the real-world.
- **Study apps** can provide all relevant information regarding a clinical trial to people willing to enrol in a study.
- After reading the subject information and consent form, patients can send their **registration online** or use the app to contact a member of the study team to clarify possible doubts.
- Enables a **massive recruitment** of trial participants in a **short time** and at **low costs.**

Schliess, F. Can Remote Decentralised Clinical Trials enhance clinical research? https://blog.profil.com/blog/can-randomised-decentralised-clinical-trials-enhance-clinical-research, 2021
Affini Dicenzo, T. & Schliess, F. Bridging the gap between clinical trials and clinical care. Are wearables fit for this purpose? https://www.openaccessgovernment.org/clinical-trials-and-clinical-care/85894/, 2020
Schliess, F. A vision on remote decentralised clinical trials. https://www.openaccessgovernment.org/a-vision-on-remote-decentralised-clinical-trials/88638/, 2020

RDCT examples

Example: Apple Heart Study

to assess the suitability of a smartwatch program using an algorithm for photoplethysmography-based detection of atrial fibrillation and to estimate the diagnostic yield in a large population in the US under everyday conditions.

Download from the App → **Onboarding and Enrollment**

- **Screening, eligibility, and consent**
  - Interested individuals download and open the Apple Heart Study App
  - Self-verification of eligibility
  - Electronic presentation of the Informed Consent Form to potential trial participants
  - Digital signature on the iPhone touchscreen
  - Provision of a 24-hour study hotline
  - Participants asked to answer a demographic and medical history questionnaire before monitoring begins

Perez, M.V. et al., **N. Engl. J. Med.** 381:1909-1917, 2019
Turakhia, M.P. et al., **Am. Heart J.** 207:66-75, 2019

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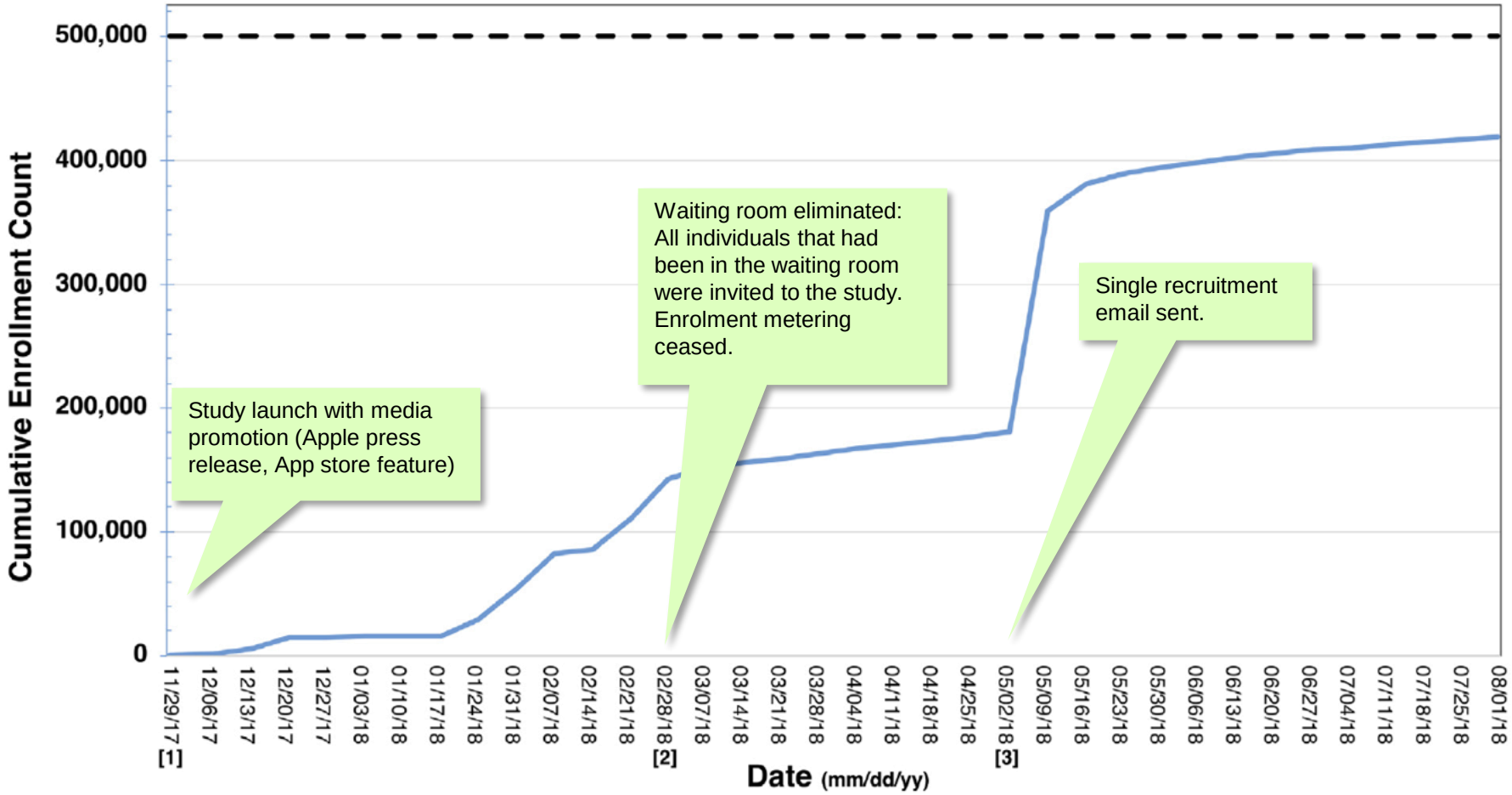
ANSWERS FOR DIABETES

RDCT examples

Example: Apple Heart Study



Perez, M.V. et al., **N. Engl. J. Med.** 381:1909-1917, 2019
Turakhia, M.P. et al., **Am. Heart J.** 207:66-75, 2019

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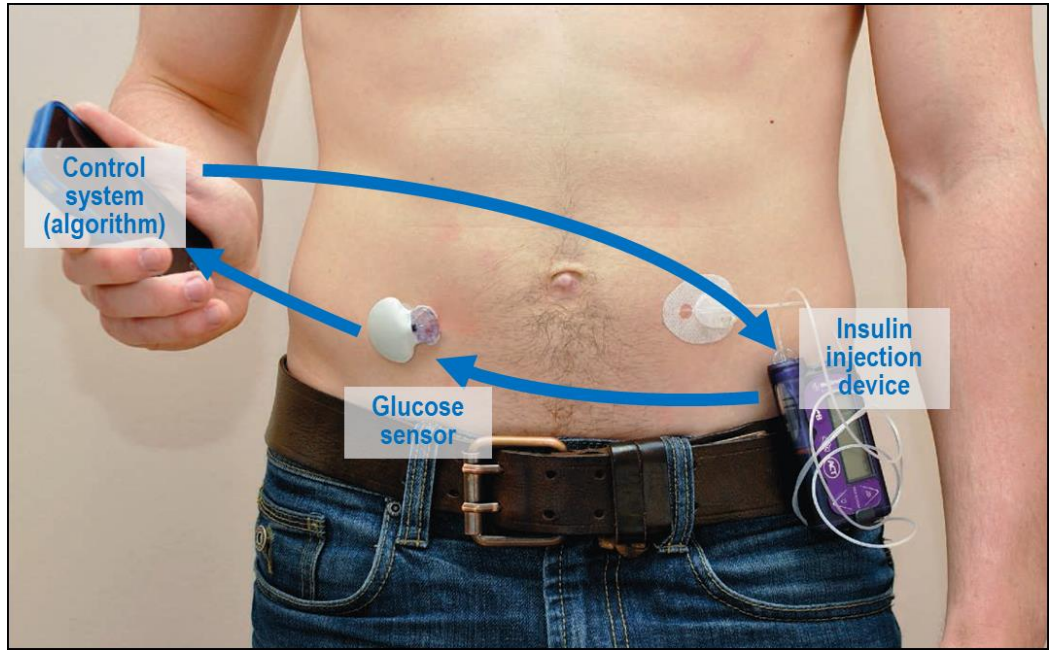
ANSWERS FOR DIABETES

RDCT examples

Example: AP@home study

Safety and effective for patients with T1D to administer their insulin at home using an automated insulin delivery (AID) system, also named artificial pancreas (AP).



Heinemann, L. et al., **J. Diabetes Sci. Technol.** 16:100-103, 2016
Thabit, H. et al., **N. Engl. J. Med.** 273(22):2129-2140
Heinemann, L. et al., **J. Diabetes Sci. Technol.** 10:950-958, 2011

- Setup as a **multi-centre** and **multi-national** randomised controlled clinical trial
- Landmark real-world clinical trial that integrated RDCT design elements to the field of **diabetes**
- During the intervention period of 12 weeks 58 participants (adults, children) performed their usual **everyday activities** under **free-living conditions,** even **without continuous remote monitoring or supervision.**
- Participants were completely free to **choose their meals**
- Access to a 24/7 helpline.

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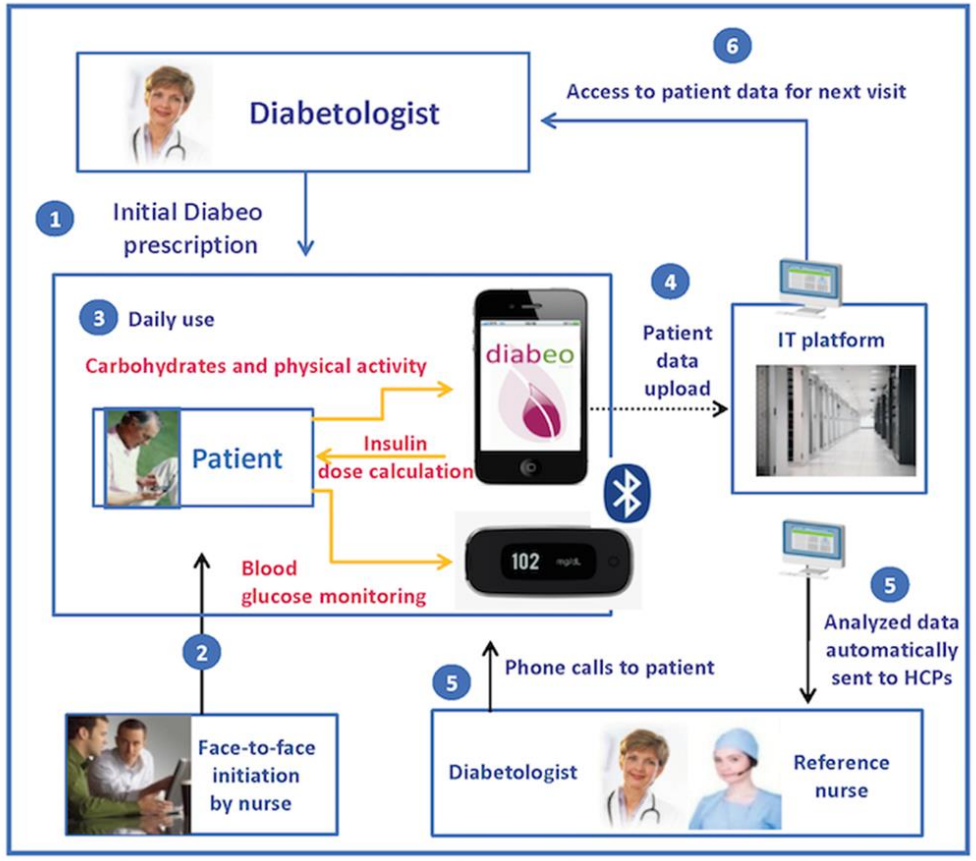
ANSWERS FOR DIABETES

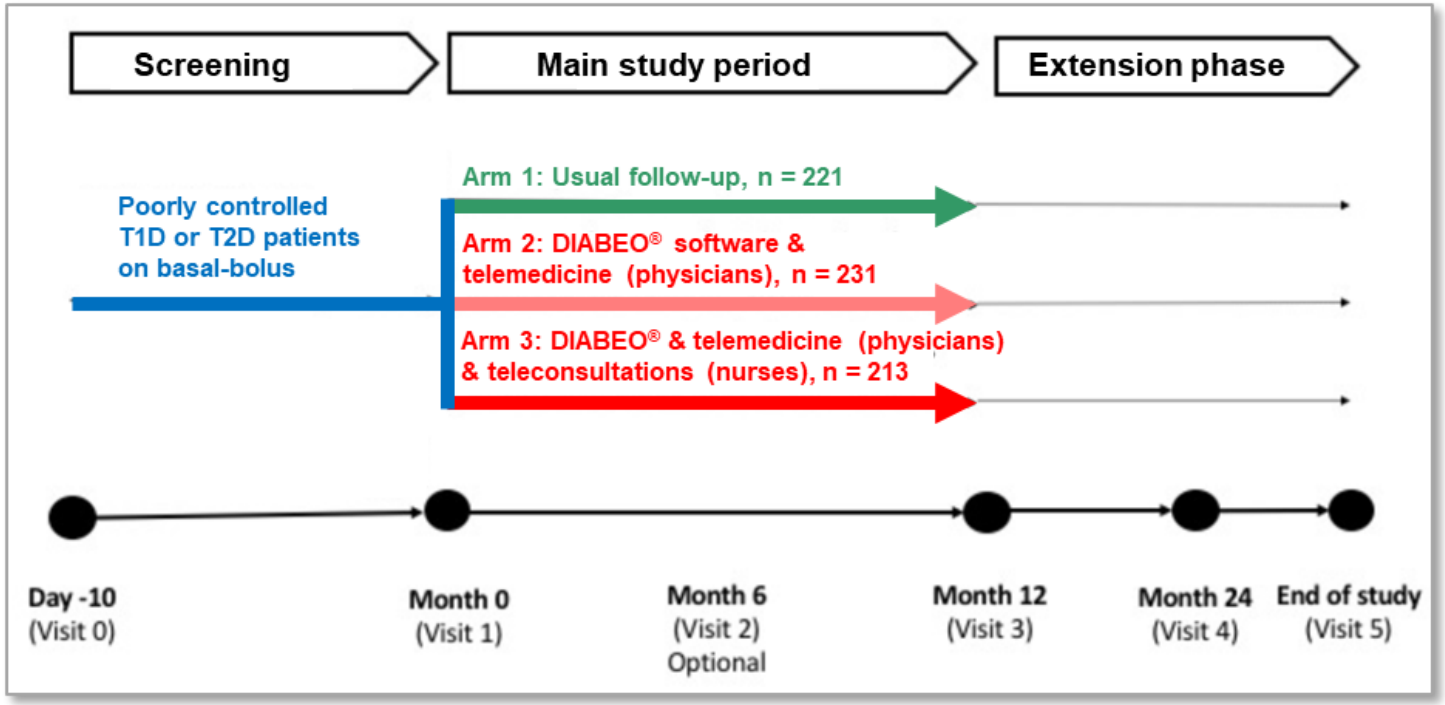
RDCT examples

Example: TELESAGE Study

Has shown safety and effectiveness of DIABEO® digital health application to support insulin dosing



- 12 month multi-center, double-randomized, open-label, three parallel–arms clinical trial, with **665 patients** allocated to **95 test centers** in France



Jeandidier, N. et al., **JMIR Res. Protoc.** 7(4):e66, 2018
Joubert, M. et al., **J. Diabetes Sci. Technol.** 13(6):1161-1168, 2019
Franc, S. et al., **Diabetes Technol. Ther.** 22(12):904-911, 2020

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ANSWERS FOR DIABETES

RDCT requirements

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.

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ANSWERS FOR DIABETES

RDCT requirements

- **Consumer-grade wearables** in clinical trials may be useful for the assessment of secondary endpoints in the context of generating hypotheses
  - Compliance of data collection and processing with the requirements for pivotal clinical trials set by EMA and FDA?*
- The use of **medical-grade wearables** validated to be **fit-for-purpose** in the specific **context-of-use** should be considered

Affini-Dicenco, T. & Schliess, F.
Bridging the gap between clinical trials and clinical care: are wearables fit for this purpose?
https://www.openaccessgovernment.org/clinical-trials-and-clinical-care/85894/, 2020

*ICH, International Conference on Harmonisation; GCP, good clinical practice; GDPR, General Data Protection Regulation; CDISC, Clinical Data Interchange Standards Consortium; 21 CFR Part 11, part of Title 21 of the Code of Federal Regulations that establishes the US Food and Drug Administration (FDA) regulations on electronic records and electronic signatures (ERES); ISO 27001, specifies a management system that is intended to bring information security under management control.

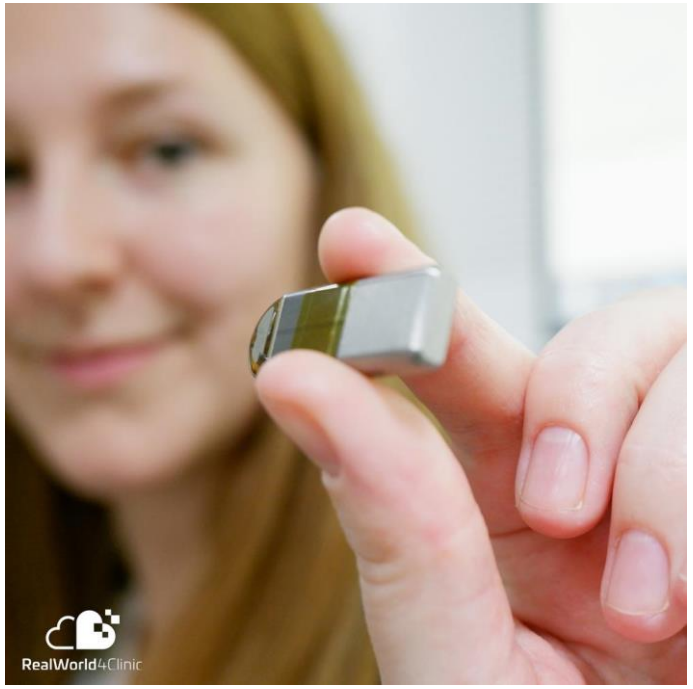
RealWorld4Clinic

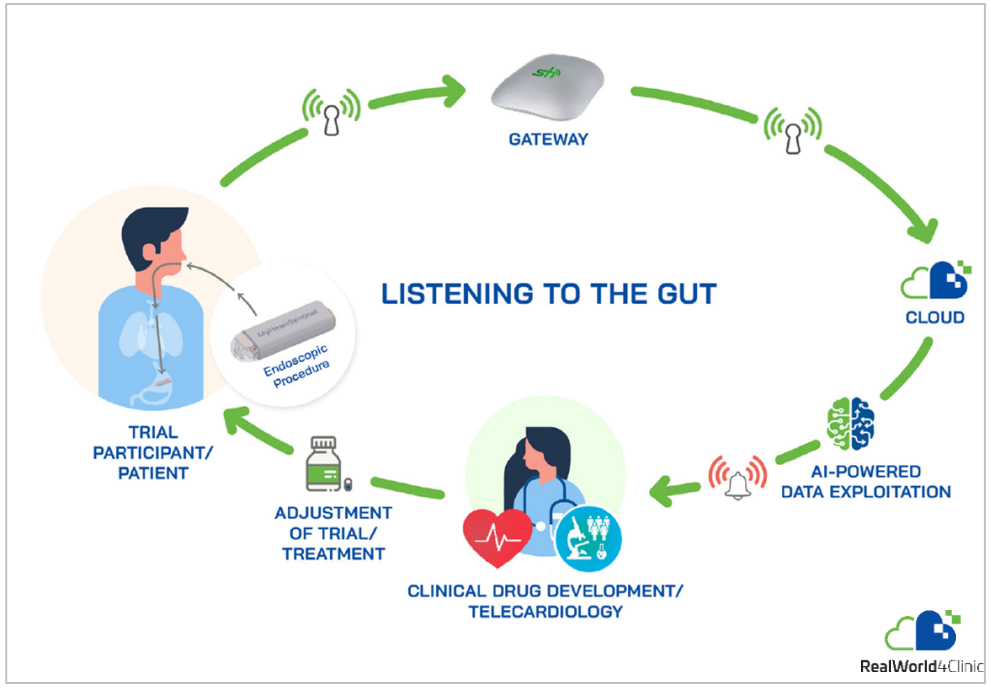
***Real-World* Cardio-Respiratory Health Monitoring *for Clinic*al Contract Research & Tele-Cardiology**

https://eit-health.de/en/realworld4clinic/

RealWorld4Clinic will accelerate market launch of MyHeartSentinel – a coin-sized medical device anchored to the fundus of the stomach. There it acquires real-life cardio-respiratory health data for exploitation in drug development and tele-cardiology

RealWorld4Clinic



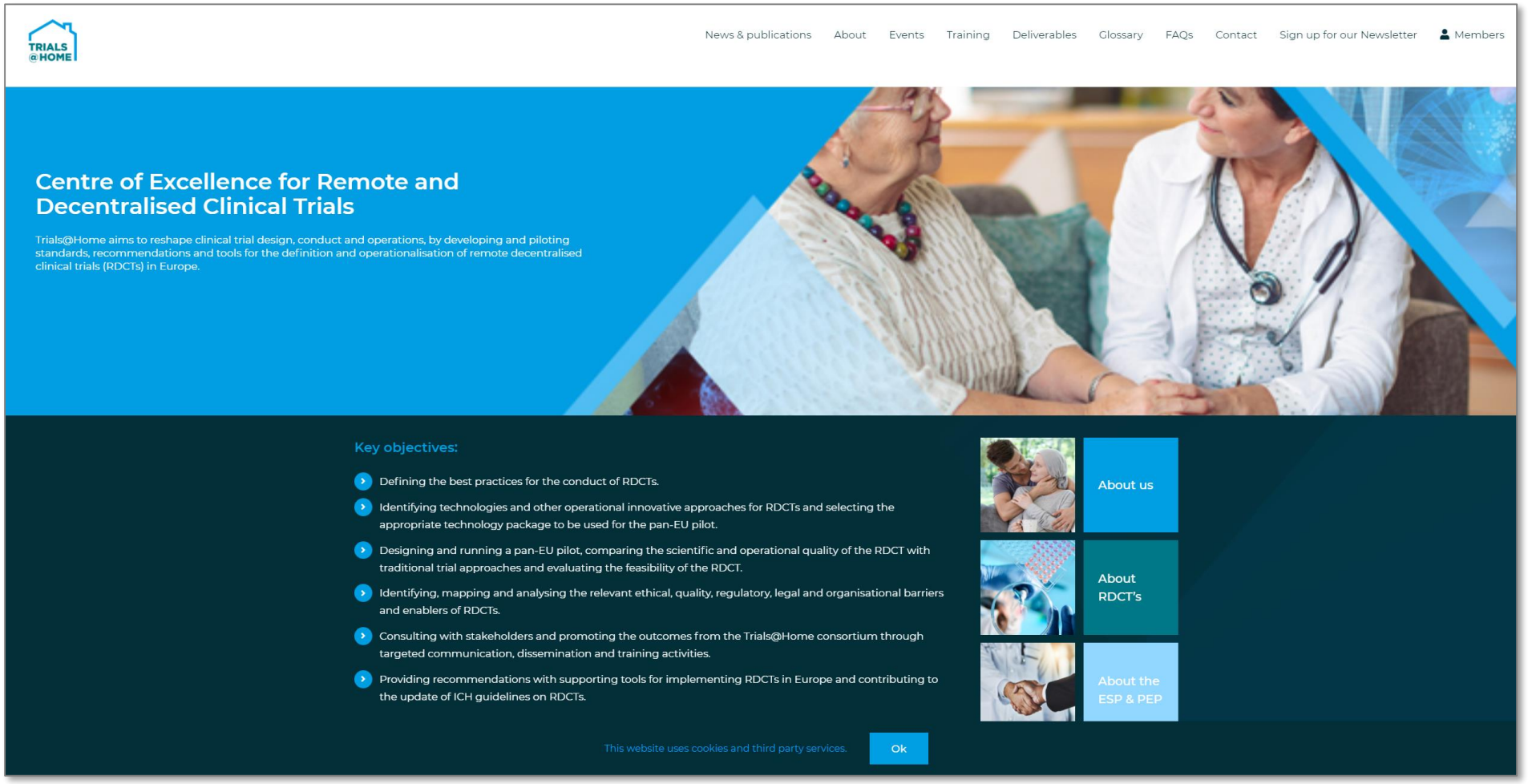


***Real-World* Cardio-Respiratory Health Monitoring *for Clinic*al Contract Research & Tele-Cardiology**

https://eit-health.de/en/realworld4clinic/

- The device will be enriched by patforms for **patient communication** and **personal data lifecycle** management.
- EIT Health-funded project phase
  - CE mark application, creating the conditions for scalability from drug development to outpatient cardiology

Trials@home IMI consortium



https://trialsathome.com/

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ANSWERS FOR DIABETES

RDCT limitations

- A “site-less” workflow may carry risks regarding the quality of trial outcomes.

RDCT limitations

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  - Lack of physical contact of trial participants with the study site may affect **engagement, adherence** to the trial protocol, **completeness** of follow-up and **reliance** on participant reported outcomes.

RDCT limitations

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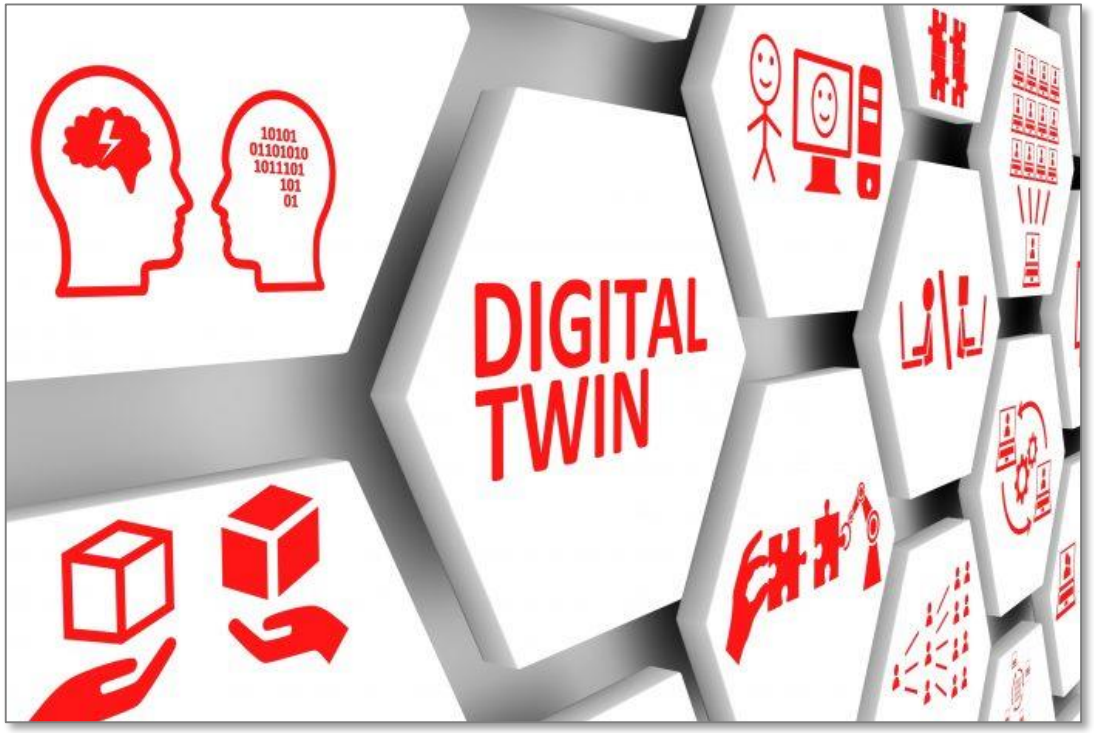
  - Considerable **loss of follow-up** may account to uncertain validity and generalizability inherent to the RDCT design.

RDCT limitations

- A “site-less” workflow may carry risks regarding the quality of trial outcomes.
  - Lack of physical contact of trial participants with the study site may affect **engagement, adherence** to the trial protocol, **completeness** of follow-up and **reliance** on participant reported outcomes.
  - Considerable **loss of follow-up** may account to uncertain validity and generalizability inherent to the RDCT design.
  - There may be a bias due to the preferred inclusion of **technology-oriented trial participants** and those who have certain communication technologies already available.

In-silico clinical trials using digital twins

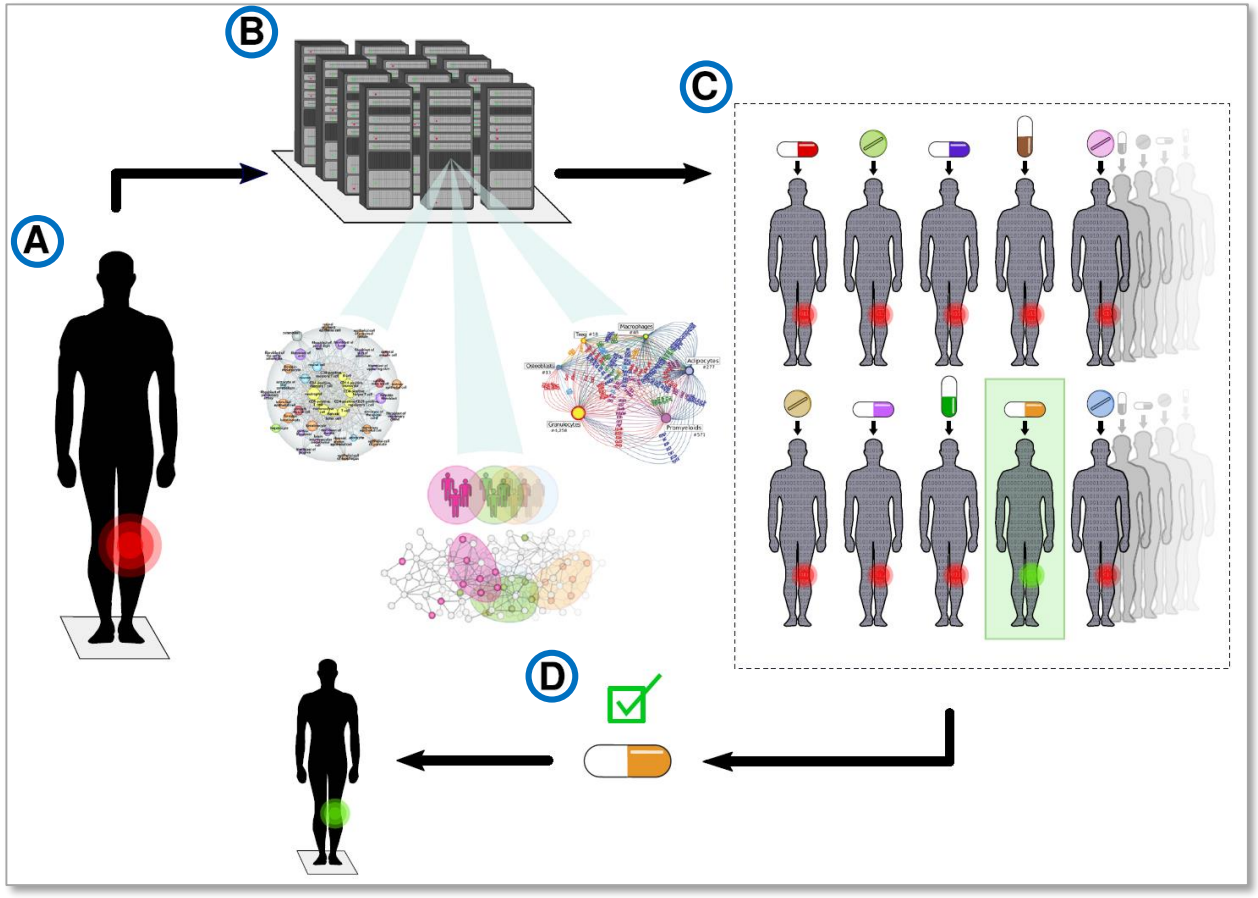


- Digital twins: **multi-scale in-silico** representation of a patient/trial participant.
- Ideally reflect the person's **metabolism, physiology, behaviour and morbidity** over time with high levels of granularity.
- Digital twins can enable
  - **In-silico clinical trials** in drug and medical device development
  - Highly **personalised treatment** of patients

Schliess, F. https://www.openaccessgovernment.org/digital-twins/93402/, 2020

profil
ANSWERS FOR DIABETES

In-silico clinical trials using digital twins

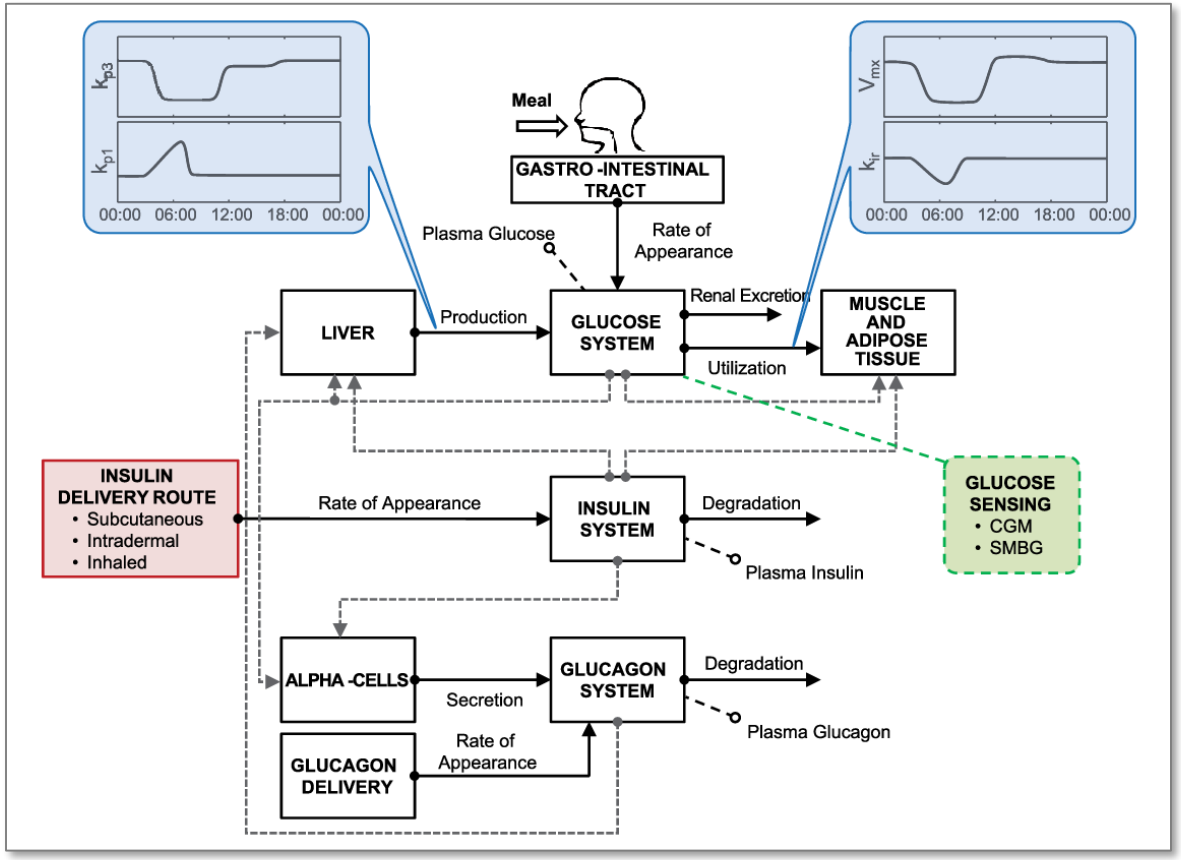


- Testing “thousands” of drugs per twin.
  - A. Individual patient with a local sign of disease
  - B. Construction of an unlimited number of copies of a digital twin
  - C. Each twin computationally treated with thousands of drugs
  - D. Drug most effective in-silico selected for treatment of the patient
- Statistical population model to generate cohorts of digital twins for testing pre-selected drugs.
- Predicting risk-benefit profiles of individuals & sub-groups, informing treatment and clinical trial design.

Björnsson, B. et al., **Genome Med.** 12(1):4, 2019

profil
ANSWERS FOR DIABETES

UVA/Padova diabetes simulator



- In 2008 **accepted by the FDA** as a **substitute to animal trials** in the preclinical testing of closed-loop control (Automated Insulin Delivery, artificial pancreas) algorithms in **T1D.**[1,2]
- Can be used to reliably assess **novel insulin treatments** and AI-powered decision support for the adjustment of insulin pump therapy.[3-5]
- Padova **T2D** simulator for testing anti-diabetic drugs. Simulates plasma glucose, insulin and C-peptide during a meal.[6]

1. Kovatchev, B.P. et al, **J. Diabetes Sci. Technol.** 3(1):44-55, 2009
2. Dalla Man, C. et al., **J. Diabetes Sci. Technol.** 8(1):26-34, 2014
3. Vettoretti, M. et al., **IEEE Trans Biomed Eng.** 65(6):1281-1290, 2018
4. Tyler, N.S. et al., **Nat. Met.** 2(7): 612-619, 2020
5. Noaro, G. et al., **J. Diabetes Sci. Technol.** doi: 10.1177/19322968211043162, 2021
6. Visentin, R. et al, **Diabetes Technol. Ther.** 22(12):892-903, 2020

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ANSWERS FOR DIABETES

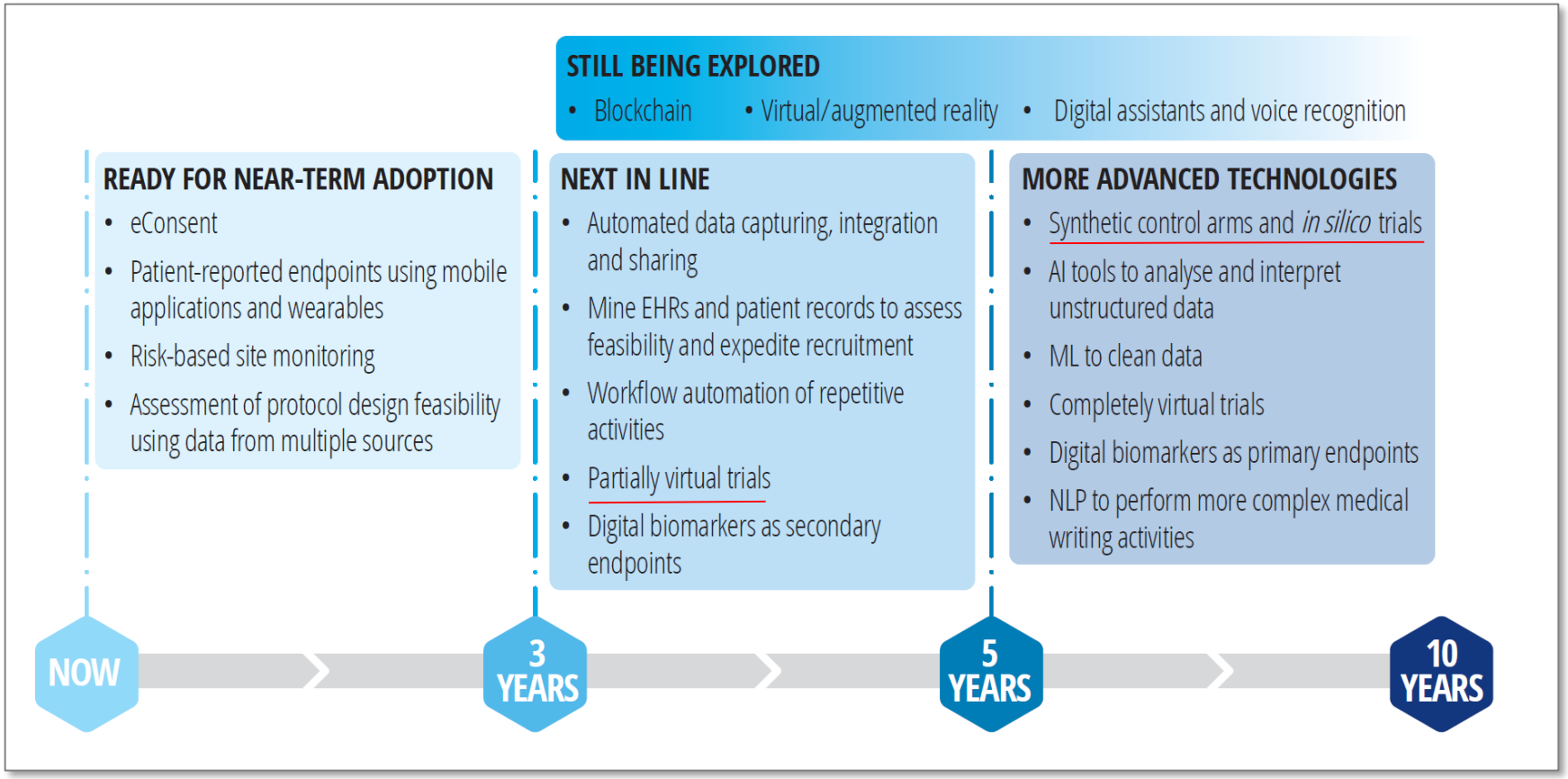
In-silico clinical trials: Where we are today

- A **comprehensive molecular and behavioural profiling** required for the construction of digital twins is not yet standard in clinical research and clinical care.
- **High potential** of digital twin/in-silico trials generally well recognized.
- **Ethical, legal and social issues** related to a personalised definition of health and disease and the fluent transition between therapy, prevention and human enhancement may require a thorough societal debate.
- Aspects of **digital twins/data ownership** and **incentives** for citizens to donate his/her digital twins for societally relevant research to be addressed.
- **Registries** dedicated to the registration and reporting of digital twin/in-silico trials missing.

Schliess, F. https://www.openaccessgovernment.org/digital-twins/93402/, 2020
Schliess, F. https://www.openaccessgovernment.org/artificial-intelligence-in-healthcare/80068/, 2020
Bruynseels, K. et al., **Front Genet.** 9:31, 2018
Kaur, H. et al. **Indian J. Pharmacol.** 53(2): 160-169, 2021

In-silico clinical trials: Where we are today

Expected timeline for the adoption of AI-enhanced digital technologies at scale



https://www2.deloitte.com/content/dam/insights/us/articles/22934_intelligent-clinical-trials/DI_Intelligent-clinical-trials.pdf

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ANSWERS FOR DIABETES

Generation of evidence

- Design approaches to trialing Digital Health Technologies
- Evidence frameworks for Digital Health Technologies
- Setting up your clinical trial program and selecting the right partners
- Q&A

European Medical Device Regulation

5.5.2017 EN Official Journal of the European Union L 117/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

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(Text with EEA relevance)

- Main objective: To enhance the **safety and quality** of medical devices available in the European **single market**
  - To offer a high level of **protection** to patients, users and other persons
- No particular trial designs are required by default.
  - Applies the principle of **proportionality,** i.e. a risk-based approach when it refers to three general stages of clinical development

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

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(Text with EEA relevance)

- Requirements for the execution of a clinical investigation include that
  - “measures should be taken to **minimize bias,** such as randomisation, and management of confounding factors”.
  - Clinical investigatios to be performed in “a clinical environment that is representative of the **intended normal conditions of use** of the device in the target patient population”.

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

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(Text with EEA relevance)

- Challenge: Many DHTs were upgraded to a **higher class** of device
  - Need of a certification from a **Notified Body** and performance of **clinical investigations** that, in many cases, were not required before.
  - Higher **costs,** longer **time** to market.

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745&from=EN

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ANSWERS FOR DIABETES

Key responsibles: Sponsor & investigator

MDR 2017/745 Chapter I (Scope and definitions), Article 2 (Definitions)

- 49 **Sponsor:** any individual, company, institution or organisation which takes responsibility for the *initiation, for the management and setting up of the financing* of the clinical investigation.
- 54 **Investigator:** individual *responsible* for the conduct of a clinical investigation *at a clinical investigation site.*

Key responsibles: Investigator-initiated trials

Investigator-initiated trials (IIT)

- IITs are different from industry-sponsored trials by mainly addressing **knowledge driven scientific questions.**
- **Sponsor: Investigator** or the body who enters into an agreement with a pharmaceutical or medical device company, takes responsibility for all scientific, regulatory, and operational issues.

Suvarna, V., **Perspect. Clin. Res.** 3(4):119-121, 2012

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ANSWERS FOR DIABETES

Key responsibles: Investigator-initiated trials

Investigator-initiated trials (IIT)

- **A company may support IITs** by providing drugs/devices, active comparators, funding, and/or specific scientific services.
- There should be **no association between IIT support and a potential ambition to promote the prescription** of the medical product under investigation.

Suvarna, V., **Perspect. Clin. Res.** 3(4):119-121, 2012

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ANSWERS FOR DIABETES

Clinical evidence

MDR 2017/745 Chapter I (Scope and definitions), Article 2 (Definitions)

- 51 **Clinical evidence** means *clinical data and clinical evaluation results* pertaining to a device of a sufficient amount and quality to allow a qualified assessment of *whether the device is safe and achieves* ***the intended clinical benefit(s),*** …

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ANSWERS FOR DIABETES

Clinical evidence

MDR 2017/745 Chapter I (Scope and definitions), Article 2 (Definitions)

- 51 **Clinical evidence** means *clinical data and clinical evaluation results* pertaining to a device of a sufficient amount and quality to allow a qualified assessment of *whether the device is safe and achieves* ***the intended clinical benefit(s),*** …

MDR 2017/745 Chapter VI (Clinical evaluation and clinical investigation), Article 61 (Clinical evaluation)

- *Confirmation of conformity* with relevant general safety and performance requirements … … shall be *based on clinical* ***data providing sufficient clinical evidence*****,** including where applicable relevant data as referred to in Annex III.
- The *manufacturer shall specify and justify the* ***level of clinical evidence*** necessary to demonstrate conformity … . That level of clinical evidence shall be *appropriate in view of the characteristics of the device and its intended purpose.*

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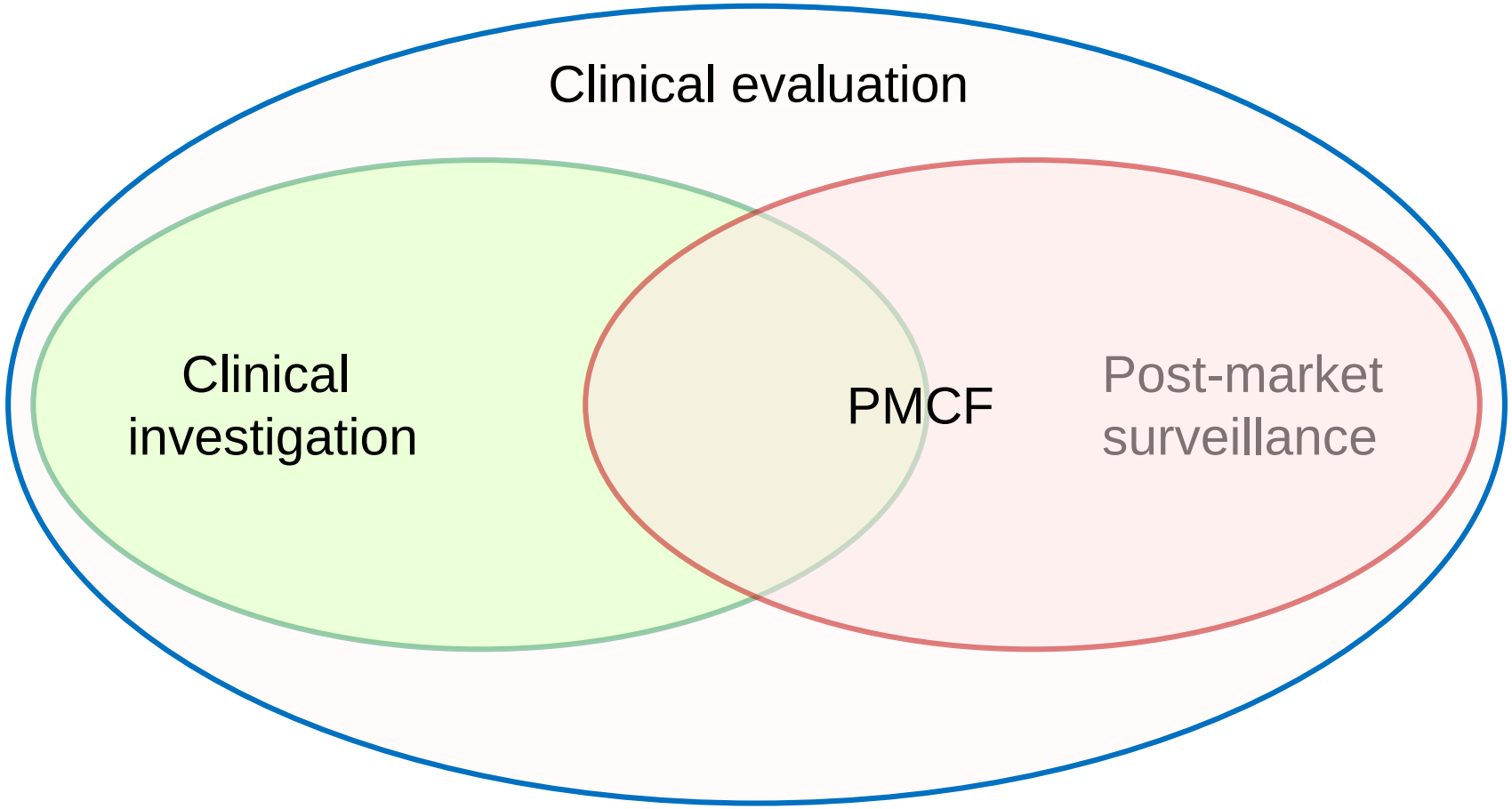
ANSWERS FOR DIABETES

Clinical investigation & clinical evaluation



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ANSWERS FOR DIABETES

Clinical investigation

Regulatory status	Pre-market	Post-market

DIN ISO 14155: 2021-05 „Clinical investigation of medical devices for human subjects — Good clinical practice”

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ANSWERS FOR DIABETES

Clinical investigation

Regulatory status	Pre-market		Post-market
Clinical development stage	Pilot stage	Pivotal stage	Post-market stage

DIN ISO 14155: 2021-05 „Clinical investigation of medical devices for human subjects — Good clinical practice"

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ANSWERS FOR DIABETES

Clinical investigation

Regulatory status	Pre-market		Post-market	
Clinical development stage	Pilot stage	Pivotal stage	Post-market stage	
Type of design	Exploratory or confirmatory	Confirmatory		Observational

DIN ISO 14155: 2021-05 „Clinical investigation of medical devices for human subjects — Good clinical practice"

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ANSWERS FOR DIABETES

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Descriptors of clinical investigations	First in human clinical investigation Early feasibility clinical investigation Traditional feasibility clinical investigation	Pivotal clinical investigation **Art. 62** **Clinical investigations to demonstrate conformity of devices (pre CE)**	Post-market clinical investigation **Art. 74** **Clinical investigations regarding devices bearing the CE marking (PMCF)**	Registry° Post-market clinical investigation

°Registry data may be used for pre-market regulatory purposes this can also apply to the post-market clinical investigation data.

DIN ISO 14155: 2021-05 „Clinical investigation of medical devices for human subjects — Good clinical practice"

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ANSWERS FOR DIABETES

Clinical investigation

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Burden to subject	**Requirements regarding other clinical investigations (IITs)**	**Interventional** **Art. 82**		Non-interventional

°Registry data may be used for pre-market regulatory purposes this can also apply to the post-market clinical investigation data.

DIN ISO 14155: 2021-05 „Clinical investigation of medical devices for human subjects — Good clinical practice"

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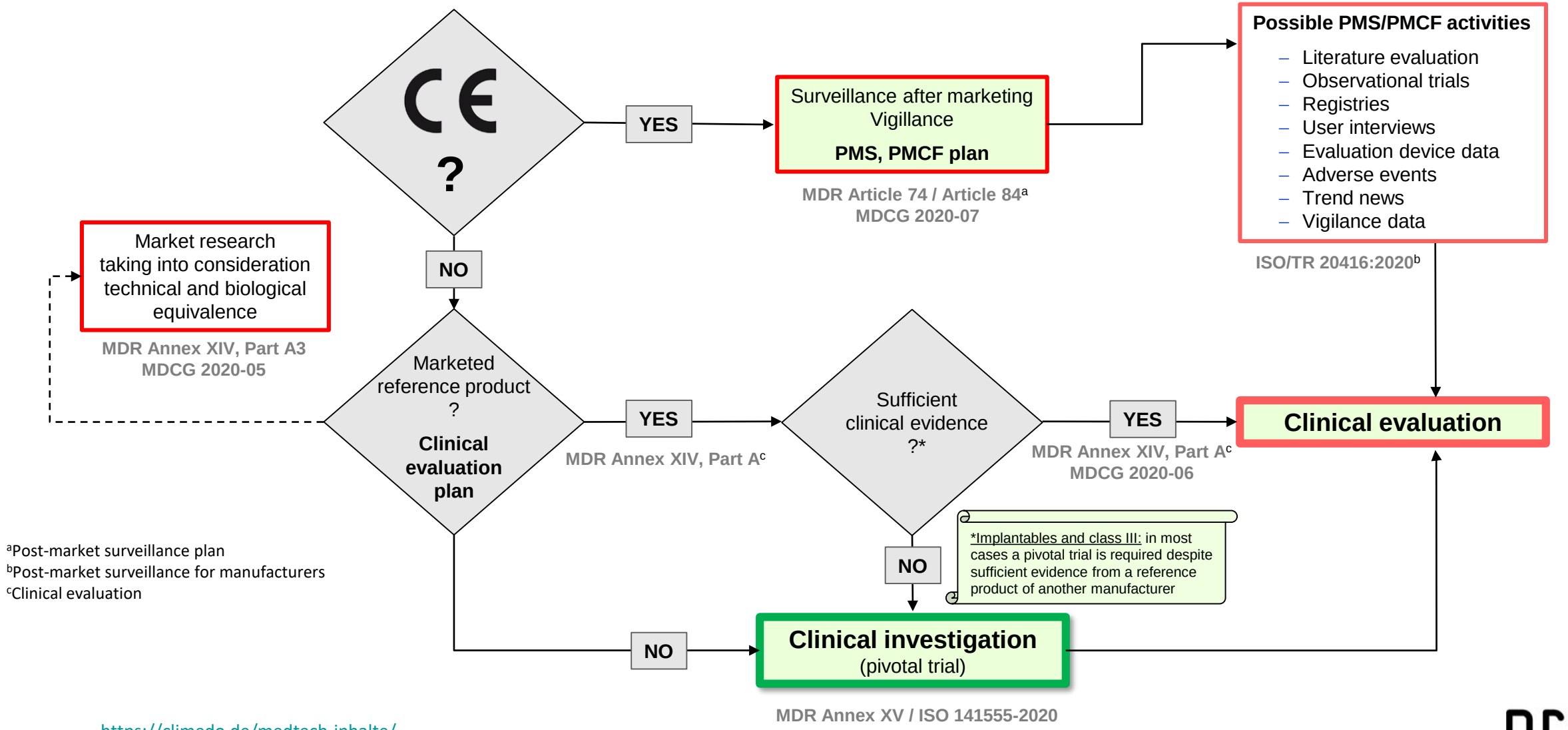
ANSWERS FOR DIABETES

Clinical investigation YES or NO?



[a]Post-market surveillance plan
[b]Post-market surveillance for manufacturers
[c]Clinical evaluation

https://climedo.de/medtech-inhalte/

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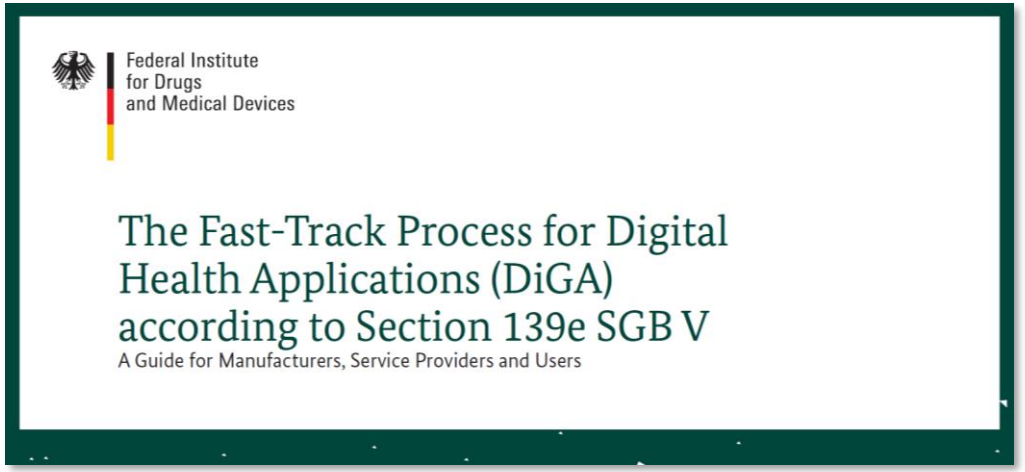
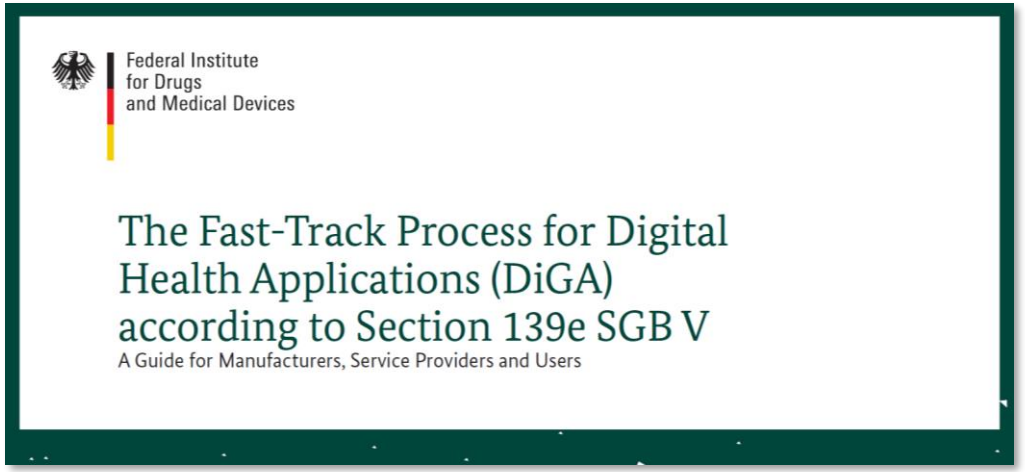
ANSWERS FOR DIABETES

DiGA-Fast-Track: Clinical trial



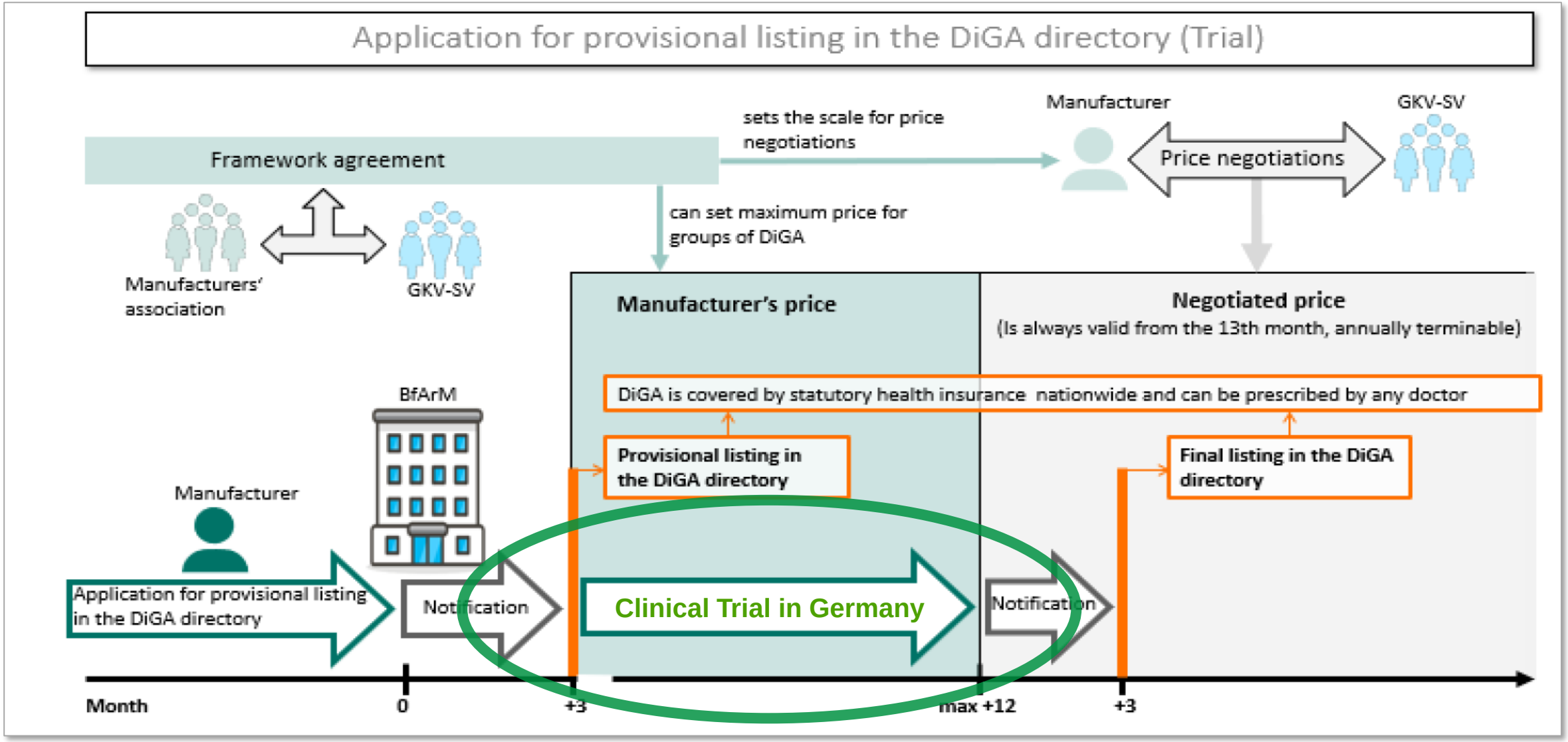
https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Beratungsverfahren/DiGA-Leitfaden.pdf?__blob=publicationFile&v=11
https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2

DiGA-Fast-Track: Clinical trial



https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Beratungsverfahren/DiGA-Leitfaden.pdf?__blob=publicationFile&v=11
https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2

Provisional listing in the DiGA directory



https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2

Demonstrate a positive healthcare effect

Scientific evaluation concept	If an application for provisional listing is to be submitted, a scientific evaluation concept must be attached to it. To prove the positive effect of care according to generally accepted scientific standards, this concept must be prepared by an institution independent of the manufacturer according to generally accepted scientific standards.
Positive Healthcare Effect	Positive healthcare effects in the sense of the DiGAV consist either of medical benefits or in patient-relevant improvements of structure and processes in healthcare.

https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2 (Glossary)

Demonstrate a positive healthcare effect

Medical benefit	Medical benefit according to DiGAV is the perceptible effect for a patient specifically regarding improvement of the state of health, the shortening of the duration of the disease, the extension of survival or an improvement in the health-related quality of life.

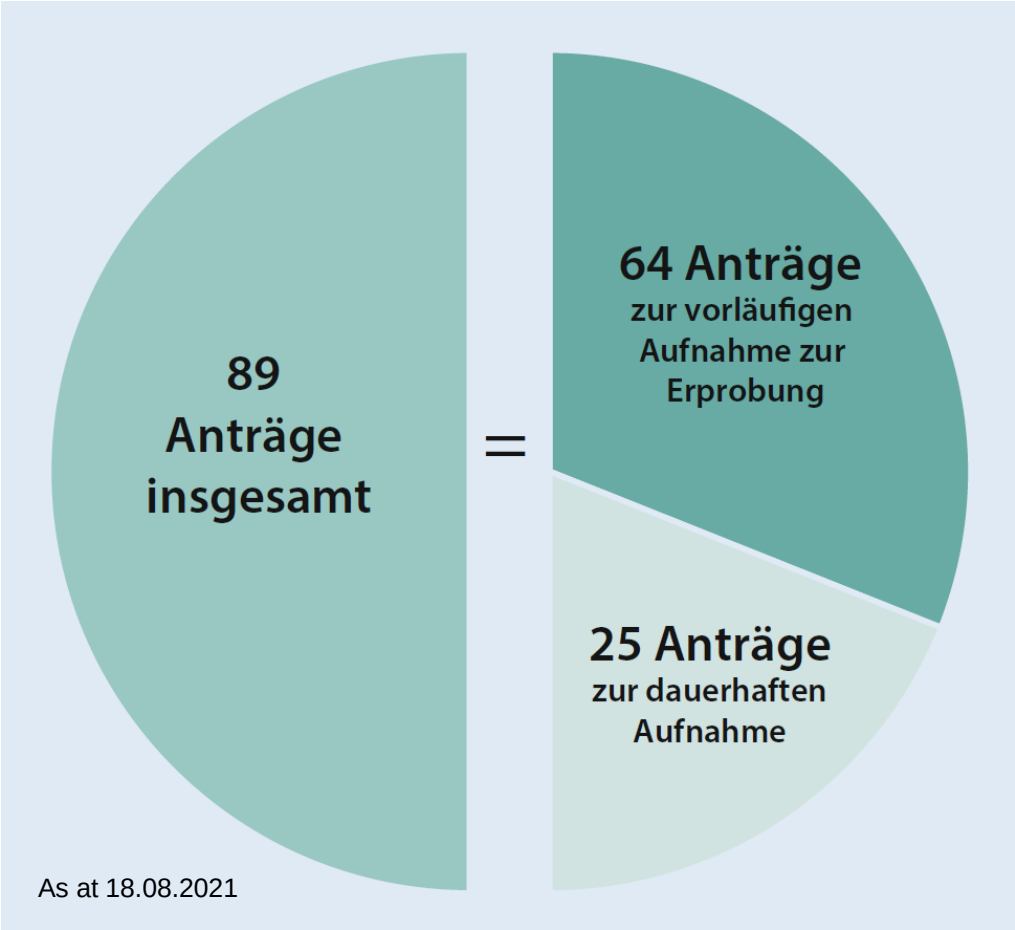
https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2 (Glossary)

Demonstrate a positive healthcare effect

Patient-relevant improvements of structure and processes	Patient-relevant improvement of structure and processes in healthcare are aimed at supporting patients' health behaviour or at integrating processes between patients and care providers in the context of the identification, monitoring, treatment or alleviation of diseases or the recognition, treatment, alleviation or compensation of injuries or disabilities. They include particularly the areas of – coordination of treatment processes, – alignment of treatment with guides and recognised standards, – adherence, – facilitating access to healthcare, – patient safety, – health literacy, – patient autonomy, – coping with illness-related difficulties in everyday life or – reducing therapy-related expenses and strains for patients and their relatives.

https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2 (Glossary)

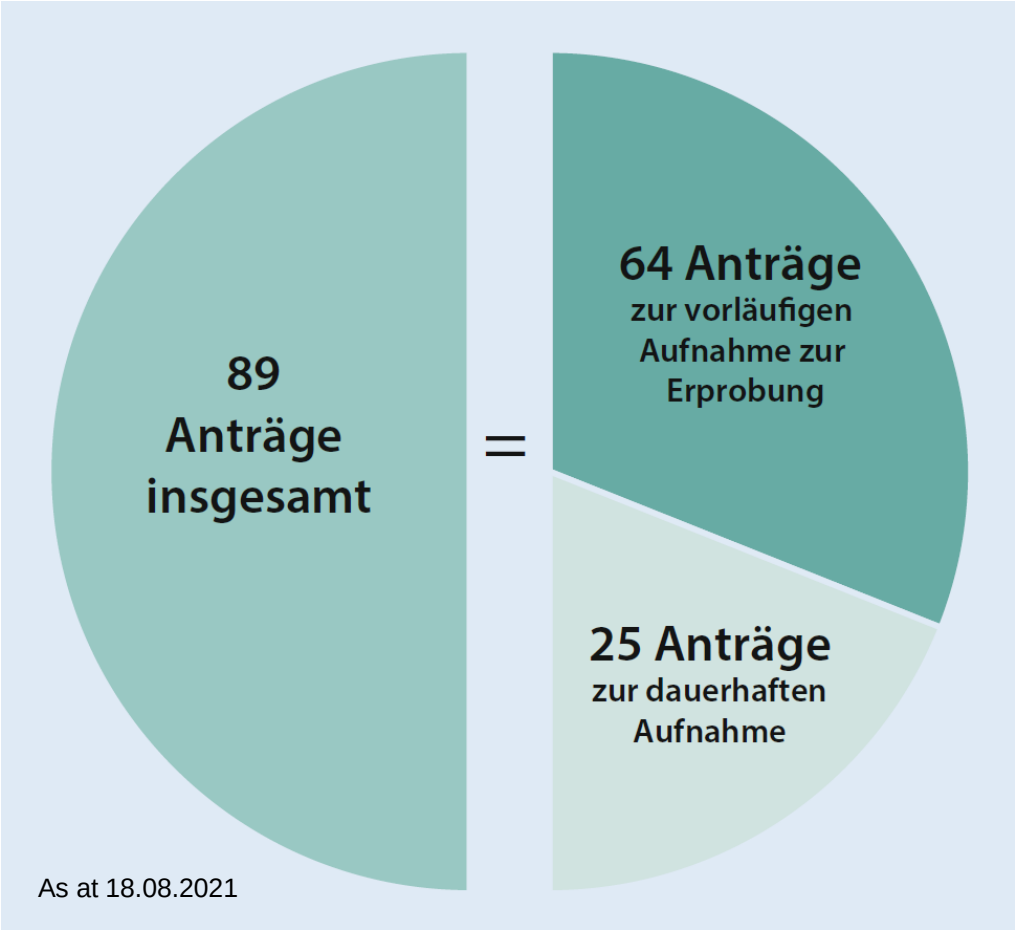
DiGA applications and listings



- 89 applications (64 for provisional, 25 for permanent listing, as at 18.08.2021).
- Of the 89 applications
  - Four were rejected
  - 42 applications were withdrawn by the manufactures, 15 of which were lately modified and resubmitted.
  - Withdrawal reasons included **data analysis problems, not enough evidence** or **unsuitable endpoints.**

Lauer, W. et al., **Bundesgesundheitsblatt** 64:1232-1240, 2021
https://link.springer.com/content/pdf/10.1007/s00103-021-03409-7.pdf

DiGA applications and listings



- 22 DiGAs listed in the DiGA directory (8.10.2021)
  - **Five DiGAs listed permanently.**
  - Four of them distributed by the one and the same company with a longstanding track record in digital therapy
  - 17 provisionally listed DiGAs
  - 10 out of the 22 DiGAs follow a **behavioural therapy** approach complementing existing treatments rather than substituting them.
  - Only one provisionally listed DiGA dedicated to the management of diabetes.

Lauer, W. et al., **Bundesgesundheitsblatt** 64:1232-1240, 2021
https://link.springer.com/content/pdf/10.1007/s00103-021-03409-7.pdf

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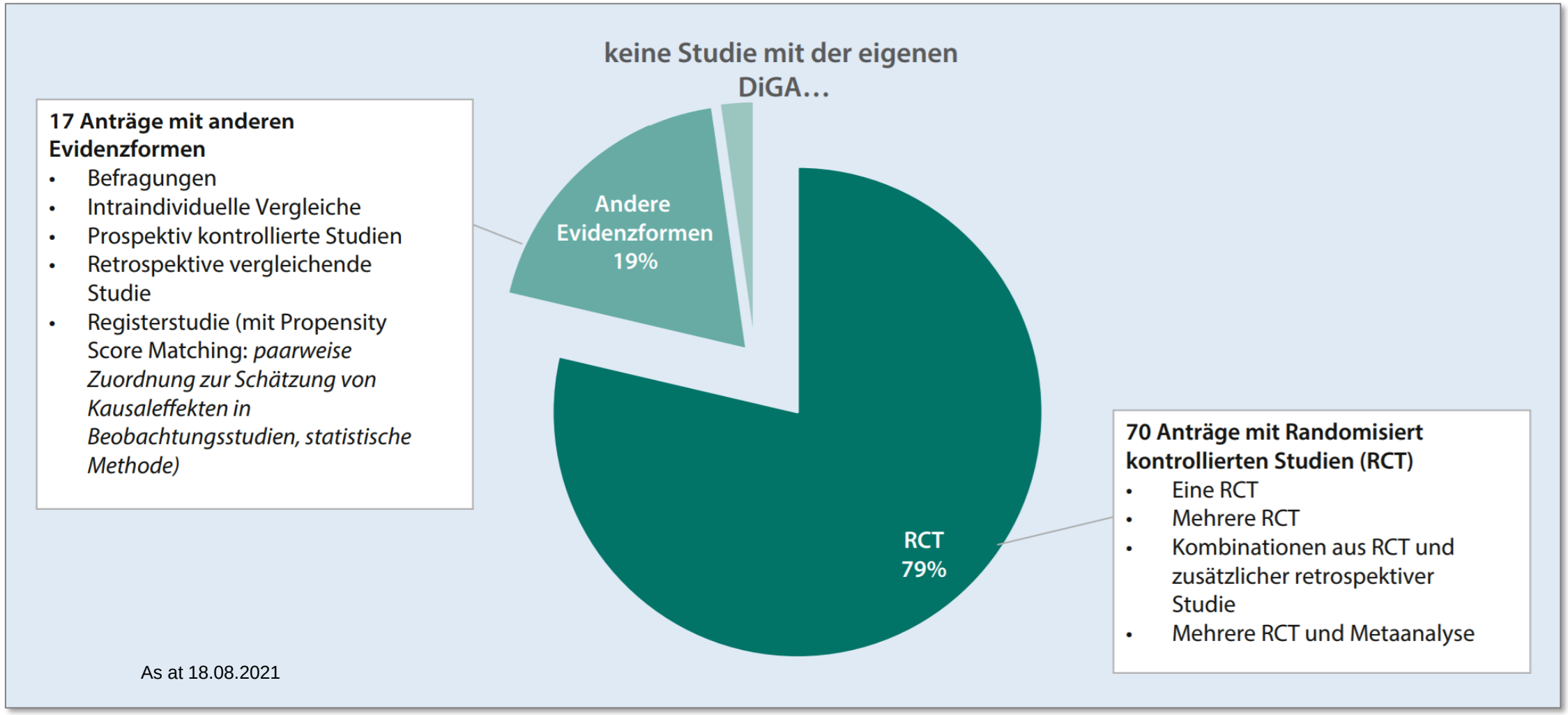
ANSWERS FOR DIABETES

Type of evidence submitted



Lauer, W. et al., **Bundesgesundheitsblatt** 64:1232-1240, 2021
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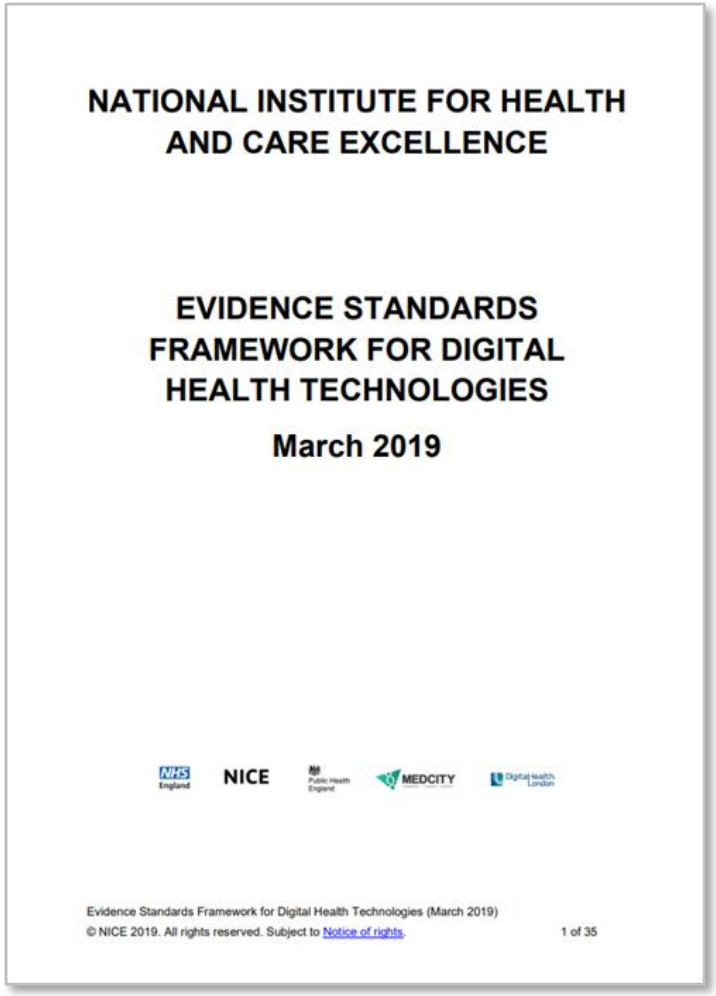
NICE evidence standards for DHTs



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

EVIDENCE STANDARDS FRAMEWORK FOR DIGITAL HEALTH TECHNOLOGIES

March 2019

NHS England NICE Public Health England MEDCITY Digital Health London

Evidence Standards Framework for Digital Health Technologies (March 2019)
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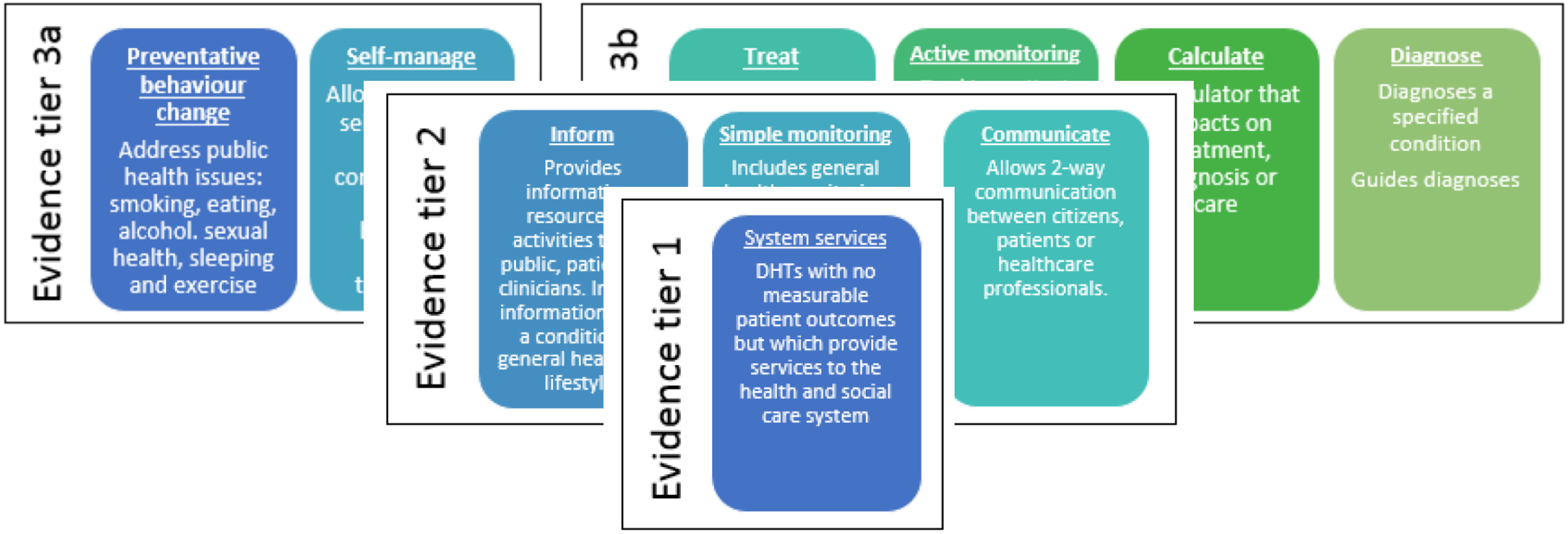
ANSWERS FOR DIABETES

NICE evidence standards for DHTs

Functional classification & evidence tiers



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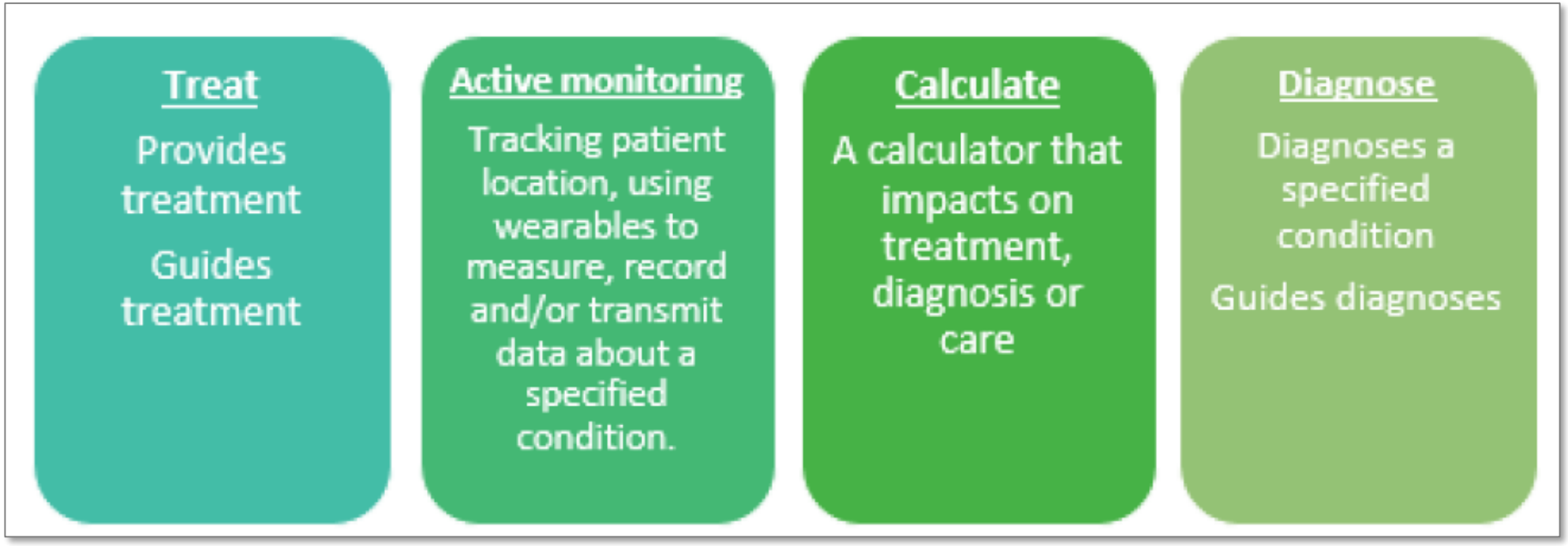
ANSWERS FOR DIABETES

Tier 3b evidence for effectiveness standards



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Tier 3b evidence for effectiveness standards

Evidence category	Minimum evidence standard	Best practice standard
Demonstrating effectiveness.	High quality intervention study (experimental or quasi-experimental design) showing improvements in relevant outcomes, such as: • diagnostic accuracy • patient-reported outcomes (preferably using validated tools) including symptom severity or quality of life • other clinical measures of disease severity or disability • healthy behaviours • physiological measures • user satisfaction and engagement. Generic outcome measures may also be useful when reported alongside condition-specific outcomes. The comparator should be a care option that is reflective of the current care pathway, such as a commonly used active intervention.	High quality randomised controlled study or studies done in a setting relevant to the UK health and social care system, comparing the DHT with a relevant comparator and demonstrating consistent benefit including in clinical outcomes in the target population, using validated condition-specific outcome measures. Alternatively, a well-conducted meta-analysis of randomised controlled studies if there are enough available studies on the DHT.

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Tier 3a evidence for effectiveness standards

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ANSWERS FOR DIABETES

Tier 3a evidence for effectiveness standards

Evidence category	Minimum evidence standard	Best practice standard
Demonstrating effectiveness.	High quality observational or quasi-experimental studies demonstrating relevant outcomes. These studies should present comparative data. Comparisons could include: • relevant outcomes in a control group • use of historical controls • routinely collected data. Relevant outcomes may include: • behavioural or condition-related user outcomes such as reduction in smoking or improvement in condition management • evidence of positive behaviour change • user satisfaction.	High quality intervention study (quasi-experimental or experimental design) which incorporates a comparison group, showing improvements in relevant outcomes, such as: • patient-reported outcomes (preferably using validated tools) including symptom severity or quality of life • other clinical measures of disease severity or disability • healthy behaviours • physiological measures • user satisfaction and engagement • health and social care resource use, such as admissions or appointments. The comparator should be a care option that is reflective of standard care in the current care pathway, such as a commonly used active intervention.
Use of appropriate behaviour change techniques (if relevant).	Be able to show that the techniques used in the DHT are: • consistent with recognised behaviour change theory and recommended practice (aligned to guidance from NICE or relevant professional organisations) • appropriate for the target population.	Published qualitative or quantitative evidence showing that the techniques used in the DHT are: • based on published and recognised effective behaviour change techniques • aligned with recommended practice • appropriate for the target population.

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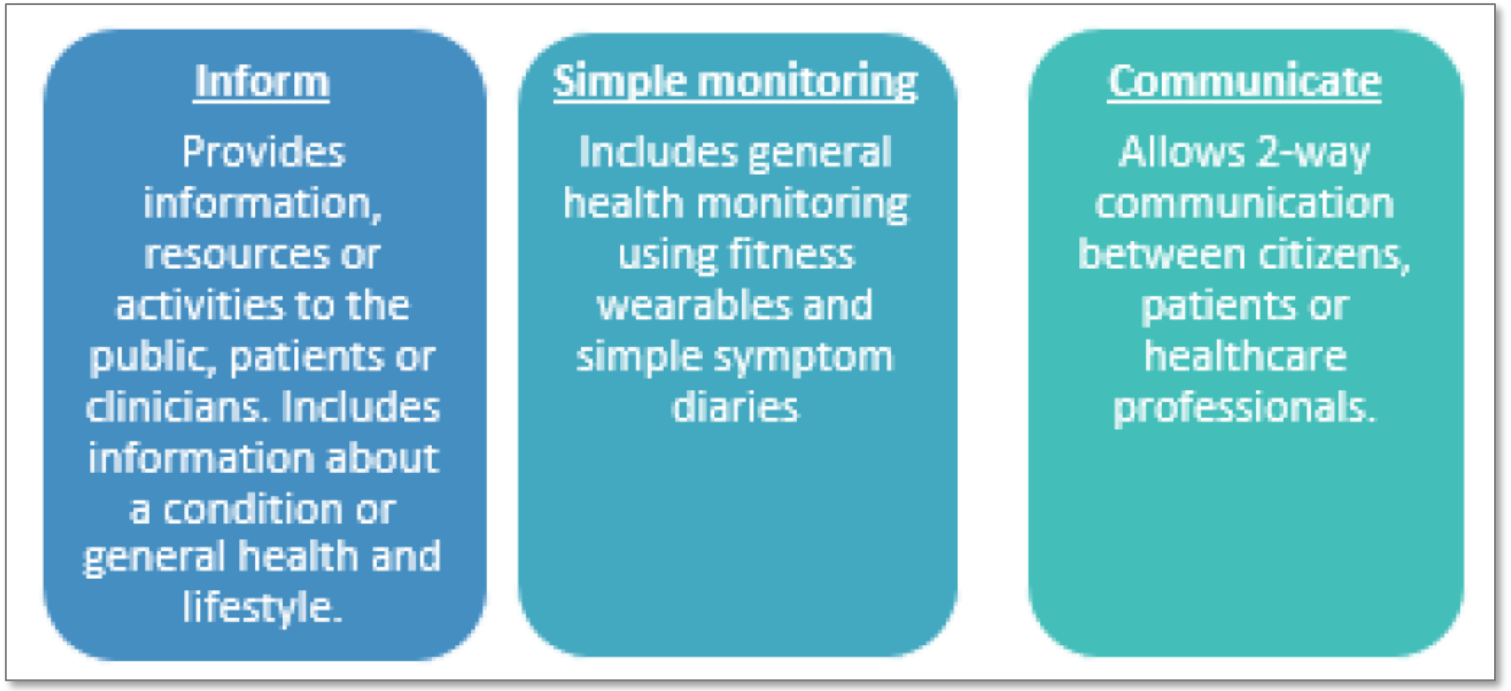
ANSWERS FOR DIABETES

Tier 2 evidence for effectiveness standards



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ANSWERS FOR DIABETES

Tier 2 evidence for effectiveness standards

Evidence category	Minimum evidence standard	Best practice standard
Reliable information content.	Be able to show that any health information provided by the DHT is: • valid (aligned to best available sources, such as NICE guidance, relevant professional organisations or recognised UK patient organisations, and appropriate for the target population) • accurate • up to date • reviewed and updated by relevant experts at defined intervals, such as every year • sufficiently comprehensive.	Evidence of endorsement, accreditation or recommendation by NICE, NHS England, a relevant professional body or recognised UK patient organisation. Alternatively, evidence that the information content has been validated though an independent accreditation such as The Information Standard or HONcode certification.
Ongoing data collection to show usage of the DHT.	Commitment to ongoing data collection to show **usage** of the DHT in the target population, and commitment to share, when available, with relevant decision-makers such as commissioners in a clear and useful format.	Evidence that data on **usage** is being collected in line with the minimum standards and can be made available to relevant decision-makers.
Ongoing data collection to show value of the DHT.	Commitment to ongoing data collection to show **user outcomes** (if relevant) or **user satisfaction** (using non-patient identifiable information) to show ongoing value, and commitment to share, when available, with relevant decision-makers such as commissioners in a clear and useful format.	Evidence that data on **outcomes or user satisfaction** is being collected in line with the minimum standard and can be made available to relevant decision-makers.
Quality and safeguarding.	Show that appropriate safeguarding measures are in place around peer-support and other communication functions within the platform. Describe who has access to the platform and their roles within the platform. Describe why these people or groups are suitable and qualified to have access. Describe any measures in place to ensure safety in peer-to-peer communication, for example through user agreements or moderation.	As for the minimum evidence standard.

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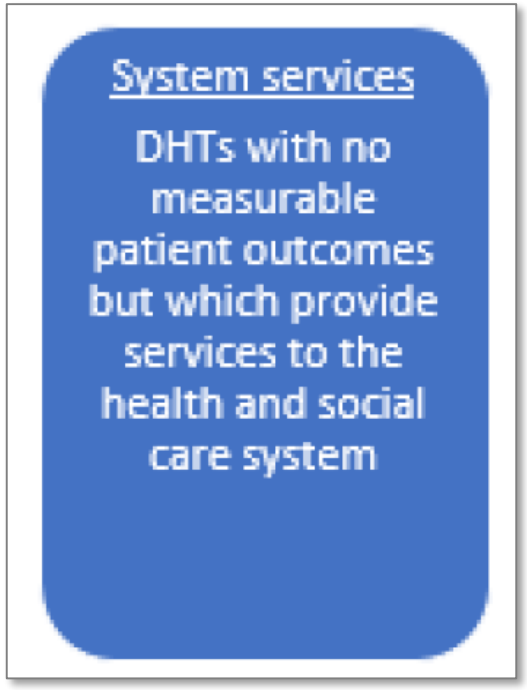
ANSWERS FOR DIABETES

Tier 1 evidence for effectiveness standards



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ANSWERS FOR DIABETES

Tier 1 evidence for effectiveness standards

Evidence category	Minimum evidence standard	Best practice standard
Credibility with UK health and social care professionals.	Be able to show that the DHT has a plausible mode of action that is viewed as useful and relevant by professional experts or expert groups in the relevant field. Either: • show that relevant clinical or social care professionals working within the UK health and social care system have been involved in the design, development or testing of the DHT, or • show that relevant clinical or social care professionals working within the UK health and social care system have been involved in signing-off the DHT, indicating their informed approval of the DHT.	Published or publicly available evidence documenting the role of relevant UK health or social care experts in the design, development, testing or sign-off of the DHT.
Relevance to current care pathways in the UK health and social care system.	Evidence to show that the DHT has been successfully piloted in the UK health and social care system, showing that it is relevant to current care pathways and service provision in the UK. Also evidence that the DHT is able to perform its intended function to the scale needed (for example, having servers that can scale to manage the expected number of users).	Evidence to show successful implementation of the DHT in the UK health and social care system.
Acceptability with users.	Be able to show that representatives from intended user groups were involved in the design, development or testing of the DHT. Provide data to show user satisfaction with the DHT.	Published or publically available evidence to show that representatives from intended user groups were involved in the design, development or testing of the DHT and to show that users are satisfied with the DHT.

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ANSWERS FOR DIABETES

Tier 1 evidence for effectiveness standards

Evidence category	Minimum evidence standard	Best practice standard
Equalities considerations.	Evidence, if relevant, that the DHT: • Contributes to challenging health inequalities in the UK health and social care system, or improving access to care among hard-to-reach populations. • Contribute to promoting equality, eliminating unlawful discrimination and fostering good relations between people with protected characteristics (as described in the 2010 Equalities Act) and others.	Show evidence of the DHT being used in hard-to-reach populations.
Accurate and reliable measurements (if relevant).	Data or analysis which shows that the data generated or recorded by the DHT is: • accurate • reproducible • relevant to the range of values expected in the target population. Also data showing that the DHT is able to detect clinically relevant changes or responses.	As for the minimum evidence standard.
Accurate and reliable transmission of data (if relevant).	Technical data showing that numerical, text, audio, image-based, graphic-based or video information is: • not changed during the transmission process • not biased by the data 'value' expected from the target patient population.	As for the minimum evidence standard, but with quantitative data.

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ANSWERS FOR DIABETES

Questions to identify higher risk DHTs

Question	Risk adjustment
Are the intended users of the DHT considered to be in a potentially vulnerable group such as children or at-risk adults?	NHS England defines an at-risk adult as an adult 'who may be in need of community care services by reason of mental or other disability, age or illness; and who is or may be unable to take care of him or herself, or unable to protect him or herself against significant harm or exploitation.' If the DHT is intended to be used by people considered to be in a potentially vulnerable group then a higher level of evidence may be needed, or relevant expert opinion on whether the needs of the users are being appropriately addressed.
How serious could the consequences be to the user if the DHT failed to perform as described?	A higher level of potential harm may indicate that the best practice evidence standards should be used.
Is the DHT intended to be used with regular support from a suitably qualified and experienced health or social care professional?	DHTs that are intended to be used with support (that is, with regular support or guidance from a suitably qualified and experienced health or social care professional) could be considered to have lower risk than DHTs that are intended to be used by the patient on their own. *This contextual question may require careful interpretation depending on the individual DHT as the involvement of a clinician may in itself indicate that the DHT presents a specific risk.*
Does the DHT include machine learning algorithms or artificial intelligence?	Refer to the code of conduct for data-driven health and care technology for additional considerations when assessing DHTs that use artificial intelligence or machine learning.
Is the financial or organisational risk of the DHT expected to be very high?	DHTs with very high financial risk should be assessed using the best practice standards to provide surety that the DHT represents good value. High organisational risks may include situations in which implementing the DHT would need complex changes in working practice or care pathways.

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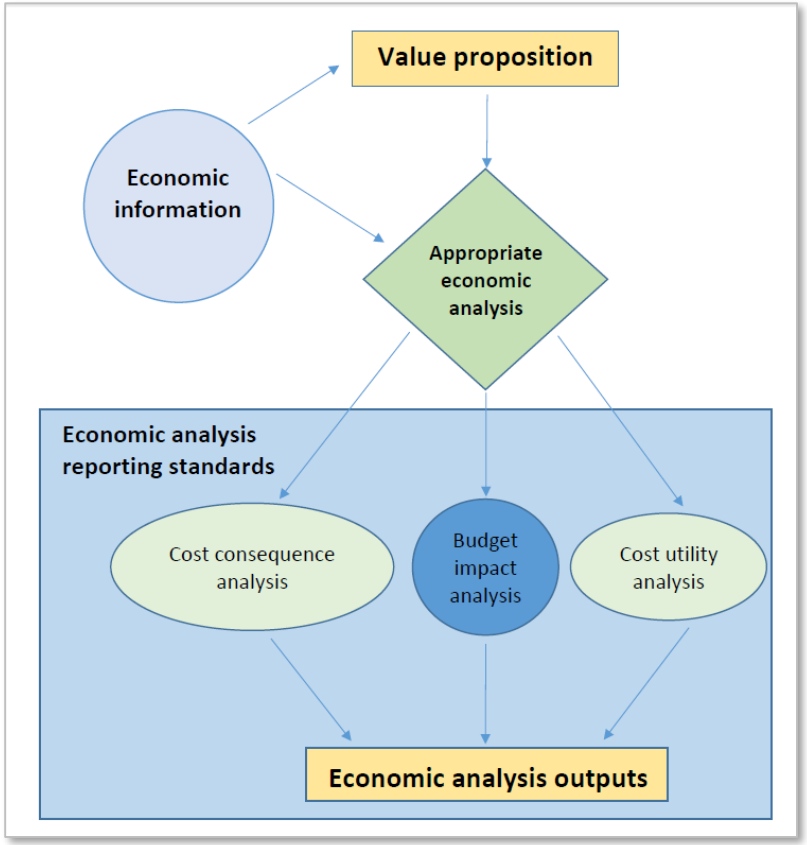
ANSWERS FOR DIABETES

Evidence for economic impact standards



- Budget impact
  - Analysis of the **financial change in the use of resources** (cost or saving) as a result of implementing a technology.
- Cost consequence
  - **Compares the costs** (such as treatment and hospital care) and the **consequences** (such as health outcomes) of a test or treatment **with a suitable alternative**.
- Cost utility
  - Benefits are assessed in terms of both quality and duration of life, and expressed as **quality-adjusted life years.** (QALYs).

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ANSWERS FOR DIABETES

NHS^{X} DITAC

- DITAC, **Digital Technology Assessment Criteria**
- New national baseline criteria for DHTs entering into the NHS and social care.
- To be used by healthcare organisations to **assess suppliers at the point of procurement** or as part of a **due diligence** process

https://www.nhsx.nhs.uk/key-tools-and-info/digital-technology-assessment-criteria-dtac/

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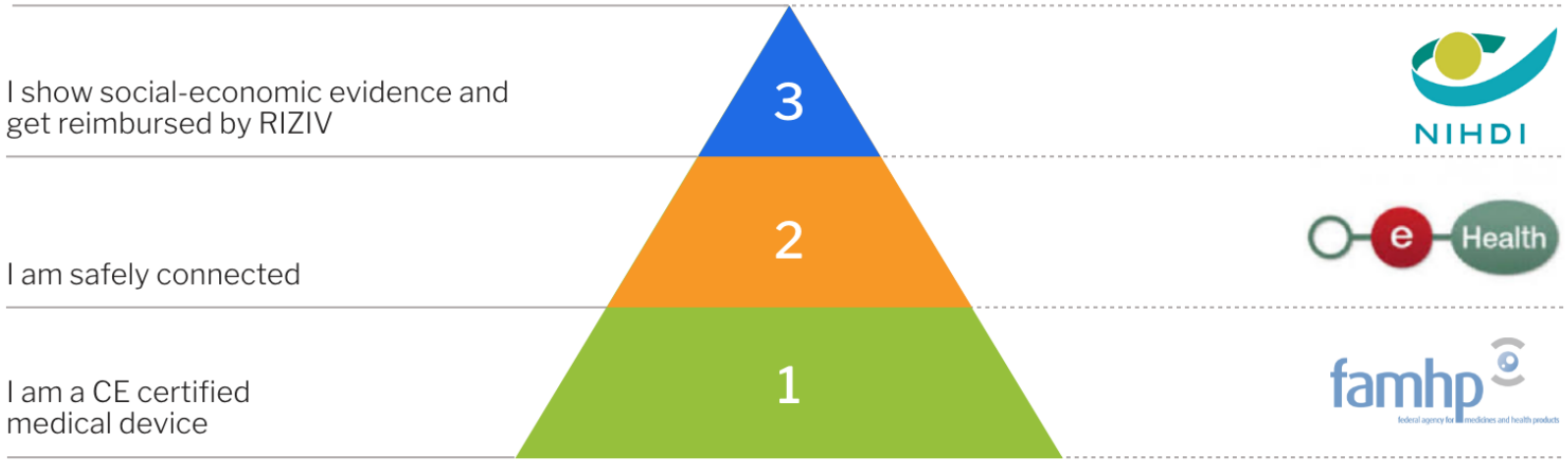
ANSWERS FOR DIABETES

mobile health Belgium

- Platform for mobile apps that are CE-marked as a medical device, consisting of a validation pyramid with three levels.
- Centralises all relevant and required information on mobile apps for patients, healthcare professionals and healthcare institutions.



- **National Institute for Health and Disability**
  - apps that have proved a social-economic benefit.
  - Eligible for reimbursement
- **eHealth Platform**
  - Federal governmental institution
  - Proving devices meet all criteria regarding data authentication, security and interoperability.
- **Federal Agency for Medicine and Health Products**
  - MDR and GDPR compliance.

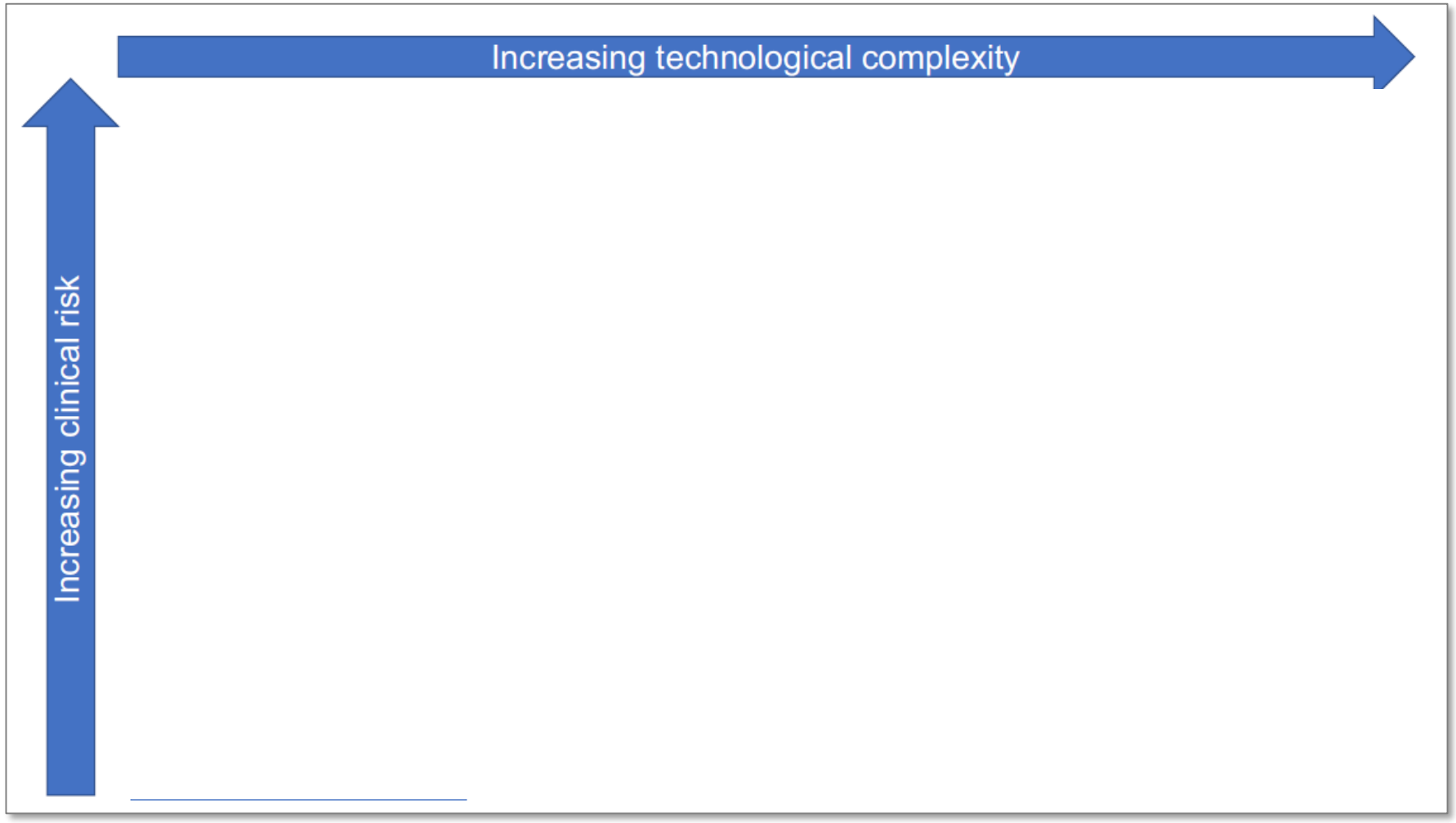
https://mhealthbelgium.be/validation-pyramid

A few comparative remarks

- **Under-representation** of diabetes and cardiometabolic disease in the German DiGA directory.
  - Might be a consequence of the limitation of medical devices classes that can qualify as DiGAs.
- In both NICE and mHealth Belgium DHTs have to show **medical benefit** and an **added economic benefit** to be reimbursed, while DiGAs provisionally listed in the German DiGA directory prior to proving a positive healthcare effect can set up their own price.
  - Scepticism from doctors and health insurance companies (GKV)* about DiGA prescription.
- Future option: Manufacturers and care providers could conclude **performance-based managed entry agreements (MEAs),**** aligning the amount of reimbursement dynamically with the outcomes measured in settings of value-based healthcare.
  - Would allow a supervised **earlier implementation** of DHTs in healthcare while some **insecurities** regarding their impact on care effectiveness and cost-efficiency still stand.

* https://www.gkv-spitzenverband.de/media/dokumente/service_1/publikationen/Positionspapier_DiGA_2021-01-07_barrierefrei.pdf
** https://www.oecd-ilibrary.org/social-issues-migration-health/performance-based-managed-entry-agreements-for-new-medicines-in-oecd-countries-and-eu-member-states_6e5e4c0f-en;jsessionid=FHoInAPsIa6L4P4KZXsd9MaT.ip-10-240-5-183

FDA’s risk-based approach to DHTs



Mathews, S.D. et al., **NPJ Digit. Med.** 2:103, 2019
Fleming, A.G. et al., **Diabetologia** 63:229-341, 2020

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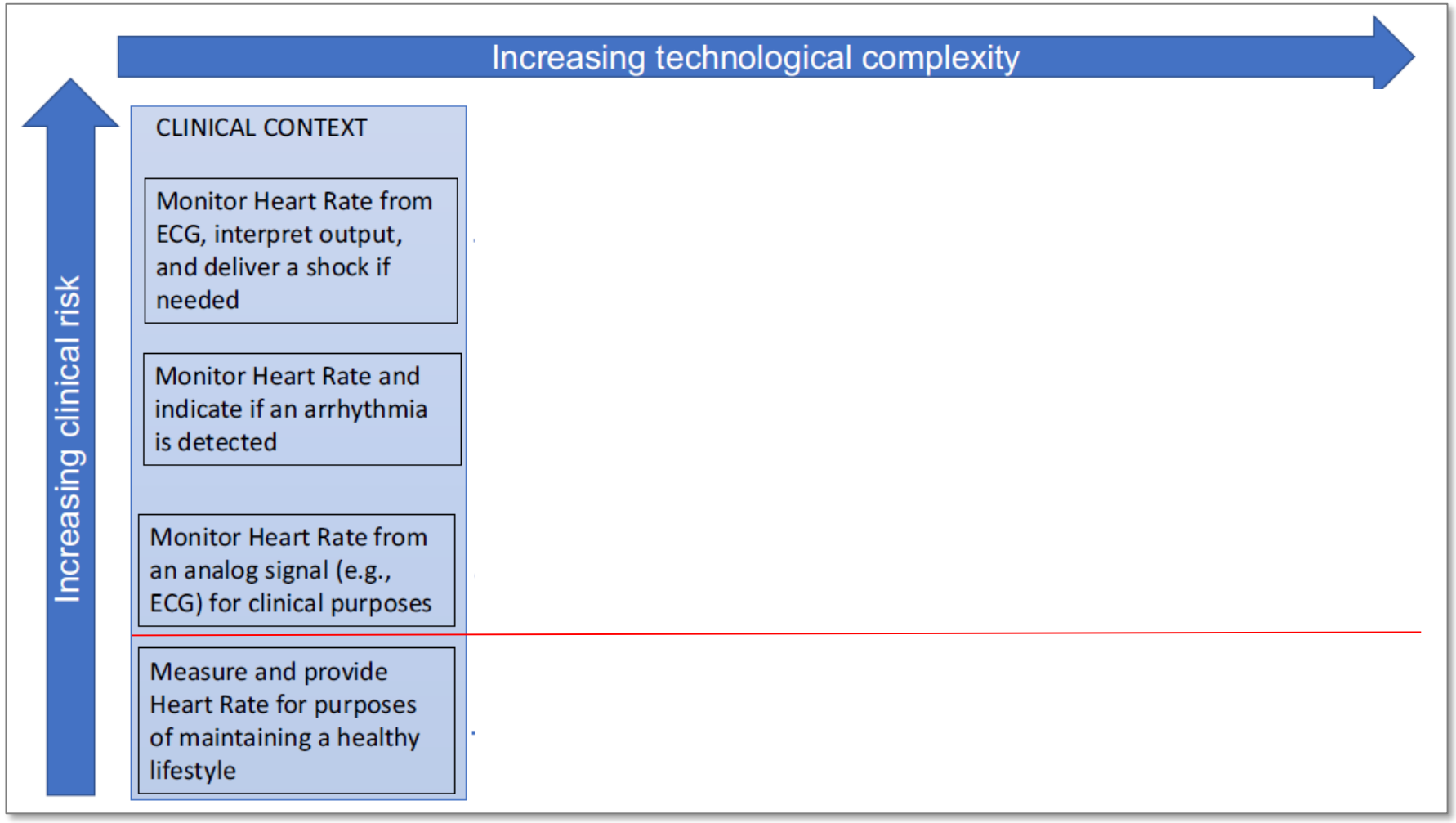
ANSWERS FOR DIABETES

FDA's risk-based approach to DHTs



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ANSWERS FOR DIABETES

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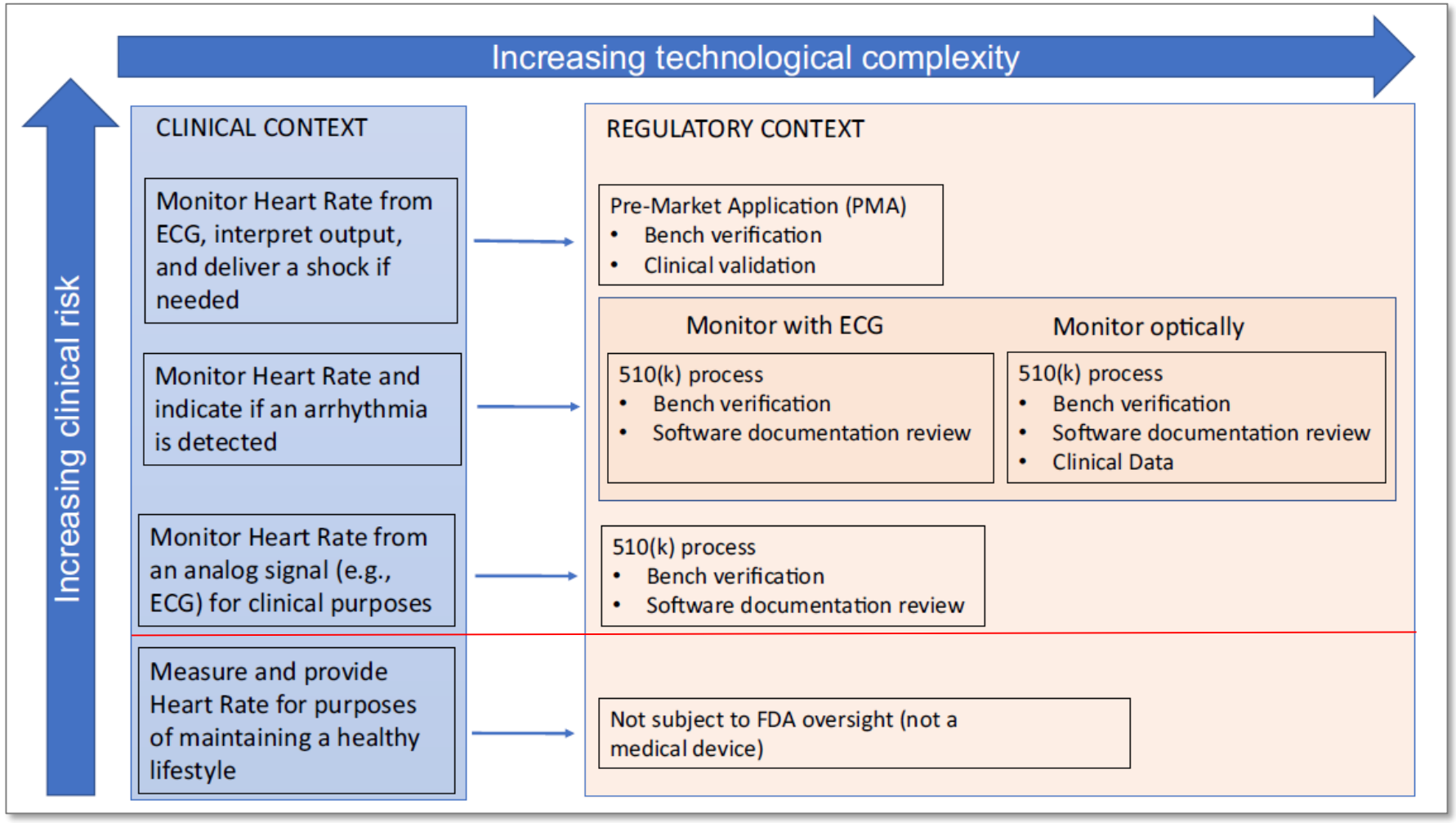

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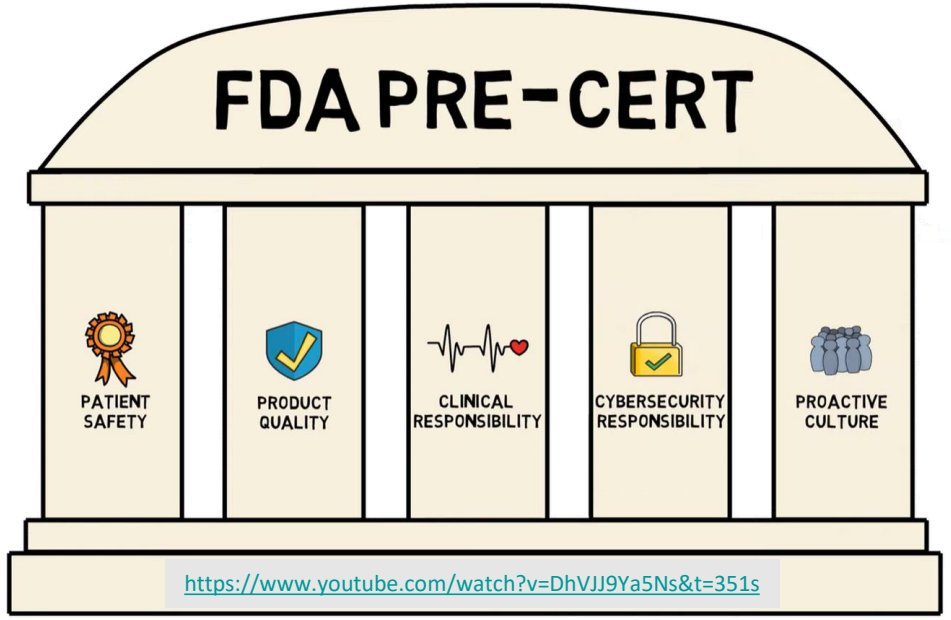
ANSWERS FOR DIABETES

FDA's Pre-Cert pilot program

- Digital Health Software **Pre-cert**ification Program
- Four components
  - Excellence appraisal: Pre-certification of **companies** applying five excellence principles



Demonstration of a **Culture of Quality and Organizational Excellence (CQOE)** and a commitment to monitoring product performance.

https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program#program

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ANSWERS FOR DIABETES

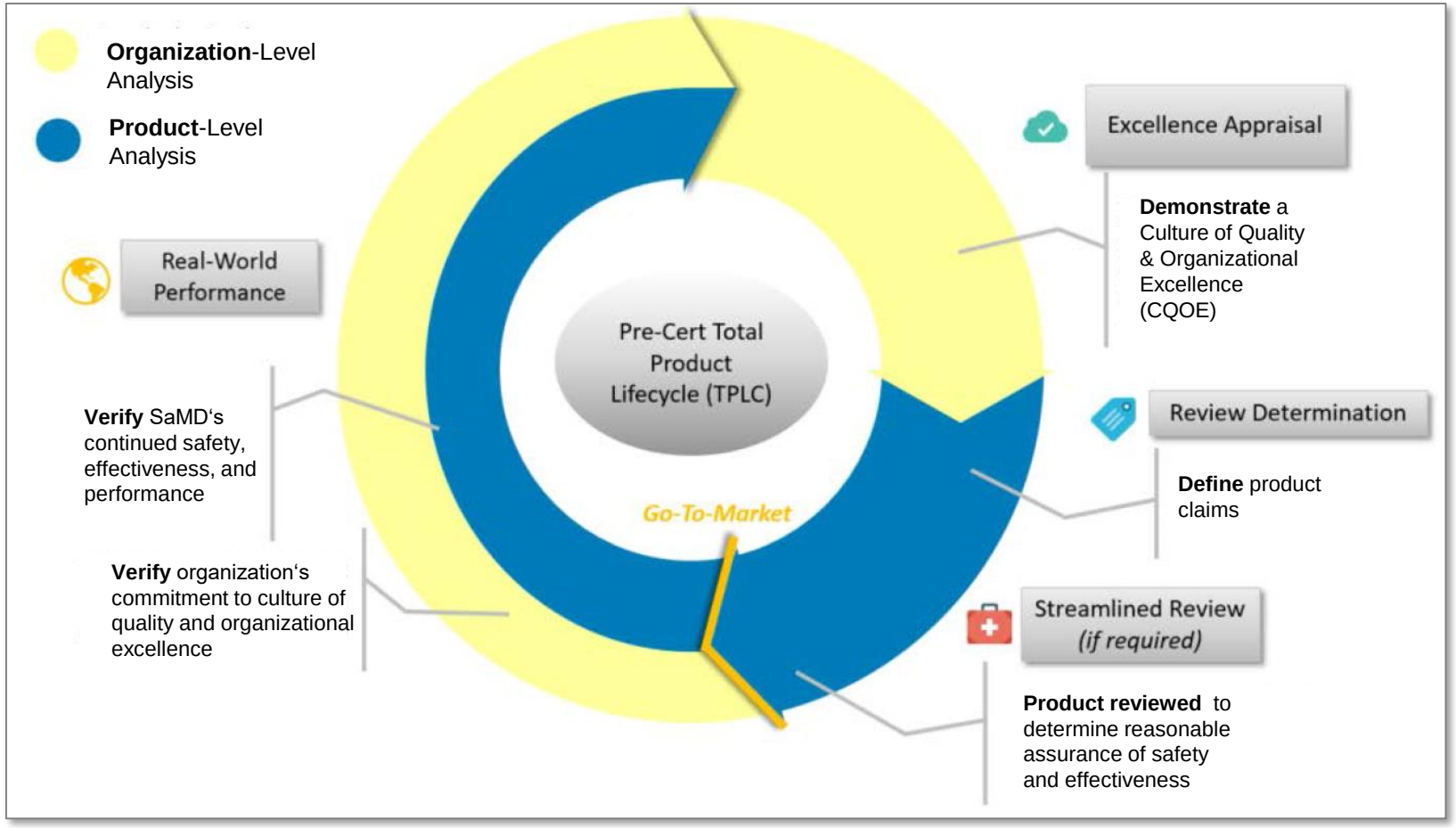
FDA’s Pre-Cert pilot program

- Digital Health Software **Pre-cert**ification Program
- Four components
  - Excellence appraisal: Pre-certification of **companies** applying five excellence principles
  - **Review pathway determination**
  - **Streamlined premarket review process,** if required
  - Continuous **real-world performance** monitoring
- Objective: Implementation of an **agile regulatory paradigm** to accommodate the faster rate of development and potential for innovation in software-based products.

https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program#program

FDA's Pre-Cert pilot program

Total product lifecycle approach to the regulation of software products



https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-software-precertification-pre-cert-program#program

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ANSWERS FOR DIABETES

Building on existing evidence

Building on existing evidence

- Thorough search of peer-reviewed literature and other resources for studies that as closely as possible address the medical need targeted by your solution
  - Disease indication
  - Patient-subgroup
  - Healthcare environment
  - Cost-drivers, healtheconomic framework
  - Affected stakeholders

Building on existing evidence

BMC Health Serv Res. 2021 Sep 6;21(1):925. doi: 10.1186/s12913-021-06950-y.

Challenges in current nursing home care in rural Germany and how they can be reduced by telehealth – an exploratory qualitative pre-post study

Susann May [1], Kai Jonas [2], Georgia V Fehler [3], Thomas Zahn [2], Martin Heinze [3 4], Felix Muehlensiepen [3 5]

Affiliations + expand

PMID: 34488746 PMCID: PMC8420146 DOI: 10.1186/s12913-021-06950-y

Affiliations

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2 bbw Hochschule Berlin, Berlin, Germany.
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5 Faculty for Health Sciences Brandenburg, Potsdam, Germany.

Abstract

Background: Telemedical care of nursing home residents in Germany, especially in rural areas, is limited to a few pilot projects and is rarely implemented as part of standard care. The possible merits of implementing video consultations in longer-term nursing care currently lack supporting evidence. In particular, there is little documentation of experiences and knowledge about the effects and potential benefits of the implementation in presently existing structures. The goal was to assess the effect of implementing medical video consultations into nursing home care addressing the following research questions: How is medical care currently provided to nursing home residents, and where do problems in its implementation arise? How can video consultations be used to reduce difficulties arising in everyday care? How does implementation of video consultations impact day-to-day nursing home care delivery?

Methods: Twenty-one guided interviews (pre-implementation n = 13; post-implementation n = 8) were conducted with a total of 13 participants (physicians, nurses and medical technical assistants). Narratives were analysed using qualitative content analysis. The results were contrasted in a pre-post analysis.

Conclusions: Telehealth cannot replace physical, in-person visits, but does offer an alternative form of service delivery when properly integrated into existing structures. Our results suggest that the use of video consultations in nursing homes can reduce the burden and additional workload, and increase the efficiency of care provision for nursing home residents. Video consultations can complement in-person visits to nursing homes, especially to address the shortage of medical specialists in rural areas in Germany. To promote implementation and acceptance of video consultation in nursing homes, we need to increase awareness of its benefits and undertake further evaluation of video consultations in nursing home care.

May, S. et al., **BMJ Health Serv. Res.** 21(1):925, 2021

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ANSWERS FOR DIABETES

Building on existing evidence

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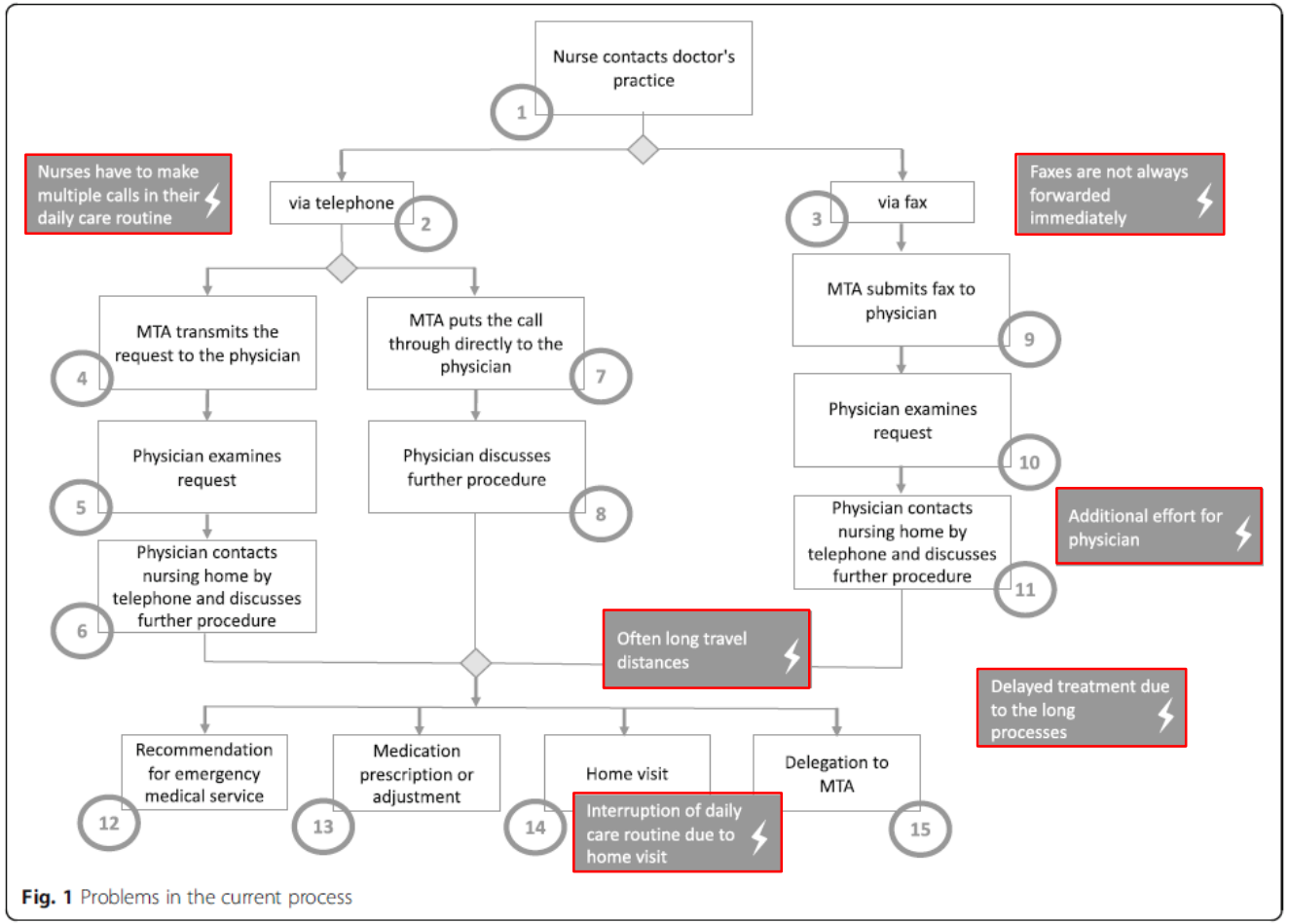

Fig. 1 Problems in the current process

May, S. et al., **BMJ Health Serv. Res.** 21(1):925, 2021

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ANSWERS FOR DIABETES

Building on existing evidence

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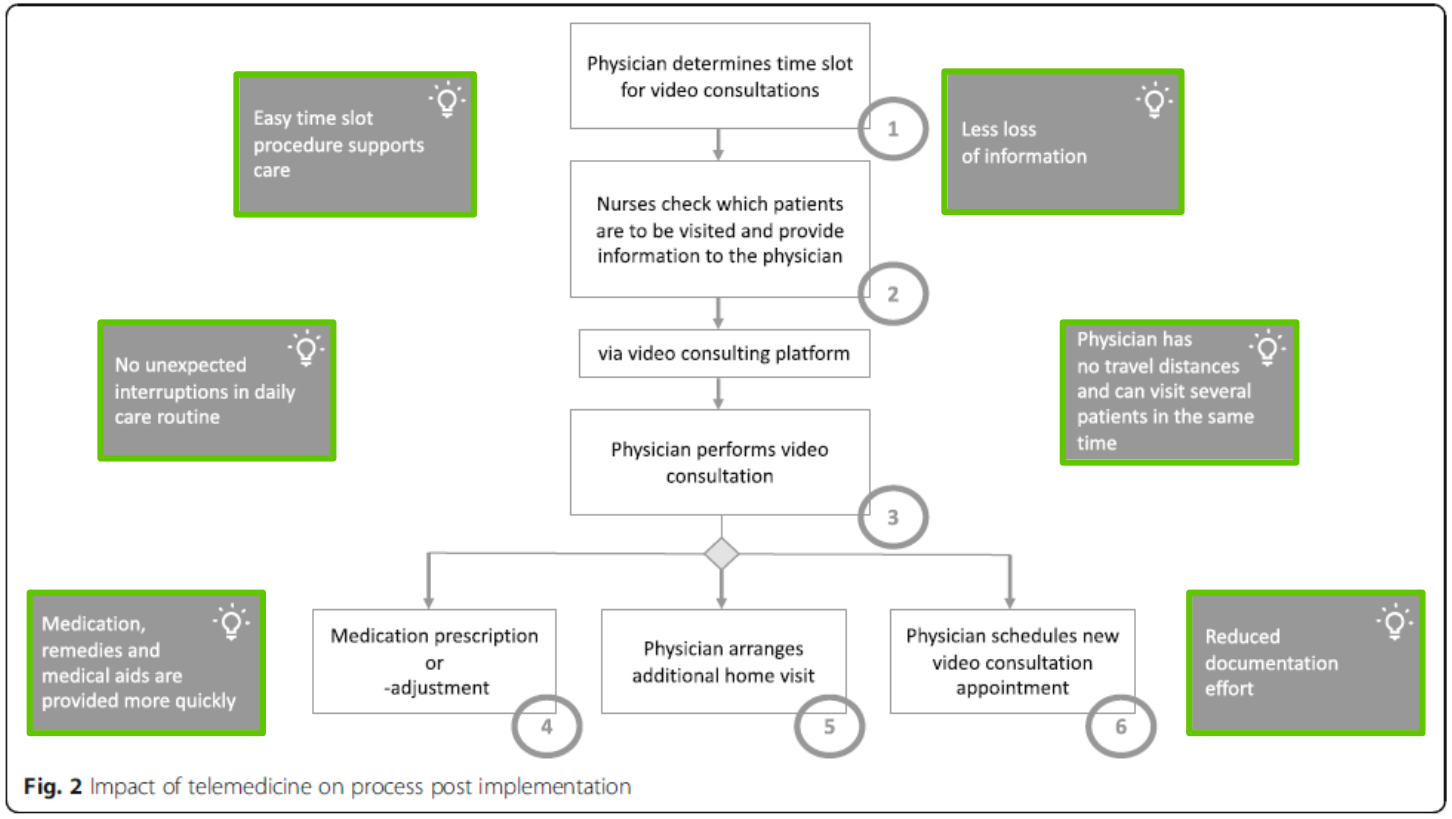

Fig. 2 Impact of telemedicine on process post implementation

May, S. et al., **BMJ Health Serv. Res.** 21(1):925, 2021

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ANSWERS FOR DIABETES

Building on existing evidence

Clin Interv Aging. 2020 Aug 18;15:1427-1437. doi: 10.2147/CIA.S260098. eCollection 2020.

Employment of Telemedicine in Nursing Homes: Clinical Requirement Analysis, System Development and First Test Results

Marian Ohligs [1 2], Stephanie Stocklassa [1], Rolf Rossaint [1], Michael Czaplik [1 2], Andreas Follmann [1]

Affiliations + expand

PMID: 32884251 PMCID: PMC7443448 DOI: 10.2147/CIA.S260098

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https://docsinclouds.com/telecare/

- Nursing homes
- Palliative care
- Hausärztliche Versorgung

Abstract

Purpose: Demographic change and lack of specialized workforces are challenging. Likewise, home visits by general practitioners (GPs) become rarer. If a nursing home resident develops acute symptoms, nurses are often inclined to call the rescue service. Besides patient-related consequences, this might lead to unnecessary hospitalization and far-reaching health economic costs. Due to legal restrictions of remote treatment in Germany, which were recently loosened, telemedicine is still in the early stages. The aim of this study was to employ a holistic telemedical system for nursing homes which facilitates the connection to a GP and thus avoids unnecessary hospitalizations in the case of ambulatory-sensitive illnesses.

Materials and methods: After an inter-professional requirement analysis, the iterative development was started. In addition to an audio-video connection, several point of care measurements were integrated. Finally, first field tests were performed in a nursing home in a rural area in Germany.

Results: One nursing home was equipped with telemedical system based on the results of the requirement analysis and tele-medically connected to a GP. Over a period of seven months, 56 routine and emergency teleconsultations took place. Only one of those required a hospital admission. In addition to video telephony, electrocardiography and assessment of vitals such as pulse, blood pressure, oxygen saturation and auscultation of heart and lungs were applied frequently.

Conclusion: A telemedical system including integrated medical devices was successfully developed and has turned out to be helpful and even necessary for careful and reliable decision-making by the GP. First test results show high acceptance for elderly care. Involved patients, nurses, and the GP itemize various specific benefits, including economic, personal, and altruistic issues. Another issue that the current COVID-19 crisis brought to light is lowering the risk of contagion; GPs can replace their home visits by using telepresence combined with point of care measures.

Ohligs, M. et al., **Clin. Interv. Aging** 15:1427-1437, 2021

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List of Major Requirements Defined by the Interdisciplinary Team of Involved Nurses, a General Practitioner (GP), and Several Elderly Patients. Prioritized by Must, Should or May

No	Brief Requirement Description	Priority	Source
1	All data is transferred encrypted	MUST	GP, patient
2	Doctor and nurse are able to see the important information of a consultation at anytime	MUST	GP
3	Doctor and nurse are able to identify information lost during the transmission	MUST	GP, nurse
4	Doctor and nurse are able to identify information distorted during the transmission	MUST	GP, nurse
5	Doctor and nurse can resume the consultation if an error occurs	MUST	GP, nurse
6	The video connection adapts compression, resolution and frame rate automatically in real-time	SHOULD	GP
7	Patient can see and talk to the doctor	MUST	patient
8	Nurse can see and talk to the doctor	MUST	GP, nurse
9	Doctor and nurse can fill out the documentation together	MUST	GP, nurse
10	Medical devices for measurement of bloodpressure, oxygen saturation and electrocardiogram are part of the system and automatically transfer the results to the general practitioner.	MUST	GP, nurse
11	Doctor can see the patient	MUST	GP, nurse
12	Doctor can see the patient and the nurse	MAY	GP
13	Doctor can navigate and zoom the patient camera	SHOULD	GP
14	The device has to be able to run as mobile device for 20 minutes without external power source	MUST	nurse
15	The device is easily movable or portable between the residents' apartments	MUST	nurse
16	The system can connect to the Internet via Wireless Local Area Network (WLAN)	MUST	nurse
17	The system can connect to the Internet via universal mobile telecommunication system (UMTS) or long-term evolution (LTE)	MUST	nurse
18	Login passwordless via smartcard	SHOULD	nurse
19	All devices touched by the nurse are medically certified	MUST	GP, nurse
20	All measurement units are certified medical devices	MUST	GP, nurse
21	All components are Communauté Européenne (CE) certified products	MUST	GP, nurse
22	Rolling stand pass the tilt-test for medical products in Germany	MUST	GP, nurse
23	The documentation device has a keyboard	SHOULD	nurse
24	The documentation device has a touch screen	SHOULD	nurse

Ohligs, M. et al., **Clin. Interv. Aging** 15:1427-1437, 2021

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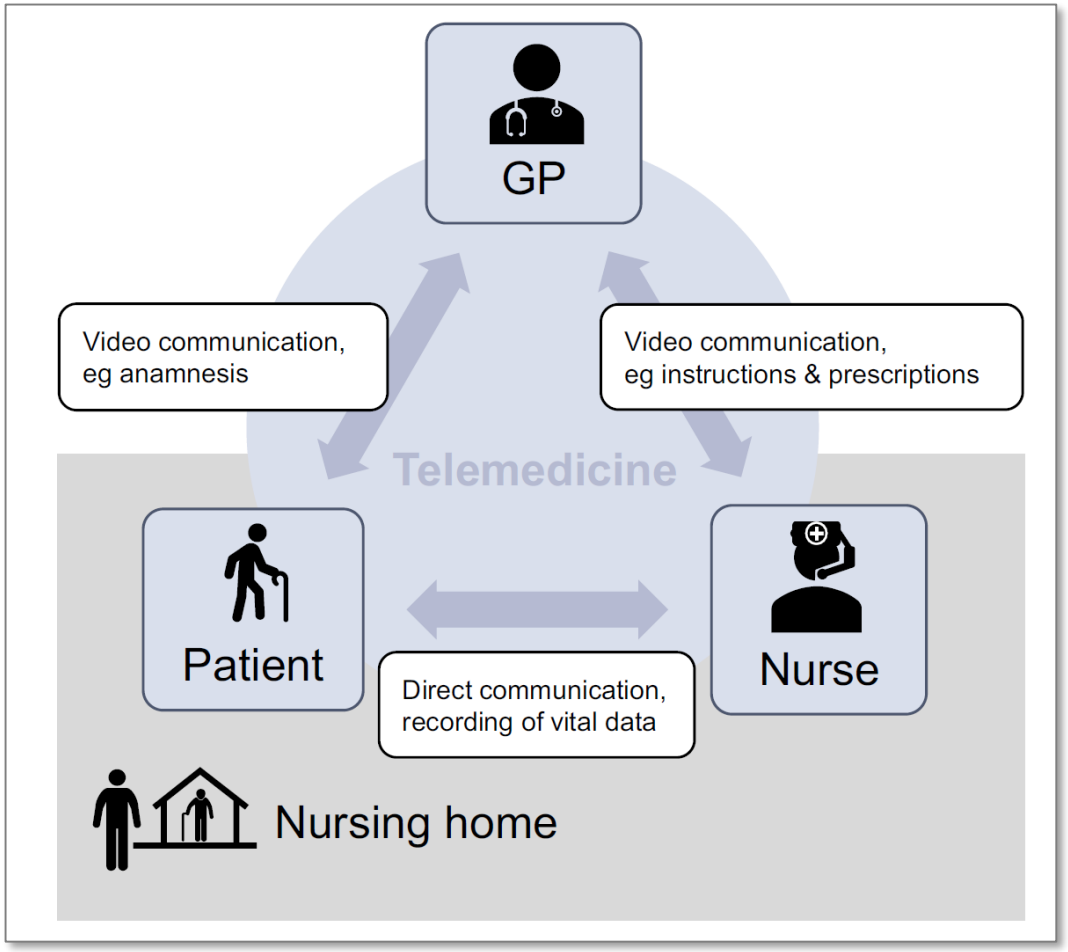
ANSWERS FOR DIABETES

Building on existing evidence



Benefits of Teleconsultations for Patient, Nurse, Nursing Management and General Practitioner

Role	Benefits
Patient	• Quick and uncomplicated access to the general practitioner • Fewer hospitalizations • Fewer adjustment problems for patients with dementia • Improvement of care quality

Nurse	• Extension of medical abilities
	• Possibility of consulting the doctor
	  ○ immediately, especially at night in emergency situations
	  ○ easily in unclear situations
	• No need to physically transport the patient to the doctor

Nursing Management	• Quality improvement of medical care • Legal certainty for staff • Unique characteristic towards competing care facilities • Fewer hospitalizations resulting in lower administrative costs and preventing loss of revenue due to patient absence
General Practitioner	• More frequent consultations • Time saving compared with regular home visits • Reduced travel time to patient

Ohligs, M. et al., **Clin. Interv. Aging** 15:1427-1437, 2021

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ANSWERS FOR DIABETES

Building on existing evidence

JMIR Cardio. 2021 Jun 1;5(1):e29101. doi: 10.2196/29101.

A Virtual Cardiovascular Care Program for Prevention of Heart Failure Readmissions in a Skilled Nursing Facility Population: Retrospective Analysis

Daniel M Friedman [# 1 2], Jana M Goldberg [# 1], Rebecca L Molinsky [3], Mark A Hanson [1 4], Adam Castaño [1], Syed-Samar Raza [5], Nodar Janas [1 5], Peter Celano [1], Karen Kapoor [1], Jina Telaraja [1], Maria L Torres [1], Nayan Jain [1], Jeffrey D Wessler [1 6]

Affiliations + expand

PMID: 34061037 PMCID: PMC8411436 DOI: 10.2196/29101

https://www.heartbeathealth.com/

Heartbeat™

Abstract

Background: Patients with heart failure (HF) in skilled nursing facilities (SNFs) have 30-day hospital readmission rates as high as 43%. A virtual cardiovascular care program, consisting of patient selection, initial televisit, postconsultation care planning, and follow-up televisits, was developed and delivered by Heartbeat Health, Inc., a cardiovascular digital health company, to 11 SNFs (3510 beds) in New York. The impact of this program on the expected SNF 30-day HF readmission rate is unknown, particularly in the COVID-19 era.

Objective: The aim of the study was to assess whether a virtual cardiovascular care program could reduce the 30-day hospital readmission rate for patients with HF discharged to SNF relative to the expected rate for this population.

Methods: We performed a retrospective case review of SNF patients who received a virtual cardiology consultation between August 2020 and February 2021. Virtual cardiologists conducted 1 or more telemedicine visit via smartphone, tablet, or laptop for cardiac patients identified by a SNF care team. Postconsult care plans were communicated to SNF clinical staff. Patients included in this analysis had a preceding index admission for HF.

Results: We observed lower hospital readmission among patients who received 1 or more virtual consultations compared with the expected readmission rate for both cardiac (3% vs 10%, respectively) and all-cause etiologies (18% vs 27%, respectively) in a population of 3510 patients admitted to SNF. A total of 185/3510 patients (5.27%) received virtual cardiovascular care via the Heartbeat Health program, and 40 patients met study inclusion criteria and were analyzed, with 26 (65%) requiring 1 televisit and 14 (35%) requiring more than 1. Cost savings associated with this reduction in readmissions are estimated to be as high as US $860 per patient.

Conclusions: The investigation provides initial evidence for the potential effectiveness and efficiency of virtual and digitally enabled virtual cardiovascular care on 30-day hospital readmissions. Further research is warranted to optimize the use of novel virtual care programs to transform delivery of cardiovascular care to high-risk populations.

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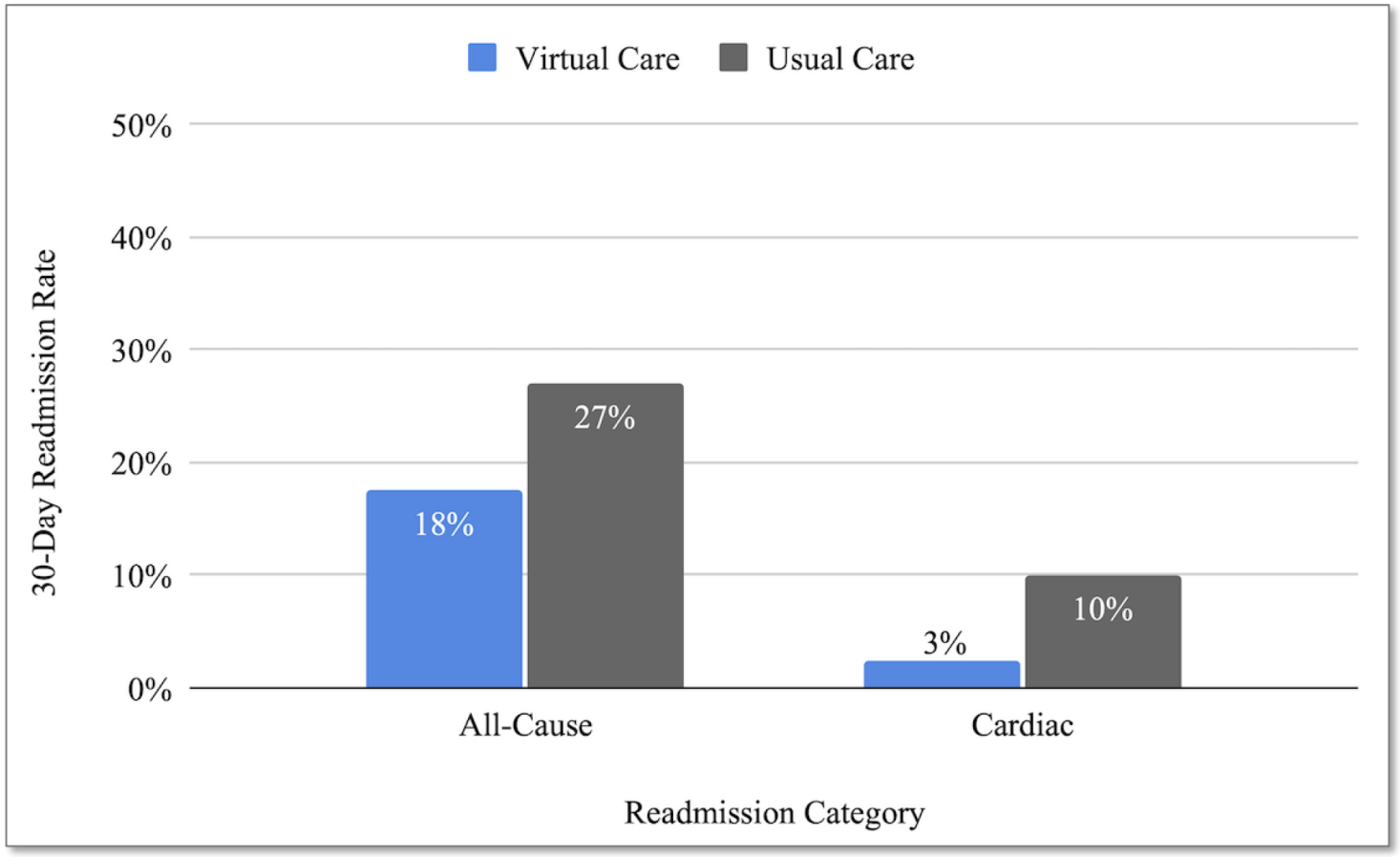
Building on existing evidence



Friedman, D.M. et al., **JMIR Cardio** 5(1):e29101, 2021

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ANSWERS FOR DIABETES

Building on existing evidence

Benefits of virtual cardiology in the skilled nursing facility (SNF) setting

Group	Potential benefits
• SNF patients	• Increased access to timely care • Increased access to follow-up visits • Reduced disruption (ie, no transport) • Reduced exposure to infectious diseases (eg, flu, SARS-CoV-2) • Reduced emergency department visits or readmissions • Reduced time to optimize guideline-directed medical theory
• Providers	• Increase care delivery to high-risk population • Reduced disruption to clinic flow • Increased feasibility of frequent follow-up televisits • History can be supplemented by SNF nurse during televisit • Physical examination can be performed by a SNF nurse during televisit
• Skilled nursing facility	• Reduced disruption (ie, no transport) • Reduced exposure to infectious diseases (eg, flu, SARS-CoV-2) for all residents • Reduced reimbursable days lost to readmission
• Payers	• Reduced costs (readmission, transportation)
• Health care system	• Reduced costs • Support research efforts

Friedman, D.M. et al., **JMIR Cardio** 5(1):e29101, 2021
Gorodeski, E.Z. et al., **J. Cardiac. Fail** 26(6):448-456, 2020
Virtual Visits for Care of Patients with Heart Failure in the Era of COVID-19:
A Statement from the **Heart Failure Society of America** (pdf)

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ANSWERS FOR DIABETES

Your clinical trial

- Design approaches to trialing Digital Health Technologies
- Evidence frameworks for Digital Health Technologies
- Setting up your clinical trial program and selecting the right partners
- Q&A

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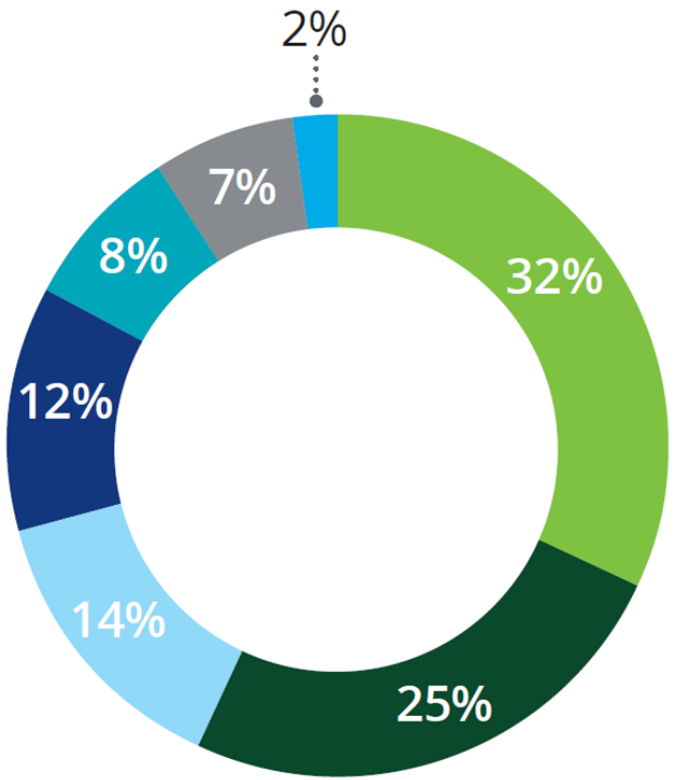
ANSWERS FOR DIABETES

Cost drivers in clinical trials



- Patient recruitment
- Outsourcing costs
- Site recruitment
- Clinical trial management system and other technology
- Site retention
- Data management and validation
- Patient retention

https://www2.deloitte.com/content/dam/insights/us/articles/22934_intelligent-clinical-trials/DI_Intelligent-clinical-trials.pdf

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ANSWERS FOR DIABETES

Your clinical trial planning

- Think in terms of your very own clinical **development program** (and not only in the category of a single study).
- Make a careful choice of the **patient group** and the **healthcare environment** you want to initially target.
- You may want to start with a small (mono-centric) **PoC** study – assessing basic functionalities such as the accuracy of an algorithm, safety & tolerability, etc., in a protected environment such as a hospital or a clinical research unit.
  - data could inform sample size calculation for a subsequent larger trial.
- Continue with a **larger (comparative) trial** investigating your device with real patients and, if possible, under conditions of real-world healthcare provision.

Your clinical trial planning

- Make a decision regarding your **benchmark / control group.**
  - Use a **placebo/mock** device/app almost indistinguishable from the solution under investigation. Think about preceding a **run-in** phase.

*International Consortium for Health Outcomes Measurement (ICHOM) https://www.ichom.org/
EIT Health, Implementing Value-Based Health Care in Europe: Handbook for Pioneers (Director: Gregory Katz), 2020
https://eithealth.eu/wp-content/uploads/2020/06/Implementing-Value-Based-Healthcare-In-Europe.pdf

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  - Use clinical endpoints and conditions of comparison which are **accepted** by the relevant experts and **expert associations.**

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  - Address **user experience** (patients, healthcare professionals) and include indication-specific **PROMs*** in order to approach value-based healthcare remuneration schemes.

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ANSWERS FOR DIABETES

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  - Address **user experience** (patients, healthcare professionals) and include indication-specific **PROMs*** in order to approach value-based healthcare remuneration schemes.
- Clinical trial results should be quickly **published in peer-reviewed journals** and **presented by the PIs/clinical experts (!)** at national and international diabetes congresses.

*International Consortium for Health Outcomes Measurement (ICHOM) https://www.ichom.org/
EIT Health, Implementing Value-Based Health Care in Europe: Handbook for Pioneers (Director: Gregory Katz), 2020
https://eithealth.eu/wp-content/uploads/2020/06/Implementing-Value-Based-Healthcare-In-Europe.pdf

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ANSWERS FOR DIABETES

Clinical service provider selection

- Scientific and operational **design** of your clinical trial, development of your clinical trial protocol (**scientific evaluation concept**), writing clinical trial submission documents.
- **Clinical Trial Application** (CTA) filing, including assistance in preparation of your Investigational Medicinal Product Dossier (IMPD) or technical documentation, CTA submission to Ethic Committees and competent authorities.
- **Data management** (full 21 CFR part 11 compliance); statistical planning, analysis and interpretation; **Clinical Study Report (CSR)** compliant with ICH E3
- Go for a clinical CRO or hospital providing a full service portfolio in **FDA/EMA compliant** quality
  - Check clinical research and scientific **track record,** FDA/EMA inspections, regulatory compliance, quality management system, information security (ISO 27001)
  - Agree on a task delegation list and timelines
  - Check trial implementation capabilities (recruitment rate, patient retention, staff qualification, etc.)

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ANSWERS FOR DIABETES

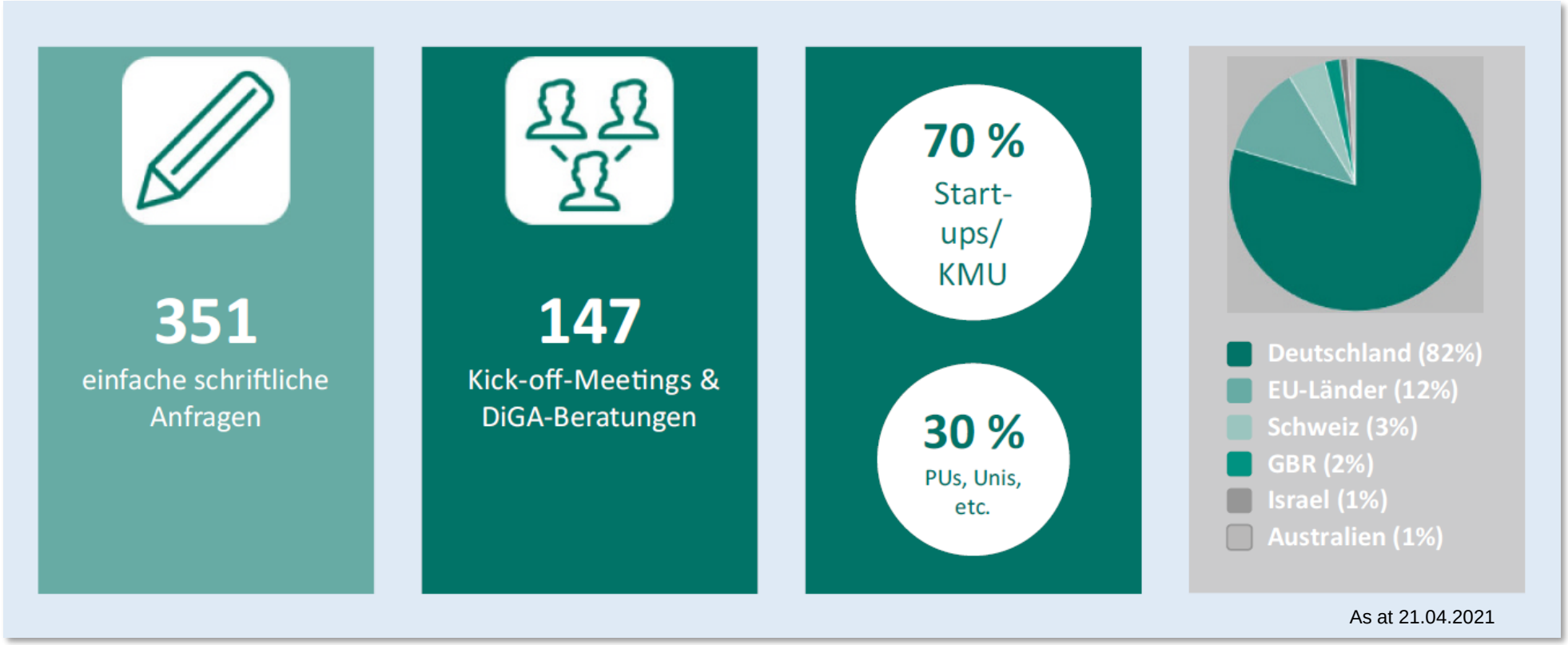
Support and counselling – BfArM

- Kick-off Meetings
  - Low-threshold offer for an early informal consultation
  - Potential topics include regulatory support, clinical trial conception, documents to be submitted for an evaluation procedure
  - Facilitating the preparation of a more extensive in-depth scientific advice
- DiGA counselling
  - Compilation of a dedicated consulting team matching the specialities and requirements of the respective manufacturer
  - Discussion of questions related to the fast-track pathway, including requirements for demonstrating a positive healthcare effect
  - Collection of fees by BfArM depending on the scope of advice
  - No preliminary decision in regard to the main application procedure

https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2

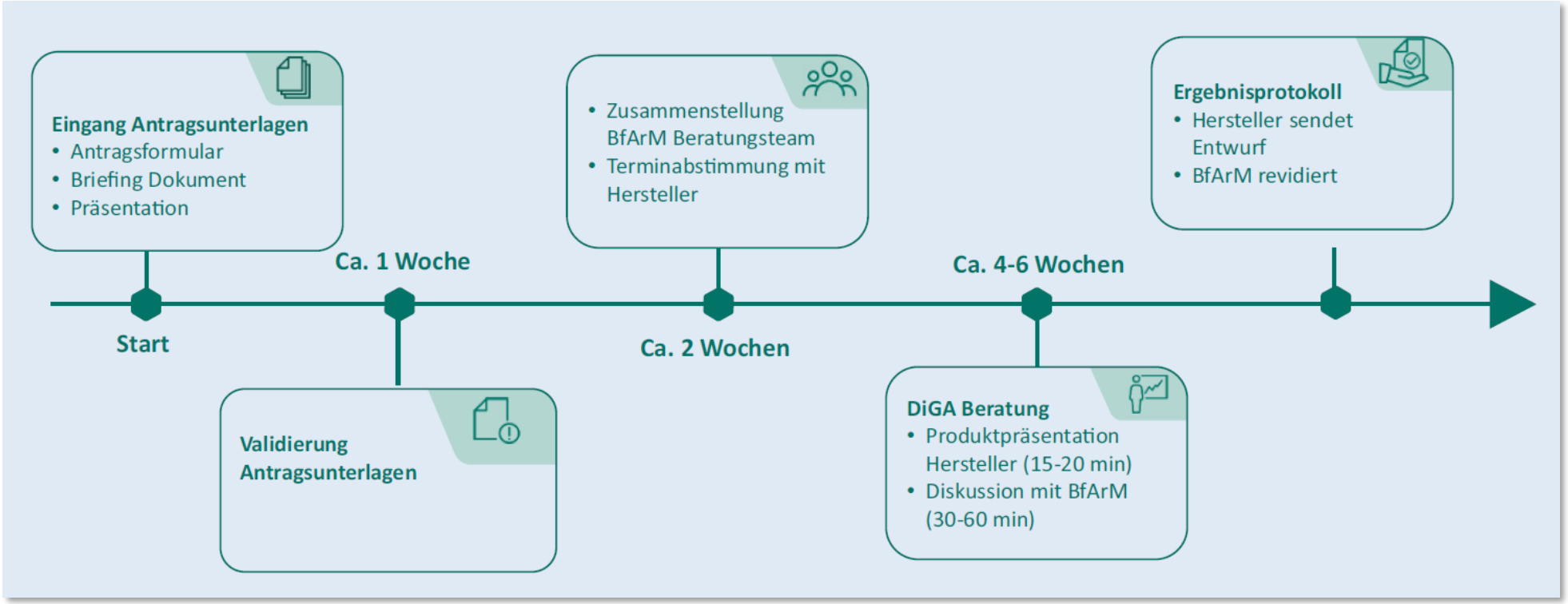
Löbker, W. et al., **Bundesgesundheitsblatt** 64:1241-1248, 2021
https://link.springer.com/content/pdf/10.1007/s00103-021-03410-0.pdf

Support and counselling – BfArM



Support and counselling – BfArM

Time scale DiGA counselling



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https://link.springer.com/content/pdf/10.1007/s00103-021-03410-0.pdf

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ANSWERS FOR DIABETES

Support and counselling – further options

- **National Association of Digital Health Care** *(Spitzenverband Digitale Gesundheitsversorgung).*[1]
- Clinical **CROs** specialized in preparing DiGA clinical trial for demonstrating a positive healthcare effect.[2]
- University **Hospitals** with **Coordination Centres for Clinical Studies** *(Koordinierungszentren für Klinische Studien).*[3]
- **AI Federal Association** *(KI Bundesverband)*: Working group **"Health"** (Dr. -Ing. Julia Hoxha).[4]
- **Docs in Clouds** Telecare.[5]
- Dmac **Medical Valley** Digital Health Application Center.[6]
- Medical **expert associations** such as the German Diabetes Association, and their working groups/committees on technology, digitalization and psychology.[7]
- EIT Health Germany GmbH.[8]

1. https://digitalversorgt.de/
2. https://diga.bfarm.de/de
3. https://www.kks-netzwerk.de/index.php
4. https://ki-verband.de/arbeitsgruppen/
5. https://docsinclouds.com/consulting/
6. https://www.mv-dmac.com/
7. https://www.diabetes-technologie.de/, https://www.deutsche-diabetes-gesellschaft.de/die-ddg/kommissionen/digitalisierung, https://www.deutsche-diabetes-gesellschaft.de/die-ddg/arbeitsgemeinschaften/diabetes-psychologie
8. https://eit-health.de/en/, https://eit-health.de/en/5-tips-for-a-successful-admission-to-the-diga-directory-henrik-emmert-ceo-of-aidhere-gmbh/

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ANSWERS FOR DIABETES

Thank you very much!

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ANSWERS FOR DIABETES

Open discussion

- Design approaches to trialing Digital Health Technologies
- Evidence frameworks for Digital Health Technologies
- Setting up your clinical trial program and selecting the right partners
- Q&A

Thank you very much!

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ANSWERS FOR DIABETES

Thank you very much!

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