



Federal Institute  
for Drugs  
and Medical Devices

# New Roles in Digitalization, Data Science and Health Care Research

Prof. Dr. Karl Broich, President BfArM  
23<sup>rd</sup> DGRA Annual Congress  
September 13<sup>th</sup> 2021, Bonn



# Overview



Digitalization, Big Data, Real World Data,... - Chances and Challenges

Activities and projects at national & European level on data-driven decision-making:  
From “DiGA-Fast-Track” to Research Data Centre – BfArM at key interfaces

Reliable data collection, exchange and further use: Interoperability

Conclusion and Outlook

# Digitalization in Healthcare – a variety of *new chances, new approaches* in daily care, for recruiting and conducting clinical trials ...

npj | Digital Medicine [www.nature.com/npjdigitalmed](http://www.nature.com/npjdigitalmed)

COMMENT OPEN 

## Digital inclusion as a social determinant of health

Cynthia J. Sieck<sup>1,2,3</sup>, Amy Sheon<sup>3</sup>, Jessica S. Ancker<sup>4</sup>, Jill Castek<sup>5</sup>, Bill Callahan<sup>6</sup> and Angela Siefer<sup>6</sup>

npj Digital Medicine (2021)4:52; <https://doi.org/10.1038/s41746-021-00413-8>

## The Use of **Social Media** in **Recruitment** for Medical Research Studies: A Scoping Review.

Topolovec-Vranic J, Natarajan K.

J Med Internet Res. 2016 Nov 7;18(11):e286. doi: 10.2196/jmir.5698.

npj | Digital Medicine [www.nature.com/npjdigitalmed](http://www.nature.com/npjdigitalmed)

REVIEW ARTICLE OPEN

## Beyond validation: getting health apps into clinical practice

William J. Gordon<sup>1,2,3\*</sup>, Adam Landman<sup>2,3,4</sup>, Haipeng Zhang<sup>3,5,6</sup> and David W. Bates<sup>1,3</sup>

## A decade of **digital** medicine innovation.

Topol EJ.

Sci Transl Med. 2019 Jun 26;11(498):eaaw7610. doi: 10.1126/scitranslmed.aaw7610.

Fueled by advances in technology, increased access to smartphones, and capital investment, the number of available health “app” has exploded in recent years. Patients use their smartphones for many things, but not as much as they might for health, especially for managing their chronic conditions. Moreover, while significant work is ongoing to develop, validate, and evaluate these apps, it is less clear how to effectively disseminate apps into routine clinical practice. We propose a framework for prescribing apps at outline the key issues that need to be addressed to enable app dissemination in clinical care. This includes: education and awareness, creating digital formularies, workflow and EHR integration, payment models, and patient/provider support. As work digital health continues to expand, integrating health apps into clinical care delivery will be critical if digital health is to achieve potential.

npj Digital Medicine (2020)3:14; <https://doi.org/10.1038/s41746-019-0212-z>

Digital Biomarkers

Viewpoint - Review

Digit Biomark 2021;5:53–64  
DOI: 10.1159/000514730

Received: December 11, 2020  
Accepted: January 19, 2021  
Published online: March 23, 2021

## Evaluation, Acceptance, and Qualification of Digital Measures: From Proof of Concept to Endpoint

Jennifer C. Goldsack<sup>a</sup> Ariel V. Dowling<sup>b</sup> David Samuelson<sup>c</sup> Bray Patrick-Lake<sup>c</sup> Ileana Clay<sup>c</sup>

<sup>a</sup>Digital Medicine Society (DiMe), Boston, MA, USA; <sup>b</sup>Takeda Pharmaceuticals Inc., Cambridge, MA, USA; <sup>c</sup>Evidation Health Inc., San Mateo, CA, USA

## The use of a predictive statistical model to make a **virtual control** arm for a clinical trial.

Switchenko JM, Heeke AL, Pan TC, Read WL.

PLoS One. 2019 Sep 4;14(9):e0221336. doi: 10.1371/journal.pone.0221336. eCollection 2019.

Subramanian et al. J Transl Med (2020) 18:472  
<https://doi.org/10.1186/s12967-020-02658-5>

Journal of Translational Medicine

REVIEW Open Access 

## Precision medicine in the era of artificial intelligence: implications in chronic disease management

Murugan Subramanian<sup>1,2</sup>, Anne Wojtciszyn<sup>3</sup>, Lucie Favre<sup>3</sup>, Sabri Boughorbel<sup>4</sup>, Jingxuan Shan<sup>2,5</sup>, Khaled B. Letaief<sup>6</sup>, Nelly Pitteloud<sup>3\*</sup> and Lotfi Chouchane<sup>1,2,5\*</sup>

### Key Points

- A common, unifying lexicon, including key terminology relevant to evaluation and regulatory acceptance and/or qualification, is necessary for the successful development of digital measures for use in medical product development.
- Early and continuous patient and stakeholder engagement is critical to defining a concept of interest that will remain relevant throughout the digital measure development process.
- Establishing proof of concept is a key step in de-risking further investment into developing a digital measure.
- Where regulatory acceptance and/or qualification is required, early engagement with regulators is critical.
- The evidence and approach required for digital measure evaluation mirror those required for regulatory acceptance and/or qualification of an endpoint.
- Evaluation in the absence of a high-quality comparator measure is highly challenging but also highly impactful, essential for innovating medicinal products in these indications and populations.

## White Paper

# Virtualization of Clinical Trials

# Example: RWD for Virtual Clinical Trial Arms





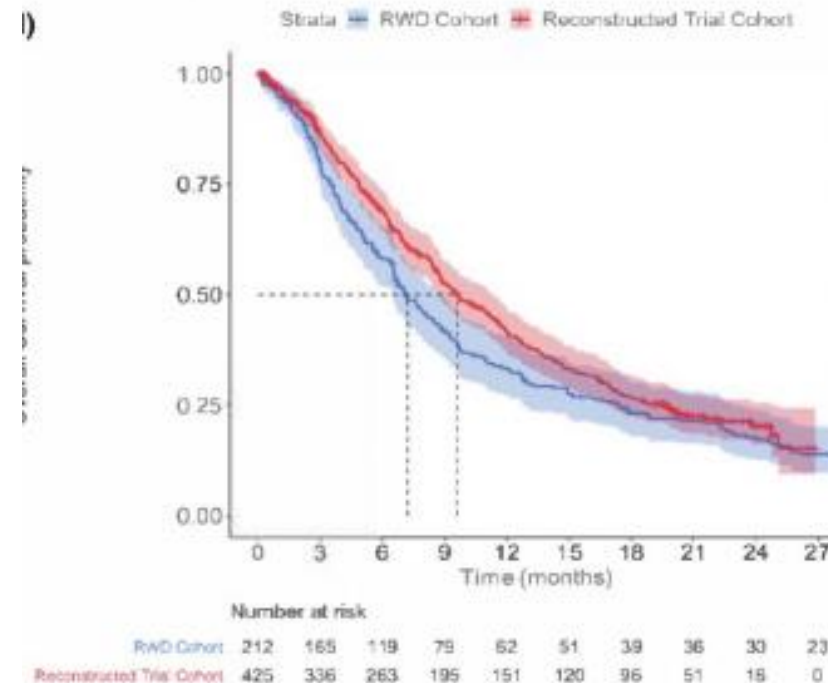
Summary of: Tan, K., Bryan, J., Segal, B., Bellomo, L., Nussbaum, N., Tucker, Torres, A.Z., Bennette, C., Capra, W., Curtis, M. and Miksad, R.A. (2021), Emulating control arms for cancer clinical trials using external cohorts create from electronic health record-derived real world data. *Clinical Pharmacology & Therapeutics*.

## Our summary

Real-world data (RWD) derived from electronic health records (EHR) can be used to create external comparator cohorts. This exploratory study assessed whether EHR-derived patient cohorts can emulate the control arms of published clinical trials that supported FDA approvals of anticancer therapies across multiple tumor types. Researchers evaluated the impact of specific real-world cohort construction analytic decisions on observed endpoints and found that results were variable depending on specific analytic decisions

## Emulating Control Arms for Cancer Clinical Trials Using External Cohorts Created From Electronic Health Record-Derived Real-World Data

Katherine Tan<sup>1\*</sup>, Jonathan Bryan<sup>1</sup>, Brian Segal<sup>1</sup>, Lawrence Bellomo<sup>1</sup> , Nate Nussbaum<sup>1</sup>, Melisa Tucker<sup>1</sup>, Aracelis Z. Torres<sup>1</sup>, Carrie Bennette<sup>1</sup>, William Capra<sup>2</sup>, Melissa Curtis<sup>1</sup> and Rebecca A. Miksad<sup>1</sup> 



# ...Fields of Application of Big Data and Algorithms..



## Optimization...

- Planning and Organization of Clinical Trials
- Regulatory Decision Making
- Optimization of health care processes / workflows



## Knowledge

- Research on the complexity and mechanisms of diseases
- Increased knowledge about rare/orphan diseases
- (Faster / better) monitoring



## Personalisation

- "Personalised" prevention
- Prediction and risk profiling
- Facilitation of specific diagnosis
- Novel, more "individualized" therapies (effect, interaction, AE)
- Individualized prognosis

# Digitalization in Healthcare – a variety of new chances, new approaches, but also *new challenges*...

## Data Protection/ Cyber Security

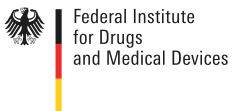


### Strategy for EU institutions to comply with "Schrems II" Ruling

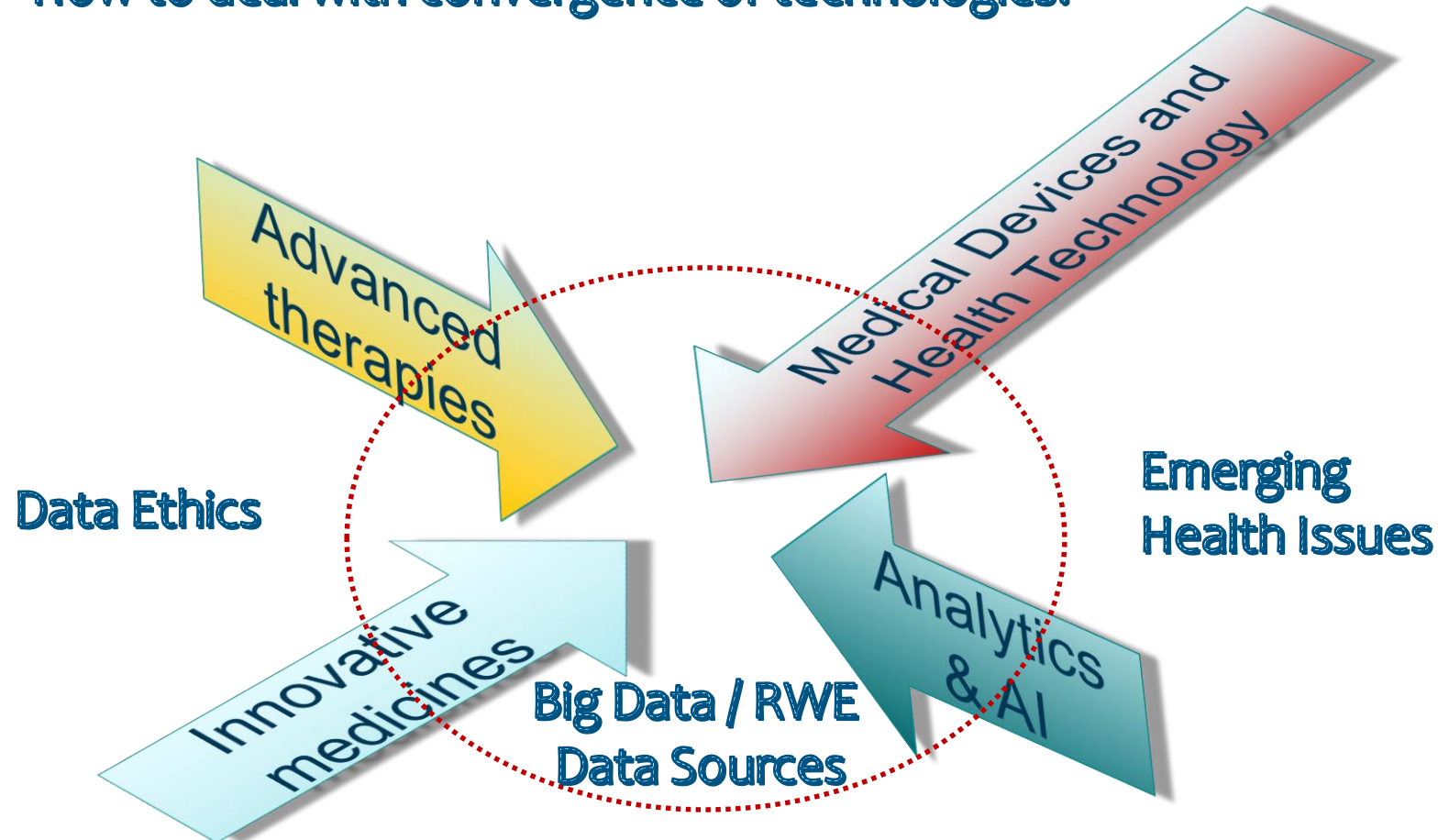
29 Oct 2020

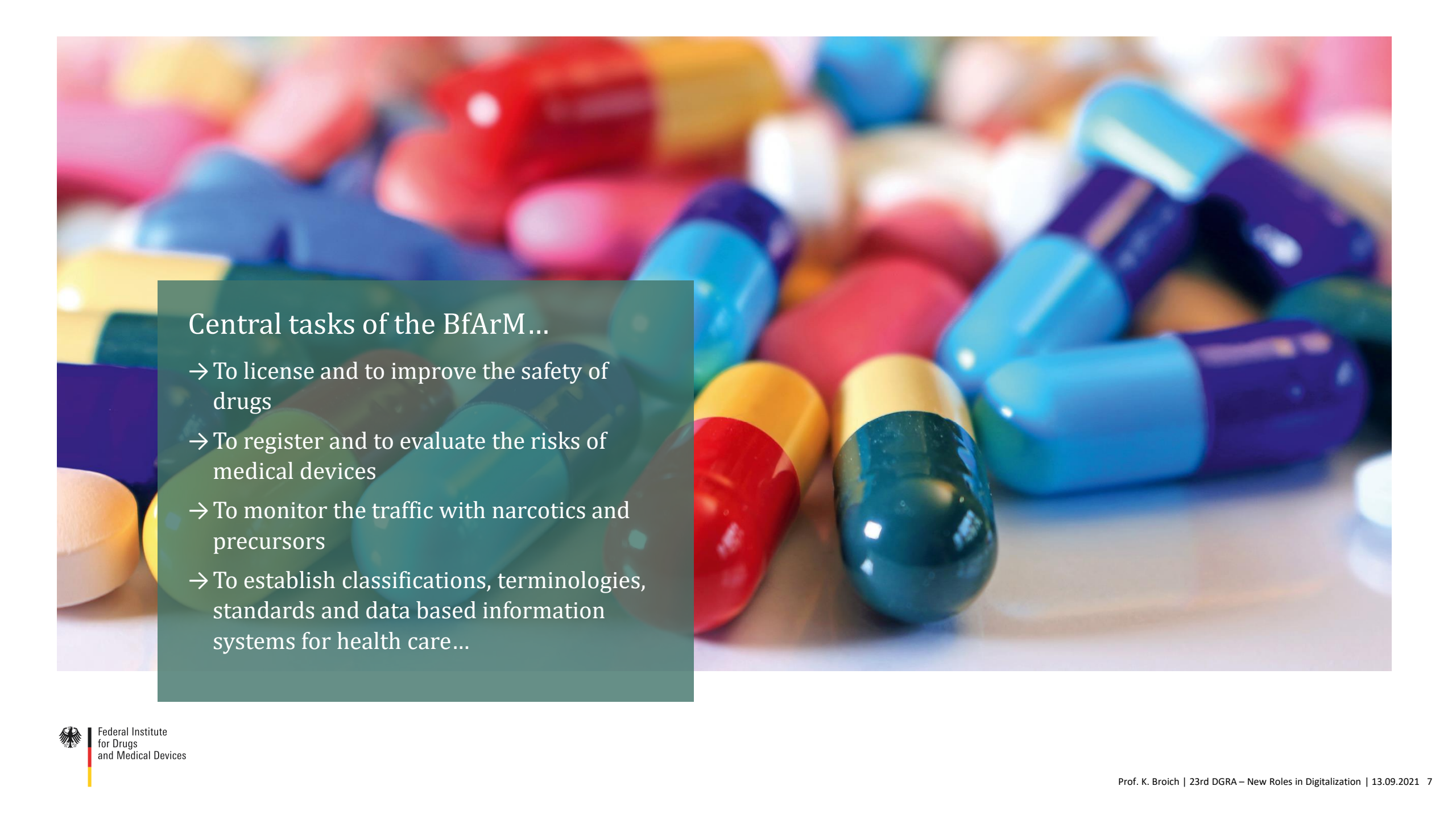
Strategy for EU institutions to comply with "Schrems II" Ruling [Press Release](#)

The European Data Protection Supervisor (EDPS) issued today a strategic document aiming to monitor compliance of European institutions, bodies, offices and agencies (EUs) with the "Schrems II" Judgement in relation to transfers of personal data to third countries, and in particular, the United States. The goal is that ongoing and future international transfers are carried out in accordance with EU data protection law.



## How to deal with convergence of technologies?

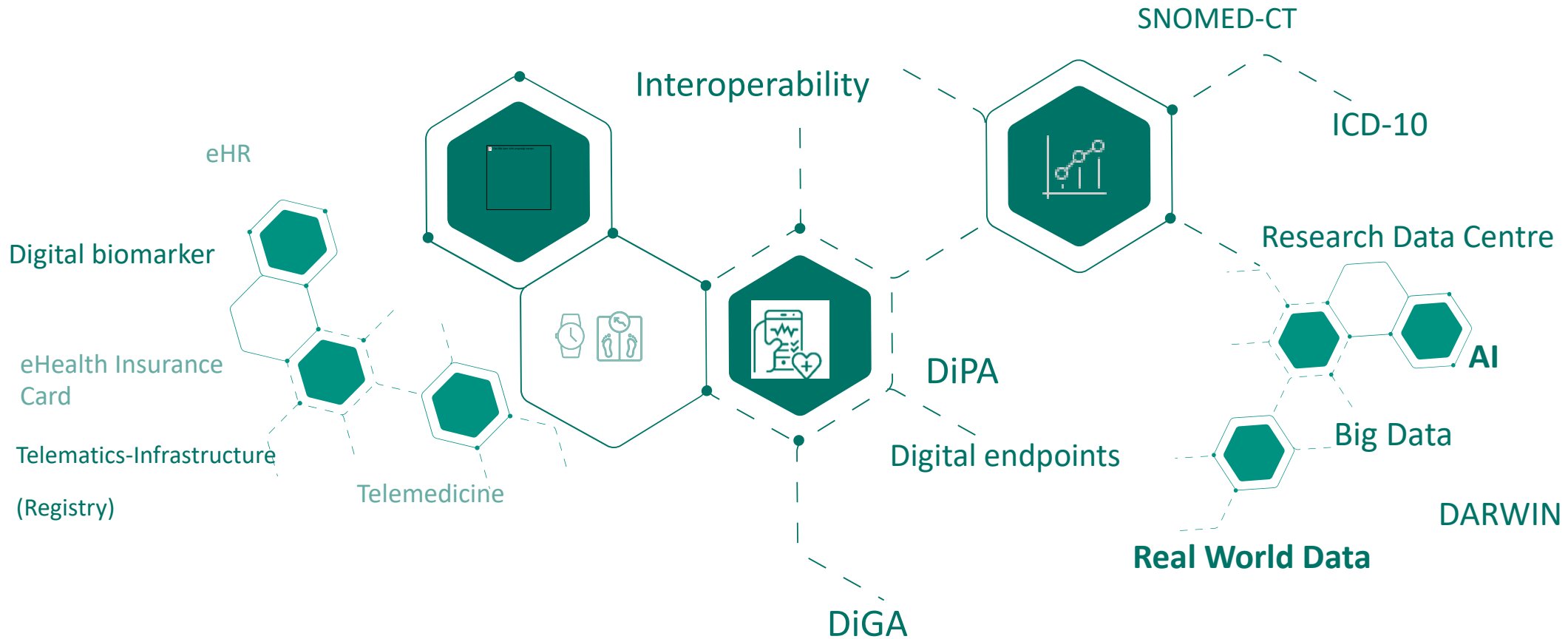




## Central tasks of the BfArM...

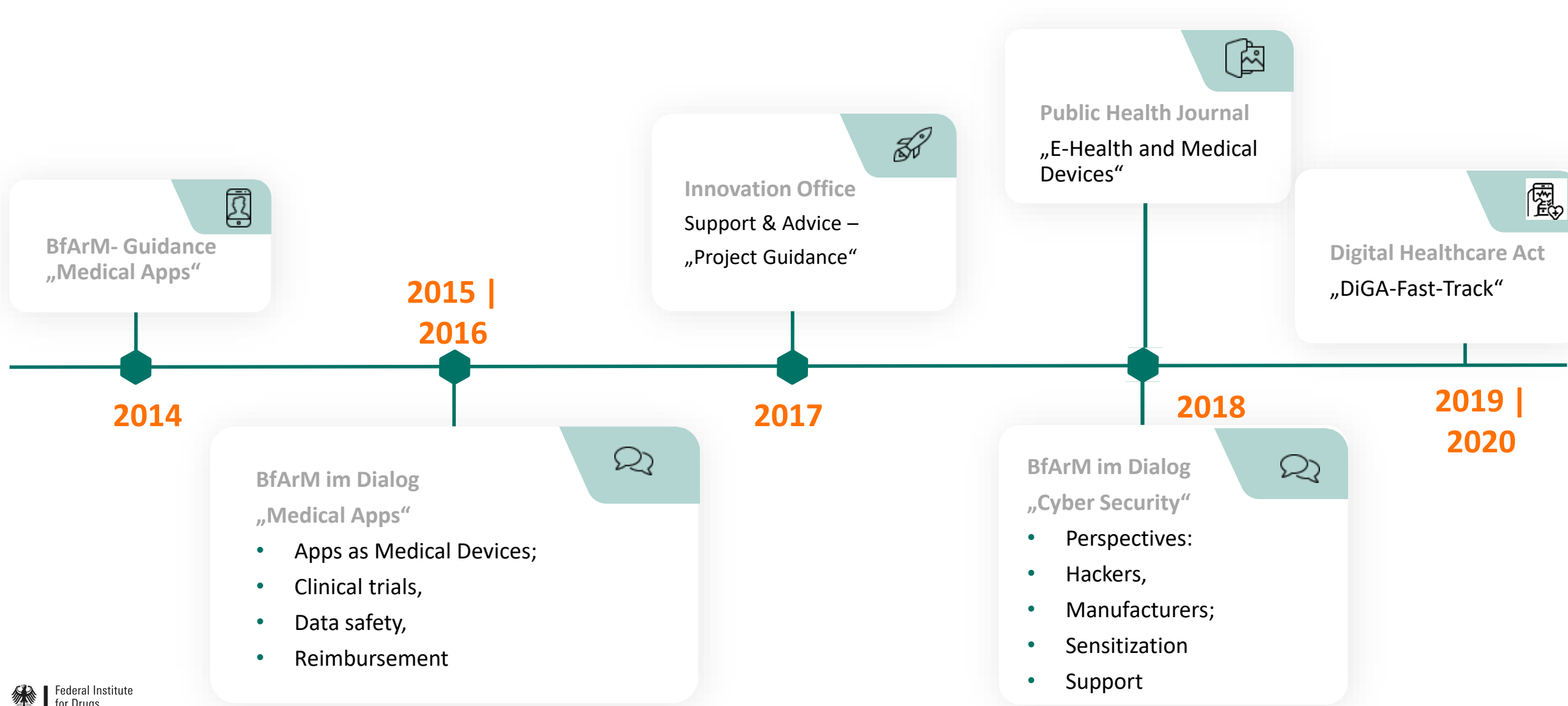
- To license and to improve the safety of drugs
- To register and to evaluate the risks of medical devices
- To monitor the traffic with narcotics and precursors
- To establish classifications, terminologies, standards and data based information systems for health care...

# ... at key interfaces in growing e-health ecosystems

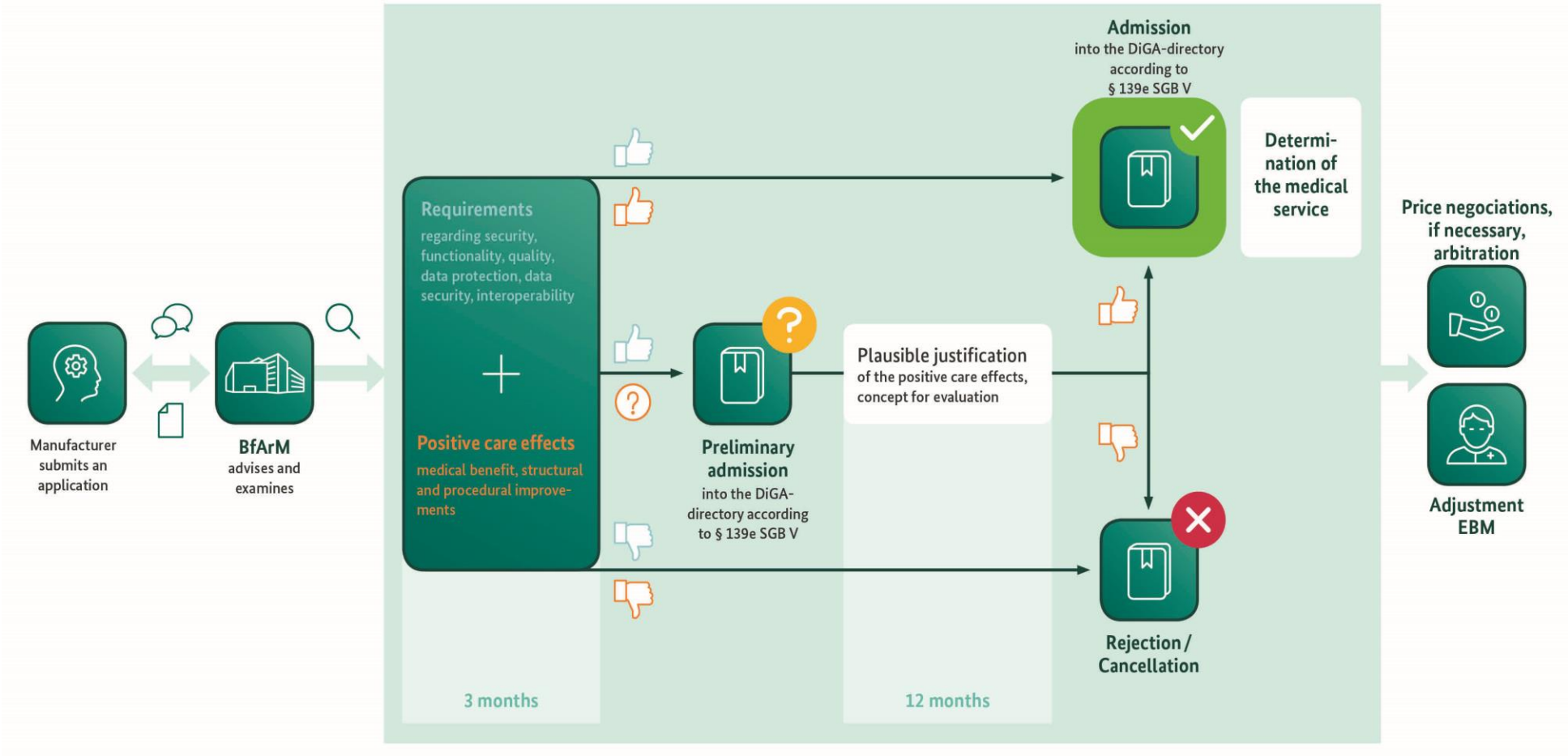




# Digital Medical Devices - Initiatives of the BfArM



# New Era for Digital Devices: App on Prescription – the DiGA-Fast Track



# What is a „DiGA“?



## Definition of Digital Health Applications (DiGA)



- CE-marked Medical Device of risk class I or IIa
- Supports the recognition, monitoring, treatment or alleviation of diseases, injuries or disabilities
- Main function is based on digital technology
- Used only by the patient or by the patient and the healthcare provider together – patient centricity

## Requirements for being listed in the DiGA Directory



- Safety and performance (CE-marking according to MDD/MDR)
- Data protection, information security and further quality requirements (e.g. interoperability)
- Positive healthcare effects

# Positive healthcare effects of DiGA



DiGA listed in the directory must have proven at least one of these positive healthcare effects:

## Medical Benefits



**perceptible effects for a patient specifically regarding:**

- improving state of health
- shortening of the duration of the disease
- extension of survival
- improvement in the health-related quality of life

**AND/  
OR**

## Patient-relevant improvement of structure and processes in healthcare (pSVV).



**supporting the health behaviour of patients or integrating the processes between patients and healthcare providers.**

**Might be one of the following:**

1. coordination of treatment procedures,
2. alignment of treatment with guidelines / recognized standards,
3. adherence,
4. facilitating access to care,
5. patient safety,
6. health literacy,
7. patient autonomy,
8. coping with illness-related difficulties in everyday life,
9. reduction of therapy-related efforts and strains for patients and their relatives



# The DiGA-Directory: Transparency and Guidance for Users, Health Care Professionals, Statutory Health Insurances...

**DiGA**  
Digital Health Applications

Tasks of the BfArM > Digital Health Applications (DiGA)

Here you will find all relevant information – advice regarding the connection with the procedure for listing in the directory of rein listing of a DiGA in that directory, information regarding prescrip documents and other webpages

- DiGA directory
- DiGA Guide
- Innovation office
- Interesting facts
- Contact
- Further information

[https://www.bfarm.de/EN/MedicalDevices/DiGA/\\_node.html](https://www.bfarm.de/EN/MedicalDevices/DiGA/_node.html)

## Finden Sie die passende digitale Gesundheitsanwendung

Treffen Sie eine Auswahl aus digitalen Gesundheitsanwendungen (DiGA), die vom BfArM gemäß § 139e SGB V bewertet wurden.

- Erstattung durch die GKV
- Zertifizierte Medizinprodukte
- Transparent aufbereitet

### DiGA-Verzeichnis

Geben Sie Ihren Suchbegriff ein...   oder

### Das DiGA-Verzeichnis

#### Antworten zur Nutzung von DiGA

Willkommen beim Verzeichnis für digitale Gesundheitsanwendungen (DiGA)!

<https://diga.bfarm.de/de>

**velibra**  
GAIA AG, Deutschland

**Plattformen**  
Webanwendung

**Anzuwenden bei**  
F40.01 Agoraphobie: Mit Panikstörung  
F40.1 Soziale Phobien  
F41.0 Panikstörung [episodisch paroxysmale Angst]  
F41.1 Generalisierte

**Eigenschaften**  
Keine Zuzahlung  
Keine Zusatzgeräte  
Verfügbare Sprachen: Deutsch und 1 weitere

### ESYSTA App & Portal – Digitales Diabetesmanagement

Emperra GmbH E-Health Technologies, Deutschland | www.emperra.com

Vorläufig aufgenommen

Informationen für Fachkreise

ESYSTA ist eine digitale Gesundheitsanwendung für insulinpflichtige Diabetikerinnen und Diabetiker. Durch automatischen Datenimport aus Blutzuckermessgeräten und Insulinpens in ein übersichtliches Tagebuch erleichtert ESYSTA die Kontrolle des Blutzuckerverlaufs und der Therapie. Eine kontinuierliche Datenauswertung erleichtert und verbessert das Diabetes-Selbstmanagement durch Feedback in Form einer nutzerfreundlichen Ampelfunktion und eines 7-Tage-Trends. Zudem unterstützt ESYSTA Ärztinnen und Ärzten, indem sie Behandlungsdaten jederzeit einsehen können, sofern ihre Patientinnen und Patienten dies wünschen. Anwendungsbeobachtungen belegen den medizinischen Nutzen von ESYSTA. Der HbA1c-Wert sank im Durchschnitt um 0,9 %. Die Verordnungsdauer von ESYSTA beträgt 90 Tage. Für nachhaltige Effekte ist eine dauerhafte Nutzung empfohlen.

**Plattformen**  
Apple App Store  
Google Play Store  
Webanwendung

**Anzuwenden bei**  
E10 Diabetes mellitus, Typ 1  
E11 Diabetes mellitus, Typ 2  
Mehr erfahren

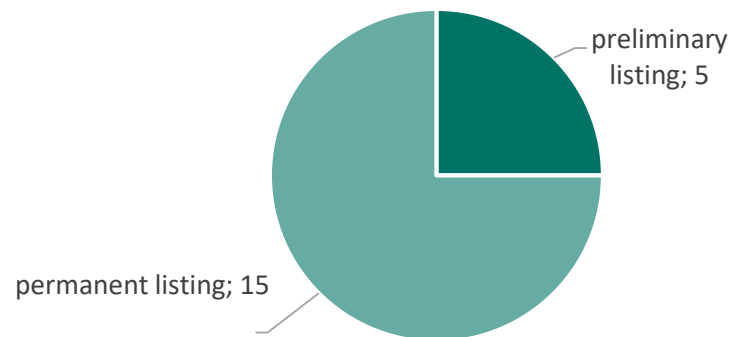
**Eigenschaften** **Informationsangebot des Herstellers**

<https://diga.bfarm.de/de/verzeichnis/316>

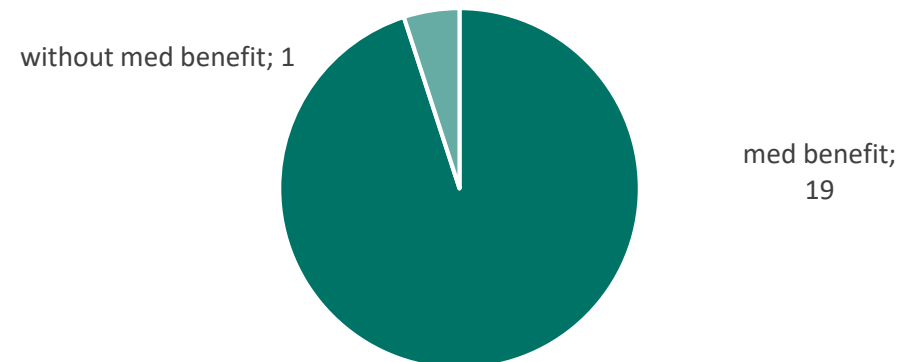
# Overview: DiGA in the Directory (n=20)



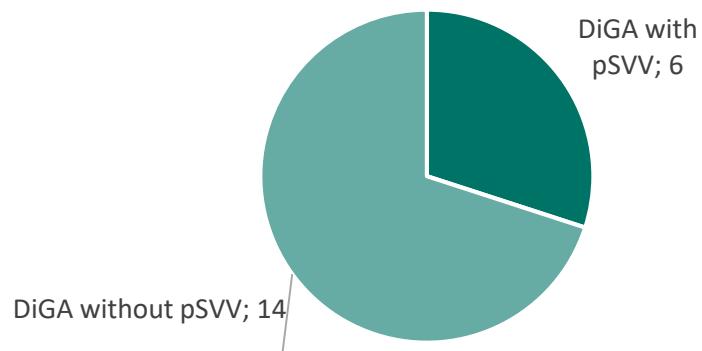
## Status



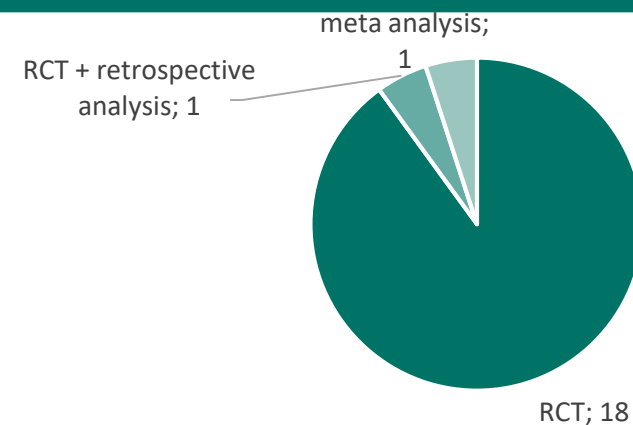
## DiGA with... a medical benefit



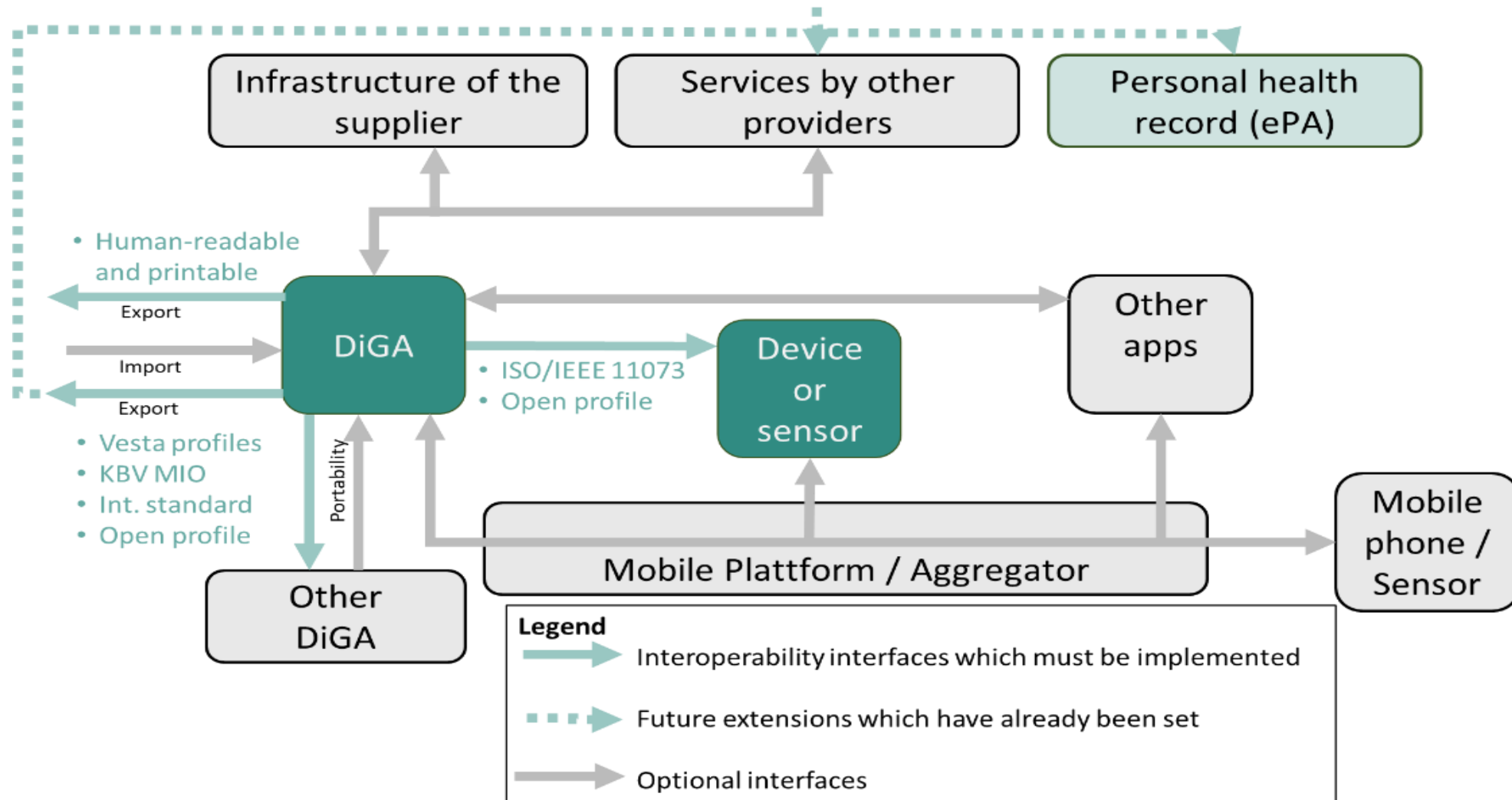
## DiGA with... patient-relevant improvement of structure & processes in healthcare



## Evidence



# DiGA as Part of German e-Health Structure: Interoperability



# National Competence Centre for Medical Terminologies / Semantics Centre at the BfArM

SNOMED CT global clinical terminology is introduced in Germany

Licenses issued through Germany's MII



## Standardisation & Semantics (inter-)national:

- Publication of official classifications such as
- **ICD-10-GM** (§§ 295 und 301 SGB V)
- Implementation **ICD-11** in Germany
- Maintenance of classifications, medical terminologies, thesauri, nomenclatures and other conceptual systems as a service for the health care system

## SNOMED-CT

- Routine licence for health care

## DVG / DiGA Ordinance:

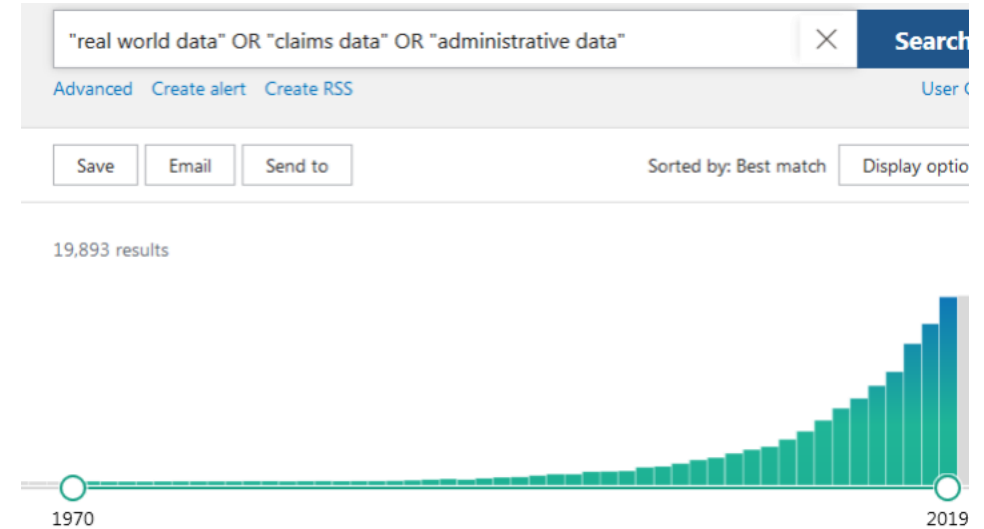
- Commitment to interoperable design of DiGA taking into account recognised standards (HL7/SNOMED CT, ...)

**Interoperability - terminology / technically**



# Usability of Real World Data (e.g. data from health insurance)

- As the **volume of data increases**, so does the scope and usability of secondary data
- **Strongly increasing** research with health insurance data
- **Increasing impact** of secondary data
- **Modern** methods allow data-driven insights



Article

**Using gradient boosting with stability selection on health insurance claims data to identify disease trajectories in chronic obstructive pulmonary disease**

Tina Ploner<sup>1</sup>, Steffen Heß<sup>1</sup>, Marcus Grum<sup>2</sup>, Philipp Drewe-Boss<sup>3</sup> and Jochen Walker<sup>1</sup>

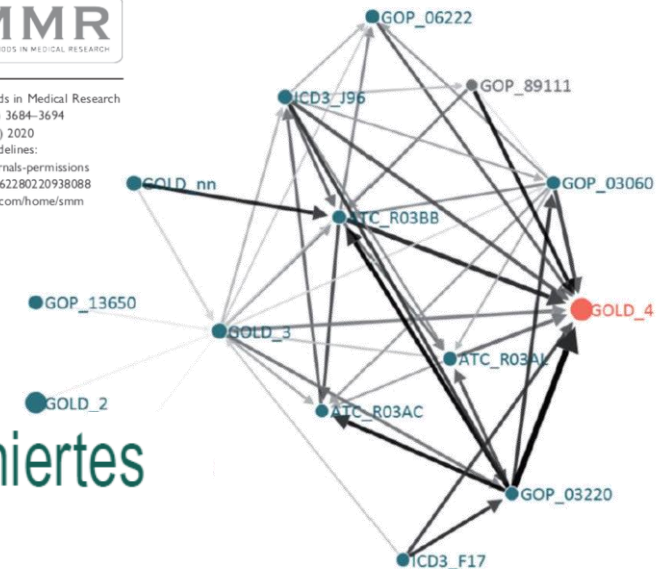
## N-Nitrosodimethylamin-kontaminiertes Valsartan und Krebsrisiko

Eine longitudinale Kohortenstudie mit deutschen Krankenkassendaten

Willy Gomm, Christoph Röthlein, Katrin Schüssel, Gabriela Brückner, Helmut Schröder, Steffen Heß, Roland Frötschl, Karl Broich, Britta Haenisch

**SMMR**  
STATISTICAL METHODS IN MEDICAL RESEARCH

Statistical Methods in Medical Research  
2020, Vol. 29(12) 3684–3694  
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DOI: 10.1177/0962280220938088  
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SAGE



# Research Data Center at the BfArM

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The Research Data Center is currently being extended to offer more data and to increase the throughput of analyses

## Research platform

- **Enabling researchers** by bringing complex **analyses to the data**
- Modern analysis tools available (e.g. R, Python)
- Data protection within the platform

## Availability

- Accessible for **authorized users and purposes**
- Data are reusable for future projects

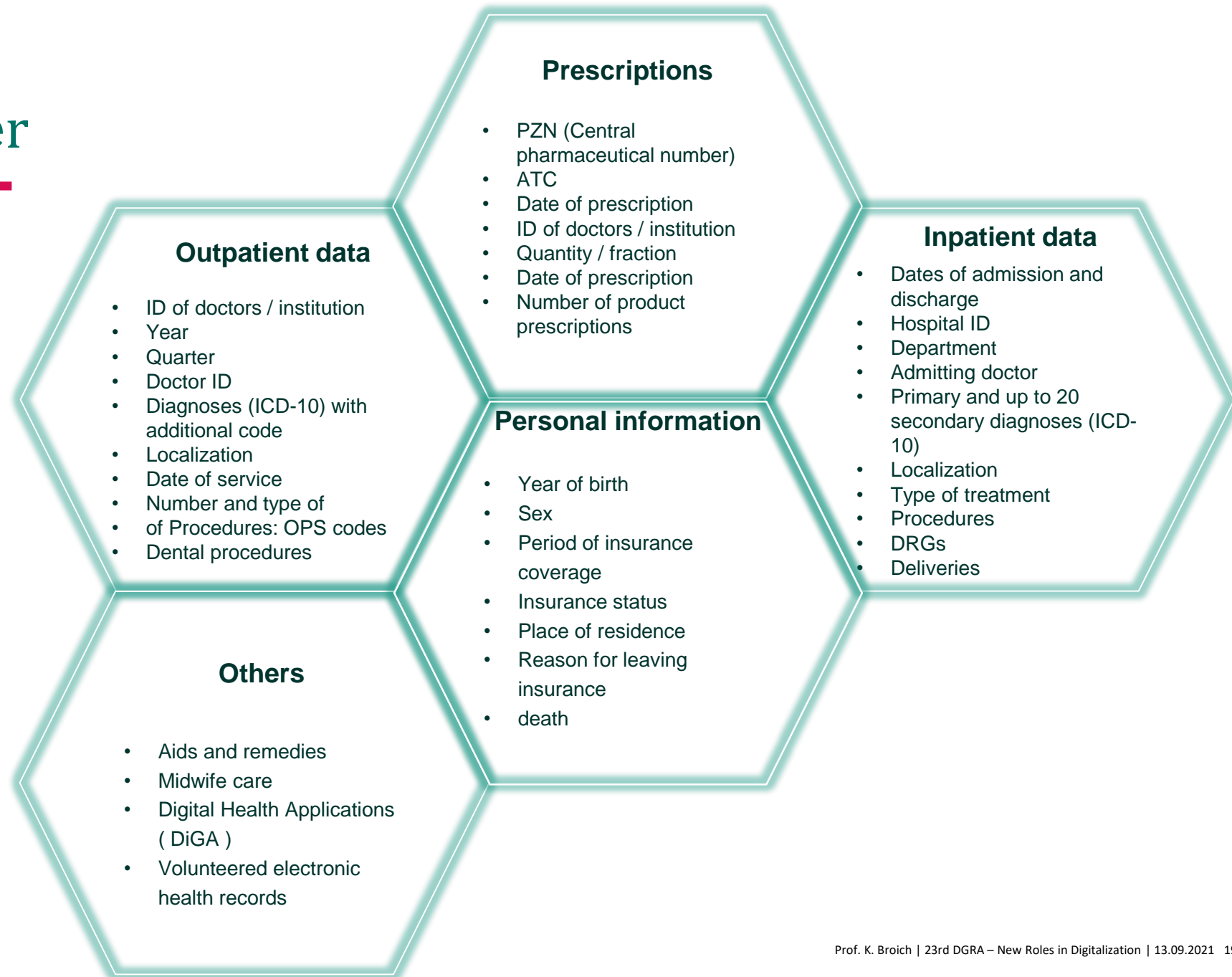
## Future-proof design

- **Scalability** to adjust resources in a massively growing field
- Design with **AI readiness** in mind

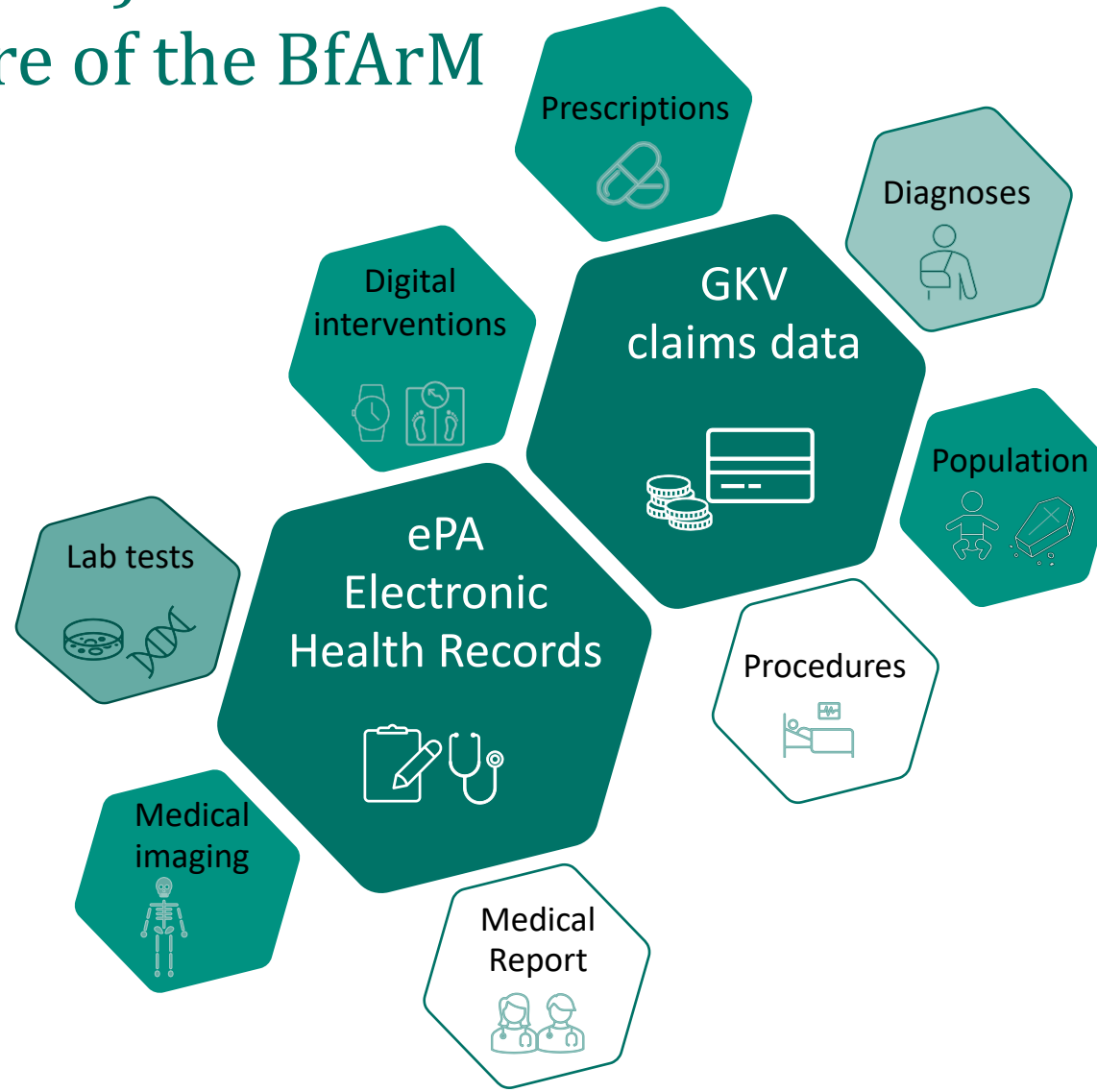
# Data at the Research Data Center

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- All 72 Mio. with statutory health insurance in Germany
- Information from all health care sectors linked on the individual level
- Longitudinal data starting from 2009
- Ensured interoperability with established code systems (ICD10, ATC, SNOMED CT)



# Real-World-Data (RWD) at the Research Data Centre of the BfArM



# AI Infrastructure in the Research Division at the BfArM

## Technical specifications of the AI/HPC network

2x IBM POWER SYSTEM AC922 server (8335-GTH)

IBM FlashSystem 5100 NVMe Storage System

IBM WATSON MACHINE LEARNING ACCELERATOR

IBM Spectrum Virtualize Software

(8 NVIDIA V100 GPUs, 512 GB DDR4, 50 TB ext. Storage)

- NVLink 2.0 for fast bidirectional bandwidth between CPUs and GPUs
- Network: 10 Gb Ethernet, I/O architectures: PCIe gen4
- OpenPOWER Linux scale-out server (Red Hat Enterprise Linux operating system)

➤ System is especially designed for Deep Learning and AI, high-performance analytics, and high-performance computing



Power System AC922 internal components

# Ongoing AI Projects in the Research Division at the BfArM



## Projects including machine-learning approaches

- **EMPAR:** Influence of metabolic profiles on drug therapy safety in routine care. Use of ANNs to predict pharmacogenetic, -epidemiologic and -economic associations. Status: near completion (sponsored by the Innovation Fund of the G-BA; support code 01VSF16047)
- **Covid19 –Risk:** Pharmacoepidemiologic study of medication- and morbidity-associated risk factors in vulnerable patient populations on COVID-19 progression. Status: in progress (sponsored extra budgeted resources of the BMG framework for Covid-19 pandemic control)
- **ANKA:** Combined analyses of adverse events and routine clinical data using machine learning methods. The project includes in part preliminary work for causality assessment of ADE-reports using sophisticated DL (deep learning) NPL- (natural language processing)- techniques. Status: in progress (sponsored by own funds of the BfArM and IMBIE)
- **In addition,** machine learning techniques are used in several bioinformatics routines and analyses, e.g. in the analysis of metabolic profiling, gene expression and sequencing data

# Current Research - Example from Medical Device Area: Propose Free-Text Classification by using Textmining and Similarity Scores

**2.5.2 Best Similar**    New incident to be classified    Already classified Incidents    Dissimilarity score    FDA classification    Reference number of the incident already classified

	New incident to be classified	Already classified Incidents	Dissimilarity score	FDA classification	Reference number of the incident already classified
	<p>high impedance of the pace/sense conductor (&gt;3000 ohms) and oversensing after 45 months of service life.</p>	<p>Information [redacted] indicated that the lead was replaced after 46 months of service life because of high impedance of the</p>	0.093	c("High Impedance", "Oversensing")	0298 [redacted]
	<p>high impedance of the pace/sense conductor (&gt;3000 ohms) and oversensing after 45 months of service life. Lead fracture was suspected. No corrective action. Monitoring and trending this type of event.</p>	<p>Information [redacted] indicated that the lead was replaced after 46 months of service life because of high impedance of the pace/sense conductor (&gt;3000 ohms) and oversensing. Suspected lead fracture was reported. No corrective action. Monitoring and trending this type of event.</p>			C

# 5G technologies - GIGA FOR HEALTH project: incident reporting app



## Goal:

- ✓ First medical campus in Europe to implement and evaluate innovative medical 5G applications



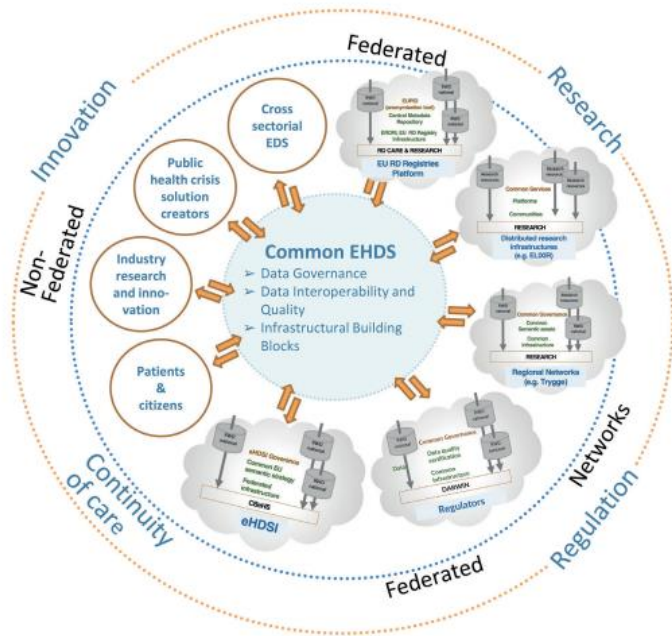
## BfArM:

- ✓ Development and evaluation of a novel **medical device incident reporting app**
- ✓ taking advantage of mobile technologies & 5G to support fast, easy and helpful reporting by healthcare professionals
- ✓ In cooperation with: University Hospital Düsseldorf; Vodafone GmbH, Düsseldorf; RWTH Aachen University; FH Dortmund University of Applied Sciences; Brainlab AG, Munich; Bergische Universität Wuppertal/ SIKoM+



# European Activities - BfArM Participation

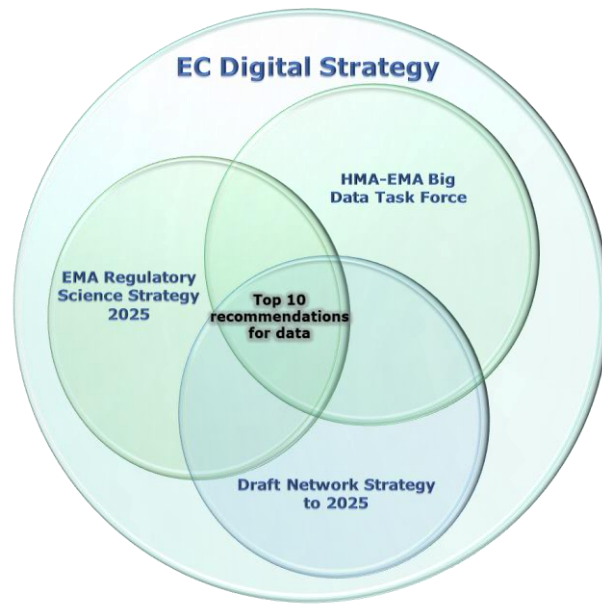
## 3. Towards a European Health Data Space



EC supporting digital "EU-Health Data Space" Pharmaceutical Strategy

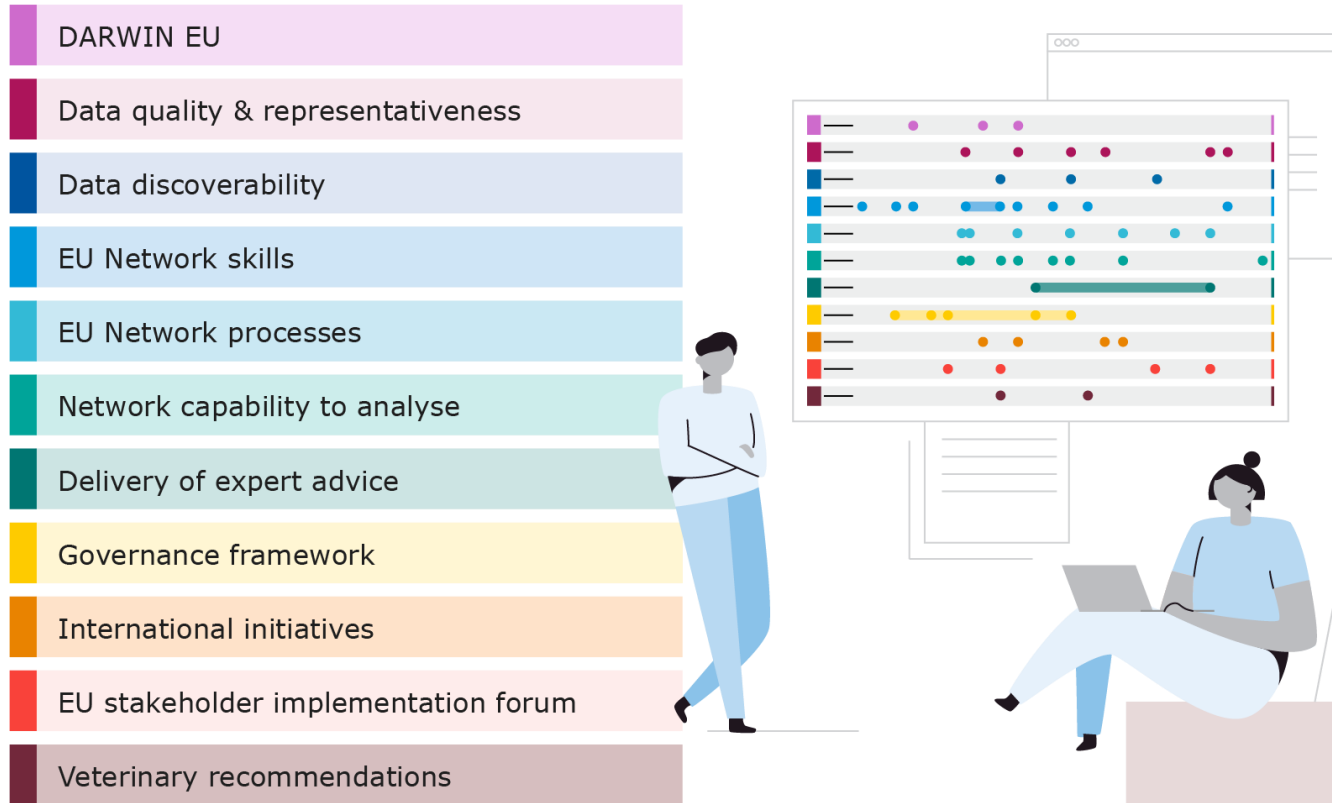


EU network strategy 2025 + DARWIN EU  
 EMA Regulatory Science Strategy 2025  
 HMA-EMA Big Data Task Force Top-Ten-Recommendations for data



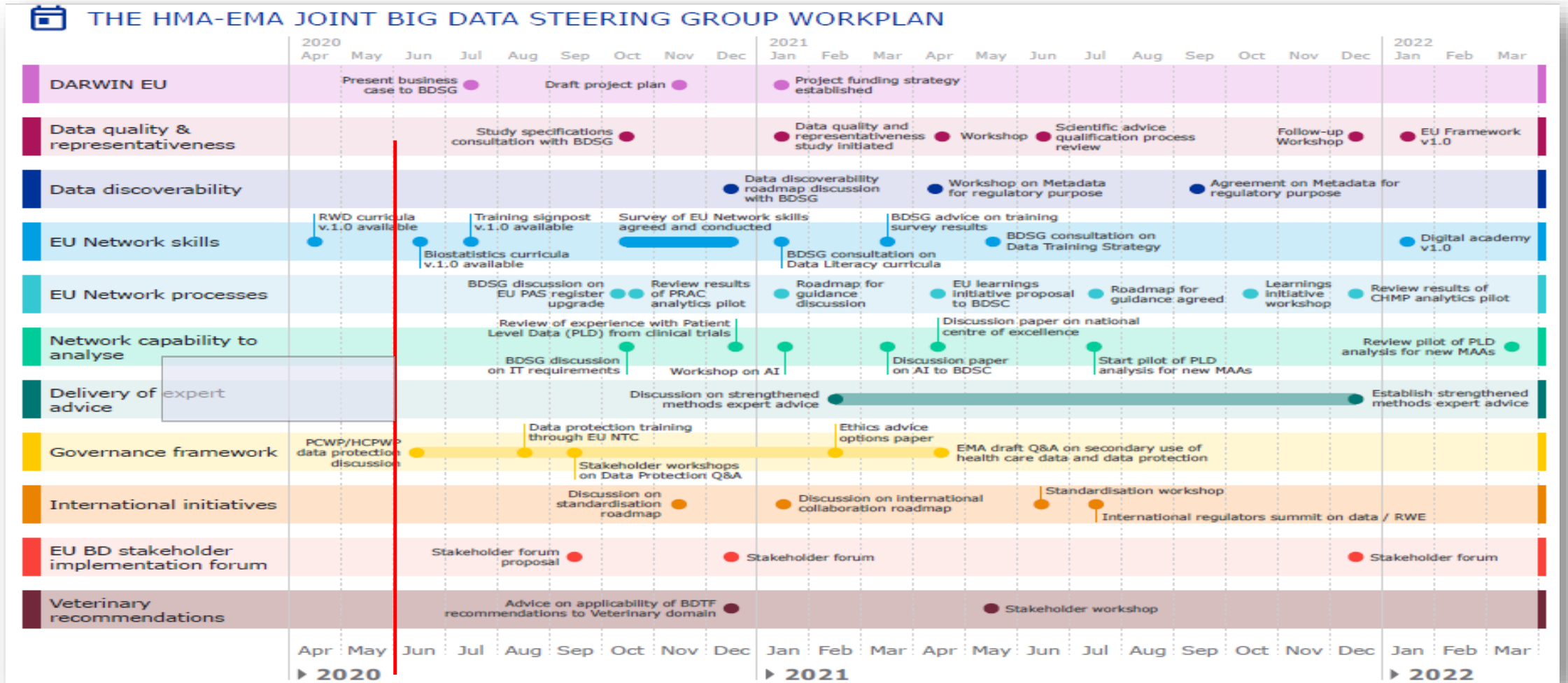
# HMA & EMA Network Strategy – Pillar Innovation & **Digitization**

Data  
analytics,  
digital tools and  
digital  
transformation



*Big Data Steering Group; EU Telematics; EU Innovation Network, ...*

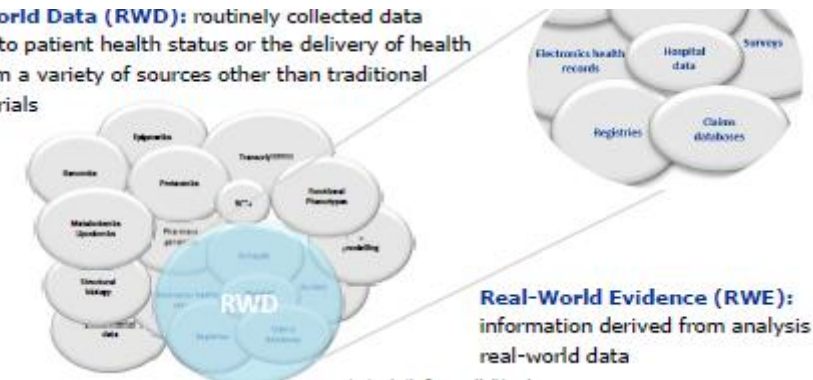
# BDSG workplan



# DARWIN (Advisory Board)

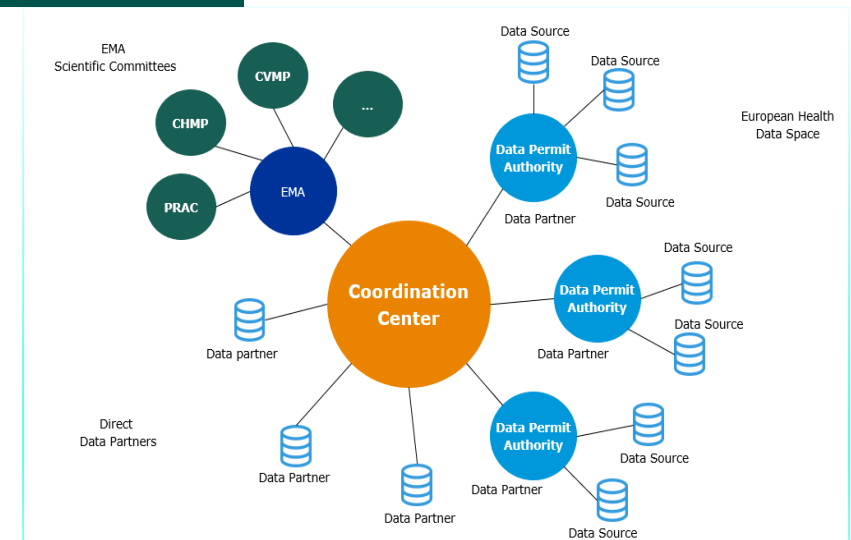
- National and EU **regulation of medicines**:
  - **Drug development** – disease epidemiology, unmet need, historical controls, planning
  - **Authorisation** – contribution to BR, controls, extrapolation to general and/or special populations
  - **Post-authorisation** – benefit-risk monitoring, extension of indication, risk minimisation measures

**Real-World Data (RWD)**: routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials

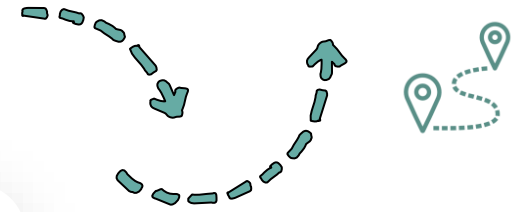


DARWIN EU will significantly **increase the capacity** of the Network to undertake high-quality observational studies based on real-world data.

- **Additional benefits** as EU partners participate and access the platform:
  - **European Commission** – key use case for the European Health Data Space
  - **National governments** to support health policy and delivery of healthcare systems
  - **HTA bodies and payers** to support better quality decisions on cost-effectiveness
  - **EU health agencies** - use cases specific for EFSA, ECDC, ECHA, JRC
  - **EU patients** - faster access to innovative medicines and safe and effective use



# Conclusion and outlook



## Digitization, big data and AI:

- many opportunities, great potential for better health care and knowledge gain, also for regulatory questions on benefits and risks in everyday health care



## DiGA Fast-Track:

- Important **component of the digitalization** of the health system
- Germany pioneer with regard to procedures for reimbursement, with a high degree of **transparency** for users, doctors, health insurers
- Continuous **further development**: From DiGA to DiPA to...?  
From checklists to certificates for more clarity and transparency – data protection



Making **data usable and available for relevant research** and/or **regulatory questions** requires **harmonised** (semantic and technical) **standards**

**Working together: BfArM is involved at national & European level** at important interfaces (classifications; research data centre, DARWIN, etc.) together with other actors and partners to support digital transformation for patients' benefits

# Thank you very much for your attention!



## Contact

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[www.bfarm.de/diga](http://www.bfarm.de/diga)

[www.bfarm.de/digitalfuture](http://www.bfarm.de/digitalfuture)

