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Digital health data: Benefits, costs, governance

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Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise qualified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

- Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,
- Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,
- Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,
- dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, an interdisciplinary dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa e.V.), and Xcenda GmbH.

The Advisory Council of the Interdisciplinary Platform on Benefit Assessment

One „winner“ of the Corona pandemic: digital data in healthcare

By Professor Jörg Ruof

Dear readers,

Few events have shaped the past year as much as the Corona pandemic. Many effects cannot yet be assessed – but one „winner“ has already been determined: whether it's home offices, home schooling, video consultations with physicians, or Internet shopping – everything is about the digitisation of essential everyday processes.

With this in mind, the present publication looks at digitisation and digital health data – from the perspective of benefits, costs and governance. Politicians need to set the right framework conditions here. The industry's task is to drive innovative products and digital processes.

After evaluation by the regulatory authorities and separating the wheat from the chaff, the statutory health insurance system is responsible for finally reimbursing products and procedures in everyday care that represent added value for the members of the statutory healthcare system. Successfully established model projects play a central role here. This publication covers this entire range of topics and provides an insight into the various facets of digitisation in healthcare – with a focus on innovative pharmaceuticals and their benefit assessment.

- Based on her experience from the Enquete Commission on Artificial Intelligence, Dr Christmann presents the vision of a „FAIR“ (Findable/Accessible/Interoperable/Reusable) approach to the opportunities, risks and possibilities for digital data in healthcare from the perspective of the Green Party.
- Since January 2021, the test run for the German electronic patient record (ePA) has begun. In his article, Dr Leyck Dieken, Managing Director of gematik GmbH, i.e. the company responsible for this process, provides a fascinating insight into gematik's diverse fields of activity and draws the vision of the ePA as a centrepiece of the

upcoming digitisation boost in healthcare.

- The ‚Health Innovation Hub' (HIH) which has been established by the German Federal Ministry of Health, aims at strengthening competence for digital innovation in Germany and promoting innovative concepts. In this interview, Professor Debatin, as head of the HIH, answers questions about the new ground that has been broken with digital health applications (DIGA).
- Mr. Steutel, President of the Association of Research-Based Pharmaceutical Companies in Germany (vfa), takes a closer look on the competitiveness of German and European pharmaceutical companies and emphasises the necessity to optimise national and European framework conditions. These include i) development of European structures for real-world data, ii) harmonisation of European data protection and ethics law, iii) regulation of access rights to health and treatment data, and iv) jointly defined standards for the use of this data in regulatory approval and HTA procedures.
- The key role of the Federal Institute for Drugs and Medical Devices (BfArM) in the digital transformation of the healthcare system is illustrated in the following article. In order to efficiently use the constantly growing volume of health data for regulatory and treatment-related issues, the semantic and technical interoperability of the various digital offerings is paramount. The development and provision of classifications, nomenclatures, terminologies, establishment of a research data centre, and the evaluation of DIGA are driven by the BfArM.
- Dr Haas and Dr Erdmann outline that the principle that additional costs for the SHI system can only be justified if there is adequate evidence for the added value of innovative pharmaceuticals increasingly loses importance. In this context, the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband) believes that, instead, the generation of high-quality health data from clinical research and patient care, the pooling of these data sources, and the networking of stakeholders should be promoted.

The two final articles deal with flagship projects of European cooperation at the level of digital health data:

- Professor Kröger, President of the European Society for Blood and Marrow Transplantation EBMT, presents the EBMT registry, that was founded about 50 years ago and in which 500 specialised centres from 57 countries systematically collect data on stem cell transplantation. This pool of data plays a significant role in the continuous optimisation of expertise, especially in rare diseases, and is also used for a variety of regulatory and HTA processes.
- Professor Vehreschild's article finally deals with COVID-19 as the first pandemic in the digital age. He outlines that the pandemic is associated with an ‚infodemic'. The great art, he says, is to identify the promising approaches, networks and collaborations at an early stage and anchor them permanently. His article provides a comprehensive and fascinating insight into this.

Even if reading this publication might take or „cost" some time, this effort is offset by a very considerable (additional) benefit. I can only warmly recommend that you realise this added value for yourself!

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Digital data in healthcare – need for regulation from the The Green's point of view

Dr Anna Christmann | Member of the German Bundestag

A responsible, point-of-care and scientifically high-quality use of digital data in healthcare is a central concern of green policy. The main focus must be on the short, mid and long-term benefit for patients.

It is particularly important here that patients are clearly informed about the added value that is created for their own care by making their own data available. This is the only way to achieve cooperation and trust on the part of the patients which creates the basis for adequate data collection. The voluntary nature of patient data sharing and a reliable digital infrastructure play a crucial role in shaping a high-quality and ethical digital healthcare data system. In addition, availability of digital data for research purposes is a key point. Under these conditions, the introduction of digital applications is reasonable in many areas of healthcare.

These aspects are also elaborated in the positions of the Study Commission on ‚Artificial Intelligence'.[1] The main contents include the voluntary and revocable sharing of data by patients, administration in decentralised trust centres, decentralised pseudonymised storage, the provision of sufficient resources for the timely creation of an infrastructure for data collection, and the standardisation of legal foundations for data protection.

At the first green AI conference it was also discussed that it is essential to actively shape digital technologies in Europe.[2] Particularly with regard to the Corona pandemic, it becomes apparent that digital data has the potential to make an important contribution to crisis management. The Study Commission of the Bundestag will issue a special report on this topic. Initial findings show that above all – both in Germany and worldwide – there is a lack of patient data in order to be able to provide electronic aids.

But the potential benefits of AI in healthcare are also foreseeable far beyond its use in containing the Corona pandemic. Image recognition in the radiology sector, monitoring of patients in intensive care units for the early detection of threatening conditions, as well as therapy optimisation for personalised treatments (e.g. innovative cancer therapies) are just a few examples.

First of all, the conditions for nationwide data collection at university clinics, hospitals, outpatient clinics and medical practices need to be created. At this point – similar to the DigitalPakt Schule, i.e. digitisation of education – a sustainable structure for securing financial resources in the sense of a DigitalPakt Klinik, i.e. digitalisation of healthcare, would be required between the federal and state governments to create the technical conditions for such data collection in a timely manner.

The issue of data protection in particular is a core element of patient trust in the development of digital systems in healthcare. Due to the German federal structure, different interpretations of individual legal aspects are interpreted differently. At this point, there is a need for standardisation, e.g. through an agreement between the Federal Government and the Federal States, so that – while fully respecting patients' interests and rights – there are no obstacles for the use of digital systems.

Furthermore, the development and design of digital applications and structures should always be tailored to the patients' needs. Helpful structures that provide a noticeable benefit to patients. Digital information, for example on the compatibility of different drug combinations, is attractive for patients and increases acceptance and trust in digital systems. One example of user acceptance is the Corona-Warn-App used in Germany, which has a very data-saving design. Confidence in this application is comparatively high – in contrast to the corresponding app in the USA – so that interest has already been expressed in the German solution from New York.

In summary, success regarding the provision of data in the healthcare sector will mainly depend on decentralised data processing, voluntary data collection, and the standardisation of the legal basis.

The FAIR principle provides orientation for the generation, management and use of data:

- **F**indable (data must be easy to find and identify by both humans and computer systems),
- **A**ccessible (data must be stored for long term such that they can easily be downloaded),
- **I**nteroperable (data exchange, interpretation and combination with other data sets must be possible),
- **R**e-usable (good description of data ensures reusability in future research).

Dr Anna Christmann *has been a Member of the German Bundestag since 2017 and is the spokesperson for Civic Engagement and Innovation and Technology Policy for the Alliance 90/The Greens parliamentary group. After studying political science, political economics and mathematics at the University of Heidelberg, she spent time abroad in the USA and Switzerland. She received her doctorate from the University of Bern in 2011 on the topic of ‚The Limits of Direct Democracy'. From 2013 to 2017 she worked as an Adviser to the Minister of Science of Baden-Württemberg.*

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Digitisation in the healthcare sector – status quo and opportunities from gematik's perspective

Dr Markus Leyck Dieken | Managing director of gematik

Digitisation of healthcare is rapidly advancing and provides a huge potential for improving patient care. Gematik monitors current developments and trends and develops and improves digital networking. For this purpose, it is very important to establish, maintain and further develop the electronic health card and the corresponding structure throughout Germany. As of January 2021, the electronic patient record (ePA) will allow patients to get a transparent overview of their health data for the first time. It can be connected to other digital tools, such as Digital Health Applications (DiGA). Thus, input, storage and transfer of digital information must be standardised. For this purpose, MIOs (Medical Information Objects) are used. So far, gematik's system includes „Germany-specific" characteristics (e.g. concerning technical standards) only that are not yet compatible with data formats of other healthcare systems. Optimising this Europe-wide digital networking is thus another focus of gematik. Optimizing this Europe-wide digital networking is thus another field of work of gematik. Such a data room must: i) be secure, there must be ii) some kind of access control, and all stakeholders must iii) abide by the rules (e.g. of data formats).

Digitisation of healthcare is advancing rapidly. Monitoring current developments and trends and developing and enhancing digital networking are essential tasks of gematik. Gematik, based in Berlin-Mitte, was founded in 2005 by the leading organisations in the German healthcare sector with the aim of promoting the introduction, maintenance and further development of the electronic health card and the corresponding structure in Germany and make full use of the potential of an improved digital networking in the healthcare sector.

The electronic patient record (ePA) that is being launched since January 2021 will provide patients with a transparent overview of their health data for the first time. Patients decide independently whether and how they want to use the ePA, which documents shall be stored

Support treatment with DiGA, generate data for the ePA and gain knowledge for the physician

- Provision of **„Apps on prescription"** by the physician and refinancing by health insurance providers
- Apps with **application procedure at the BfArM**, possibly in connection with hardware and servicesse
  - Medical device of risk classes I and II
  - Interoperability with the ePA
  - Evidence of positive treatment effects
- Collect **data about medical devices, wearables and sensor systems** with DiGA

Source: Dr. Leyck Dieken/gematik

Figure 1: Digital technologies can be used to improve the detection, monitoring or treatment of diseases.

there and which physician shall have access to the data. Patient sovereignty is strengthened and data protection concerns fully taken into account. Thus, the ePA is not comparable to a traditional paper patient record. Only data released by the patient on diagnoses, findings, therapy procedure and treatment course, medication plans, vaccinations, physician's letters or emergency records are recorded with the aim of avoiding duplicate examinations and improving treatment by providing more information.

Digital health applications (DiGA) are another step in digitisation in the healthcare sector (see figure 1). This involves creating applications that use digital technologies to optimise the detection, monitoring or treatment of a disease. The DiGA can be combined with the ePA – if the patient so desires; data can be exchanged and entered into the ePA. If appropriately approved, physicians can use DiGAs as a basis for their prescription. Thus, via ePA, data generated via DiGA could also enhance patient care.

The National Association of Statutory Health Insurance Physicians (KBV) defines the content that is exchanged between practices, clinics and other parties via the telematics infrastructure. Currently, KBV is defining approx. 300 laboratory values as a set of biodata, which could then also be entered into the ePA. This could facilitate and accelerate many procedures, especially in rare diseases. In October 2020, there were two approved DiGA applications, „kalmeda" and „velibra" (see figure 2). To incorporate this data into the ePA, close collaboration is mandatory. So far, any further use e.g. also in combination of data from DiGA and ePA can only take place at ePA level.

In order to standardise input, storage and transfer of digital information, MIOs (Medical Information Objects) are used (see figure 3). MIOs are digital information modules enabling interoperability of different healthcare data sets provided they have been standardised. The KBV aims at standardising e.g. vaccination cards, maternity certificates or child's examination records, but also physician's letters and laboratory values. Nursing documentation represents another field of work, and initial applications are tested that cover a broad spectrum of the data fields representing the care provided and in which it must be defined which data are relevant for potential interfaces.

The involvement of research is also important in the context of standardisation (see figure 4). The main focus here is on establishing the conditions through appropriate data release by the patient and enabling reasonable use of data for research by means of compatibility. Data must be released for specific fields so that patients are not put in the position of having to release the entire ePA for research. At present, these requirements are still a relevant hurdle for the current version of the ePA; however, the

Dr Markus Leyck Dieken *is a specialist for internal medicine and emergency physician. After his medical studies at the universities in Cologne and Freiburg, he spent many years in the industry in positions of increasing responsibility, including Novo Nordisk, Novartis, InterMune Inc., Teva and most recently as Senior Vice President and Managing Director Germany at Shionogi Europe. In 2019, he took over the management of gematik GmbH, whose majority shareholder is the Federal Ministry of Health.*

The first two apps in the DiGA directory* - and many more to come

kalmeda

- For the treatment of tinnitus
- Apple App Store
- Google Play Store
- No co-payment
- No additional devices

velibra®

- For the treatment of anxiety disorders
- Web application
- No co-payment
- No additional devices

APP

- BfArM currently evaluates > 21 applications
- Consulting sessions are currently taking place with the innovation office of the institute for > 75 apps
- > 500 requests by manufacturers

*https://diga.bfarm.de/de/verzeichnis

Source: Dr. Leyck-Dieken/gematik

Figure 2: In October 2020, the first two apps were listed in the DiGA list of the BfArM. Several dozen other applications are under review or in development.

Using medical information objects to ensure semantics and syntax of documents in the ePA

- **Collection of information** on medical, structural or administrative matters, self-contained or nested
- **Can be implemented across sectors in all primary systems**
  - Vaccination certificate, maternity certificate, child's examination record, dental bonus booklet
  - Hospital discharge letter, laboratory findings, care record, etc.
  - Evidence of positive treatment effects
- **Prerequisite** for release and reasonable use of data **for research**

Source: Dr. Leyck-Dieken/gematik

Figure 3: MIOs are digital information modules enabling interoperability of standardised

planned third ePA version (ePA 3.0) claims to be research-compatible.

A successful pilot example is the merging of health insurance accounting data and treatment data from the ePA at the Research Data Centre (RDC). But this first step has already sparked an ethical debate. Thus, these applications are being developed further step by step involving patients or depending on the acceptance by patients, respectively. A comprehensive data set on the progression, prognosis, and treatment success could be created, but informed consent and the patient's right to withdraw are prerequisites for a secure, pseudonymised data release. In this context, the further development of the ePA was associated with the problem of decoupling and partial release of data fields.

So far, gematik's German system only includes „Germany-specific" characteristics (e.g. concerning technical stan-

Support medical research with ePA

- Pooling of **accounting data** by health insurance providers and treatment data from the ePA at the Research Data Centre (RDC)
- **First such comprehensive data basis** about the course of diseases and recoveries in Germany
- **Informed consent and right of revocation** provide the basis for a voluntary, pseudonymised and secure release of data from the ePA

Quelle: Dr. Leyck Dieken/gematik

Figure 4: An important prerequisite for research involvement and reasonable use of data is to define data release by patients.

dards) without compatibility to data formats of other healthcare systems. It is therefore necessary to create data formats that can operate together in order to be able to use and enrich the European data space. At this point, the establishment of a European gateway for telematics infrastructure applications should be mentioned. As of 2023, Germany will participate in the European „National Contact Point eHealth" network. At present, more than 22 nations participate and cross-border data traffic without language barriers is currently being developed. In order to have access to this entire European data space and be able to use corresponding structures, Germany must become active as an interlocutor and take an active part in the discussion – an important field of work for gematik.

gematik is also involved in the development of the European exchange format for the ePA (EHRxF). These formats must be further defined and it is important that they are compatible with the ePA from the beginning. Moreover, gematik is a partner in the EU-funded X-eHealth project that coordinates and promotes the exchange of electronic health records in a collaborative network (see figure 5). Over a period of 24 months, 36 partners from 22 countries have been participating. The focus is on EU datasets for laboratory findings, medical image data, and discharge letters. Here, the National Contact Point will act as the central technical converter of these health data from different countries.

Secondary use of this health data for research should also be made possible across borders. The German-Dutch „Stroke Project" is a pilot project for this. Furthermore, an EU funded project ‚European Health Data Space' is being prepared that will create a network of 26 EU countries over a period of three years with a clear focus on sharing data from ePAs and disease registries.

In this process, gematik develops the definitions for the data fields of the German ePA so that these European standards can also be achieved. First, for example, hospital owners need to agree on standardised physician letter formats so that the data fields in the ePA can be set up accordingly.

If future European health research becomes possible through the sharing of disease registries and ePA, this would also increase acceptance of this type of data use by making the societal benefits of this research transparent.

The upcoming changes require, in fact, a technical leap of more than ten years. As the coordinating body, gematik will approach these changes gradually and in a modular way in close cooperation with working groups in order to be able to adequately incorporate the special features of existing structures in Germany. The aim is to establish a standardised space which provides an orientation guide and creates the basis for existing and new projects, irrespective of their specific content.

Participation in the EU funding project X-eHealth

Exchanging Electronic Health Records in a common framework

Type: Coordination and Support Action

Netwirk: **36 partners from 22 countries**

Duratzion: **Since sept. 2020 for 24 months**

Focus: **EU data sets** for exchange of **laboratory data, medical image data and hospital discharge letters**

X-eHealth

Exchanging Electronic Health Records in a common framework

Source: Dr. Leyck Dieken/gematik

Figure 5: Secondary use of health data for research should be made possible across borders. The EU-funded X-eHealth project promotes the exchange of health data sets in a common network.

This data space:

(i) must be secure,

(ii) must be secured by some kind of access control,

(iii) all stakeholders must comply with the rules (e.g. data formats).

Gematik sees its key role in ensuring these three aspects and describes the advantage that there does not have to be any government control. This data room would include applications for the insured (such as ePA or eDental Bonus Booklet), for administrative processes (ePhysician's Letter, eAU or ePrescription) and for care management (eMedication Plan, eMaternity Certificate or eChild's Examination Record). Looking ahead, research-compatible ePatient records, access to research registries, or use of the ePatient Summary would be possible across borders.

The Fast Track procedure for digital health applications

Professor Jörg Debatin | Chairman of the health innovation hub of the German Federal Ministry of Health

The healthcare system is on a comprehensive digital transformation journey. The so-called Fast Track and initial approvals of digital health applications (DiGA) are milestones on this journey. For many physicians, the benefits of digital medicine first became tangible through Corona. This has significantly increased the overall acceptance with regard to supplementary digital offerings for patient care. The approval procedure of the German Federal Institute for Drugs and Medical Devices (BfArM) ensures that patient safety is ensured without compromise for DiGA that have been approved for Fast Track. In terms of content, listed DiGA will provide direct patient benefits in standard care.

Question: How do you assess the status quo of digital health apps in Germany after the first DiGA were approved beginning of October?

Professor Jörg Debatin: The first approvals represent a milestone – even if there is criticism from some KV regions. It is important for me to emphasise that we have not changed anything in terms of CE approval with the Fast Track procedure. Manufacturers still have to overcome many hurdles. Moreover, Fast Track has special privacy hurdles built in, so these applications are in fact secure. What we don't know – and this is a deliberate difference from the previous process – is whether these DiGA actually provide benefits. The only thing that has changed with Fast Track is that the respective product gets into reimbursement faster.

At the beginning of October, approximately 20 applications were under review and more than 80 consultations have been held. What spectrum of apps are we talking about?

This is a very broad range. One example is the monitoring of diseases, for example through applications that make it easier to keep a digital record. Think of migraine patients who, when they see the doctor every four weeks, are supposed to remember when they had an episode. Through digital documentation, this information can be made available on an ongoing basis so that a physician can detect a crisis or switch to another medication at an early stage. In some cases, monitoring is also combined with smart sensor technology, for example in the case of diabetes where blood glucose values are automatically transferred in certain cases.

Moreover, there are applications for therapy accompaniment. Think of a patient who has a new hip joint and is gets physical therapy. He now has the opportunity to in-

tensify the convalescence process with an app tailored to his needs so that one does not only have therapy applications twice a week for an hour, but can continuously do the appropriate exercises without forgetting them. And there's a whole range of convalescence-accompanying ideas that we hope will translate into digital health applications.

Furthermore, there are applications that support diagnostics – people with sleep disorders, for example, where vital parameters such as breathing rate can be recorded to make it easier to diagnose sleep apnoea, for example.

Or think of the field of psychosocial medicine. Here we know that we often reach our limits with conventional methods. An example would be patients with tinnitus, for whom the physician usually has little to offer. Or patients with anxiety disorders. There, the focus is on psychotherapy, but we know the sometimes long waiting times. Here, new and interesting offers are available with DiGA.

Professor Jörg F. Debatin *has been Chairman of the health innovation hub (hih) of the German Federal Ministry of Health (BMG) in Berlin since March 2019. The radiologist was appointed to the Chair of Diagnostic Radiology at the University Hospital in Essen in 1998 and moved to the University Hospital Hamburg-Eppendorf as Medical Director and Chairman of the Board in 2003. From 2011, he has been CEO of the European laboratory operator amedes AG. Since 2014, he was responsible for global technology and product development at GE Healthcare as Vice-President.*

We are deliberately breaking new ground with the Fast Track procedure.

We are talking about class 1 and 2a medical devices. Can you outline a strengths and weaknesses analysis for DiGA at this time?

It is too early for this. In general, you could say that we are trying to lower the threshold of medical assistance. To this end, we are deliberately breaking new ground with the Fast Track procedure. There is no other country in the world that currently offers digital health apps in standard care, i.e. apps on prescription.

Critics of the DiGA contend that many patients do not want such services at all. This reminds me of the discussion about video consultations. In January, there were only a few physicians offering this service – now, more than 100,000 video consultations have been conducted. And 100,000s of patients have accepted this offer. I think there will be a similar habituation effect with DiGA and I am optimistic that there will be users. That's what we're all about: gain experience. We want to know if these new offerings will be prescribed. That is the key question for me. And further steps will be aligned with this. If DiGA should hardly be prescribed, we do not even need to worry about suitable applications for risk classes 2b and 3.

Prescription also depends to a large extent on how well informed physicians are. The German National Association for Digital Healthcare sees a need to catch

up here – how do you assess this?
There is no doubt about it. That's why appropriate training should be offered – as is the case for other new launches. Professional associations will take up this topic so that a scientific discourse can begin. To make that happen, we first had to bring DiGA into the reality of care – and that has now happened.

These new applications will not replace other forms of therapy, they are an additional offer. As far as integrating DiGA into physicians' daily work, I'm not worried. If they are useful, word will spread quickly – and physicians will prescribe them.

What effort do manufacturers have to make in order to furnish proof of the hoped-for positive healthcare effects after Fast Track?
There will be no pattern here. Developers may also be able to demonstrate the required positive effects on care with studies beyond randomised clinical trials. These studies must be tailored to the corresponding application. Among other things, the Innovation Office of the BfArM provides valuable advice. In consultations, it helps developers set the right course from the beginning. In this context, one message is important for all app developers: It is not something that can be taken for granted. This also applies if a provider was listed following the Fast Track procedure.

Listing is the moment of truth for DiGA providers. Then they see whether physicians prescribe the product and patients accept it. And most of the applications that are actually accepted by patients also develop a benefit. It's the same with non-medical applications in other areas of life.

Do you dare to predict to what extent digital data will influence patient pathways and therapy decisions in the future?

DiGA will not replace other forms of therapy, they are an additional offer.

They already do that today. As a radiologist, I can't imagine it any other way. It's just that in the past decades we took a long detour of „analogising" digital data by printing it on X-ray images. But ultimately, digital data is the basis of CT or MRI. The same applies, of course, to laboratory diagnostics.

What has changed: In the past, we had the problem that too little data was available. Today, the problem is rather that the amount of data tends to be too large and we have to check what data is actually relevant. And for that, we need the support of digital tools. Digital data are the basis for individually optimised diagnostics and therapy. And that's why the electronic patient record provides the basis, because that's where data is collected – initially only cursorily in the first phase – that will be relevant later on.

The volume of future digital data will continue to increase. To what extent will this data influence treatment guidelines, approval processes, or HTA procedures?
This is an exciting aspect. If we take the premise that people are different, then we reach a limit with randomised clinical trials. That's why I think it's important that we open ourselves up to new forms of evaluation. Time and again, we will find that the notion that one only needs to study enough patients to arrive at a measurable result reaches the limits of methodology.

Take the website „Patients like me" in the USA as an example. There, patients with a rare disease, for example,

can have a look how many other affected people there are with a comparable constellation. And they can find out how those other patients were treated. I think we are only at the beginning of a discussion here in Germany. But the question of generating evidence with new methods is not limited to DiGA. We have a comparable discussion about new active ingredients.

The Federal Data Protection Commissioner, Professor Kelber, warns that the electronic patient record in its current form will undermine data protection. Do you see the high level of data protection in Germany in danger?

Il am not a lawyer, but as far as I know, even among lawyers Professor Kelber's position is controversial. What is it about? If I want to have an ePA, I first have to explicitly state this, as we have an opt-in procedure. Secondly, I must say: I want to have this or that document in my ePA – again, an active decision is required. Thirdly, I need to authorise a specific physician to look at the data. Professor Kelber's criticism is aimed solely at the fact that a so-called fine-grained authorisation concept is still missing, which means that I cannot yet withhold certain data in the ePA from a physician. But if a patient doesn't want his dentist to look at his psychosocial history, he can just not give him access to the ePA. So there are three consent steps built in which is a very high level of data protection in my view. In this respect, I do not share Professor Kelber's criticism.

In your view, what opportunities and possibilities does the DiGA present for the pharmaceutical industry?

I see great opportunities here. This will enable the pharmaceutical industry to get closer to patients for the first time. Companies are given multiple opportunities to use digital tools to get feedback from patients, such as on the tolerability of a certain pharmaceutical. Pharmaceutical companies are well advised not to leave this to start-ups alone, which generate and develop new applications on this basis.

If we take the premise that people are different, then we reach a limit with RCTs.

Will a different level of evidence be required for DiGA than for pharmaceuticals?

The requirement level has been adjusted, which becomes apparent by the term positive care effects: It is not just defined by measurable medical effects, but also structural, organisational or other effects that make it easier for a patient to deal with his disease. This is actually a deliberate extension of the previous definition and handling of evidence. I believe that the discussion and the experience we gain from it will do us good.

In the last few weeks, it has been repeatedly emphasised that Germany took a special position with the new reimbursement procedure for DiGA. Where do we stand in Germany compared to the rest of Europe?

There is no reason for us to sit back. We are only at the beginning. In 2018, the Bertelsmann Foundation ranked Germany 16th out of 17 countries evaluated. Even now, we are certainly not playing in the top positions. And that's where we should actually want to go.

In addition, we must be careful when making comparisons. Let's take the USA as an example. There, digitally fully integrated healthcare systems can be found that are in fact closed. The insured are being told which physicians they

We shouldn't see digitisation as an end in itself; instead, we should always evaluate whether it actually makes medicine better.

have to see. And they can't take their data with them when they change insurance companies because it's not portable. Thus, such approaches are not transferable to Germany.

We said from the beginning: We stand by the German system with the free choice of health insurance, physician or hospital. We do not want to sacrifice this degree of freedom. However, this freedom is associated with a higher level of complexity in the healthcare system. We therefore have to use technology in such a way that we also find solutions under the German framework conditions. In my opinion, this has been achieved with the ePA as a basis. Against this background, the listing of the first two DiGA is only one puzzle piece of an overall picture of digital medicine. But we still have a long way to go.

Thus, we shouldn't see digitisation as an end in itself; instead, we should always evaluate whether it actually makes medicine better. This reality check is important. We are entering uncharted territory with DiGA – but we are taking it one step at a time.

Note

The interview was conducted on 9 October 2020 as part of the 12th meeting of the Interdisciplinary Platform for Benefit Assessment. The questions were asked by Wolfgang van den Bergh, Editor-in-Chief of Ärzte Zeitung, Springer Medizin

Digitalisation and European benefit assessment – from the vfa's perspective

Han Steutel | President of the Association of Research-Based Pharmaceutical Companies in Germany (vfa)

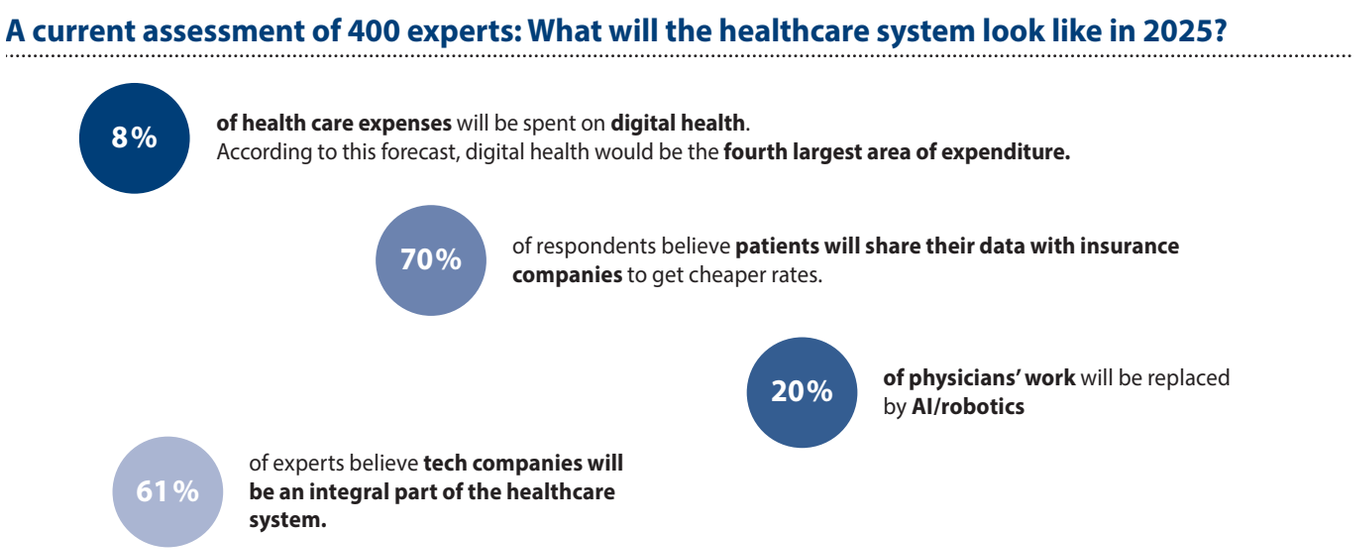
In the course of the German EU Council Presidency, work is being done on the prerequisites for a European health data area. An initiative which research-based pharmaceutical companies expressly welcome. However, more is needed to harness the opportunities of health data for patient care in Europe: (1) Development of decentralised databases, structures and standards for real world data across Europe, (2) harmonisation of European data protection and ethics law, (3) regulated access of private research to health and treatment data, and (4) jointly defined standards for the use of digital health care data in regulatory approval and HTA.

Digitisation. Benefit assessment. Europe. Three big keywords and their future shape will have a massive impact on healthcare systems in general and patient care in particular. The question then is: Where is the healthcare system heading?

The management consultancy Roland Berger tried to find this out in a large survey among 400 healthcare experts (such as patients, physicians, hospitals, health insurance companies, as well as the pharmaceutical and medical device industry) around the world. The results show that the digital health market is facing a bright future. The experts estimated that in 2025, approximately eight percent of healthcare spending will be spent on digital health (see figure 1).

From today's perspective, this would make digital health the fourth largest service area. Thus, technological development will have an enormous impact on all areas. One example is data sharing, where 70 percent of experts estimate that patients will share their data with insurance companies to get cheaper rates. Similarly, experts predict that approximately 20 percent of physicians' work will be replaced by AI systems/robotics. The introduction of digital health will probably also lead to a significant increase in the importance of those companies that can cope with this technological progress. A total of 61 percent of the experts assume that large IT companies will become an integral part of the healthcare system.

This view concerning the importance of digital health is also increasingly shared by politicians. For example, digitisation of the healthcare system is one of the declared healthcare policy goals of Federal Health Minister Jens Spahn – a topic that enjoys wide support at both national and European level and is also of utmost importance for the German EU Council Presidency. Accordingly, it is not a questi-



Source: Roland Berger „Future of Health", 2019

Figure 1: According to healthcare experts surveyed by management consultancy Roland Berger, the digital health market is facing a bright future.

Han Steutel *has been the President of the Association of Research-Based Pharmaceutical Companies in Germany (vfa) since 2019. He had been a member of its board since 2009 and its chairman since 2016. Prior to that, he was Chairman Senior Vice President & General Manager Germany at the research-based pharmaceutical company Bristol-Myers Squibb.*

on of whether, but of how. The most recent example: Germany is currently working on the implementation of a European Health Data Space in the course of its EU Council Presidency.

German EU Council Presidency drives European Health Data Space and thus medical progress

The availability of large amounts of high-quality data is essential for the development of new diagnostic and treatment methods. The systematic collection and use of health data enables new research approaches and not least – based on health data – improved patient care. But there is still a lot of work to be done before that happens. So far, there are neither defined governance and infrastructure nor a consistent interpretation and interpretation of the

General Data Protection Regulation (GDPR) for the secondary use of health data. Thus, regulatory gaps should be gradually closed by developing and implementing Codes of Conduct (CoCs).

By the end of the German EU Council Presidency, the first guidelines for the development of a general CoC can be expected. Moreover, there will be a Joint Action under Finnish leadership as of next year that will work on the legal and organisational framework of a European Health Data Space over the next two to three years. Overall, the promotion of digital networking and increased use of data within the European healthcare sector is to be welcomed. The same applies to efforts towards harmonised health data governance within the EU, if it is open to private research and thus strengthens Europe as an industrial and research location. From the perspective of the pharmaceutical industry, three global trends should also be taken into consideration in the discussion of the right design.

Three global trends shape the pharmaceutical industry

First, the pharmaceutical industry's research and development pipelines enjoy a steady increase in innovative active substances and treatment options. This reveals a second trend: the advance of personalised medicine. This medical progress leads to a more precise characterisation of the diseases and determination of new treatment approaches. Personalised medicine thus results in ever smaller patient numbers required in the development of pharmaceuticals so that conventional study designs reach their limits and new approaches to evidence generation need to be considered.

Therefore, the third global aspect is of importance, i.e. digital health data. Thus, more and more patient data are available for more accurate assessments, and these health data – and ultimately data science – create new insights.

In order to further promote research and development – the centrepiece of the pharmaceutical industry – and align it with the technological possibilities and changing needs of patients in their everyday lives, consistent integration is required in all phases of the value creation process: From Research & Development, Production and Market Access to Care. For example, clinical studies cannot only be optimised by means of big data applications, but the reliability of results in the production of pharmaceuticals can be secured and optimised by means of digital monitoring and intelligent cross-linking of production units. The combination of modern diagnostics and innovative medicines enables personalised medicine, which further sharpens the efficacy profiles of pharmaceuticals thus providing a therapy that is tailored to the individual patient's disease.

Ultimately, treatment adherence and evidence can be improved through data use and digital offers. Thus, the collection and analysis of (real time) data from daily clinical practice can provide additional evidence of the benefits of pharmaceuticals, and digital offers can actively support patients in increasing their adherence to treatment and further improving the safety and quality of pharmacotherapy through medical monitoring of treatment data, in some cases even in real time.

Digital health data provide opportunities for research and improved healthcare

When talking about health data, the first thing that needs to be clear is the definition. Hence, here is a small digression: Real world data (RWD) are data related to the health status of patients and/or their healthcare from various data sources that are collected under real everyday conditions. They are a central basis to harness the opportunities of digital transformation in the field of medicine for better healthcare.

Digital health data can complement and simplify clinical studies

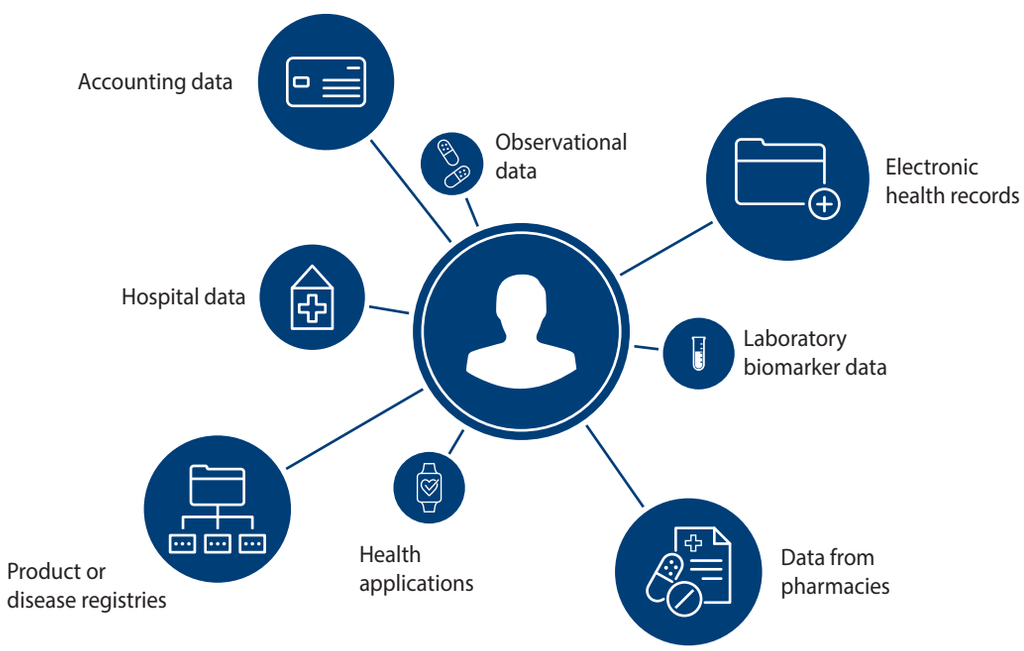


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Figure 2: Due to the multitude of potential data sources, study planning and conduction can be facilitated in the context of clinical research.

Data can come from a variety of sources, e.g. electronic patient records, treatment and accounting data from providers or health insurers, registry data from disease and product registries, observational studies, and patient-generated data from mobile devices (wearables) or digital apps. These are important data sources for use in research and development in the industrial health care sector.

If RWD shall be a credible source of scientific evidence, it must be of suitable quality for the purpose and evaluated or analysed in an appropriate manner. Only then will real world data become real world evidence. Real world evidence (RWE) must therefore be „fit-for-purpose" in terms of scope, data quality, and evaluation methodology. If these conditions are met, RWE can support research and development and contribute to better healthcare for patients. With the multitude of potential data sources, study planning and conduction can be facilitated in the context of clinical research (see figure 2).

The following example shows why the use of and access to health data is so important.

One example: Clinical studies can be supplemented with digital health data

Clinical studies are complex, time-consuming, and expensive. So-called virtual control arms (also called „external", „synthetic" control) can provide significant improvements. Up to now, a group of patients in clinical studies receives the new therapy under investigation in addition to the standard therapy. However, a comparison to a control group is always required to furnish proof of efficacy.

Thanks to digitisation, this process can be accelerated. In some cases, the control group can be virtually simulated with existing patient data. Data from comparable patients who received standard care outside of clinical studies serve as a basis. This allows for smaller studies in which patients only receive the new and maybe better therapy. It also enables accelerated approval processes providing faster access to a better therapy option for more patients. This benefits patients in a very tangible way. And it saves both time and money (see figure 3).

Research-based pharmaceutical companies have already gained practical experience with this. Among other sources, data for the virtual control group comes from electronic patient records (currently only from the United States). In order to make full use of this approach, data from Germany is also required, because the larger the database, the more reliable the results can be. It must be ensured that researchers use anonymised and aggregated patient data.

Digitisation needed to strengthen Germany as a study location

In order to set up and conduct high-quality clinical studies, competitive framework conditions are required. These conditions depend on many factors, one of which is the degree of digitisation of the respective study location.

Until 2016, Germany was the top location in Europe for the number of industry-initiated clinical trials and the number of clinical study sites, and ranked second worldwide after the USA. However, international competition among study sites has increased, and since 2017, Germany has fallen behind the United Kingdom to third place in industry-initiated clinical studies and even behind China and Spain to fifth place in 2019 (see figure 4).

Germany's lagging behind in digitisation in the healthcare system can currently be identified as a negative competitive factor in this area. Many countries are already further ahead in this respect. One example: Some countries allow a faster and more efficiently start of studies, among other things, by better selecting centres to participate based on

One example: Clinical studies can be complemented with digital health data

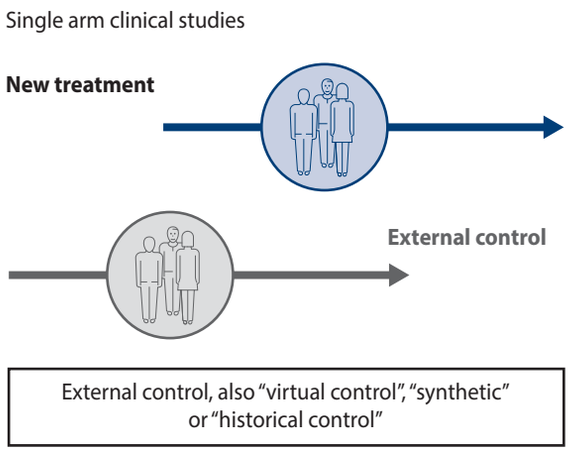

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Figure 3: In some cases, the control group of a clinical study can be virtually simulated with existing patient data.

real-world data (RWD) from the study centres. Moreover, in some countries data on the study participant can be exchanged via electronic media directly from the patient record. The current Corona situation has shown that countries enabling such approaches were partly better able to cope with these constraints in the study sector, as it was e.g. easier to set up remote monitoring there.

Another disadvantage of the location is the fragmentation into many small study centres. Although this is advantageous from the patient's point of view due to the short distances involved, it creates problems in the conduct of clinical studies, as this requires significantly more effort. Here, too, digitisation can help to link study sites, thus enabling a comprehensive exchange of data between the sites that have joined together in the network without jeopardising the benefits for patients. In addition, wearables can accompany study participants and create new opportunities to collect more health-related data.

In order to strengthen Germany as a study location, the standardisation of requirements regarding data protection in the context of clinical studies should be thoroughly discussed. Other countries have set clear guidelines and created common regulations. In Germany, by contrast, the 16 state authorities are struggling with this issue and have not yet managed to define clear and consistent requirements. This creates problems for clinical study applicants, but also for ethics committees that are supposed to review data protection cursorily on the basis of patient consent wording.

The medical informatics initiative can be the first step for German university medicine into the right direction, but a German master plan is required to be able to use the data comprehensively across all hospitals and physicians in private practices. Therefore, many steps must be taken, from electronic patient records, common data standards, standardised medical coding, ensuring interchangeability of data between different systems, up to enabling access to collected health data also for private research purposes (subject to specific data protection regulations). Only a comprehensive overall concept can help to set the course to ensure that top-level research will still be possible in Germany in the future.

Strengthen the use of digital health data

In addition to the essential value of health data for research and development, this topic is also increasingly determining the discussion in the context of market access. Where do we stand here in Germany? With the Law for More Safety in the Supply of Pharmaceuticals (GASV), the German legislature has cleared the way for an increased use of digital health data for pricing of new pharmaceuticals. Accordingly, the G-BA (Federal Joint committee) can request post-market data collection for specific pharmaceuticals that should be taken into account in the additional benefit assessment.

However, the current discussion is limited to indication-based registry data as potential data sources, although many more data sources could provide valuable insights. In particular, data from electronic patient records or accounting data from health insurers are explicitly excluded from the discussion. At the same time, hopes for quality and evidence improvements in healthcare are currently focusing on this type of data, because knowledge generation based on these data can improve healthcare for patients. It is therefore time to set the course into the right direction. Will more digital health data be included in the additional benefit assessment in future or not? Not only patients would benefit, but ultimately the healthcare system as well.

Digitisation is a competitive factor

Number of clinical studies conducted by research-based pharmaceutical companies

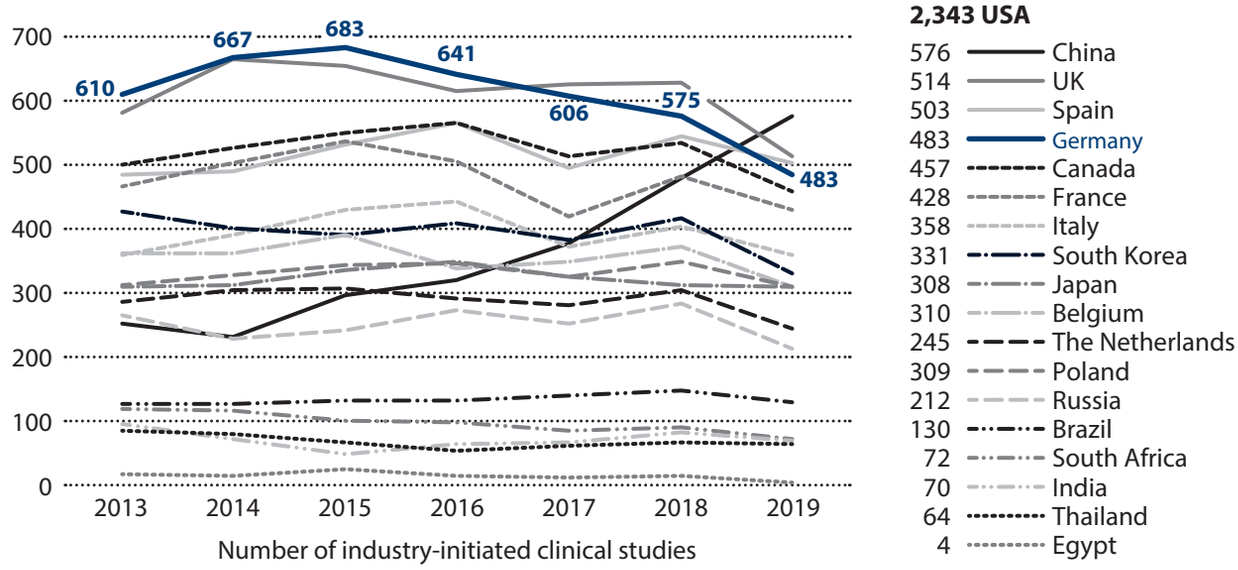

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Figure 4: Until 2016, Germany was the top study location in Europe. In 2019, however, Germany has fallen to fifth place behind the USA, China, United Kingdom, and Spain.

Advancing common standards for the use of digital health data

The more that digital health data and its importance for medical progress are discussed, the more the question arises: What is needed to make synergies as effective as possible?

From the perspective of the pharmaceutical industry, future evidence bases for proof of efficacy of therapeutic interventions within the scope of approval, as well as for proof of an additional benefit for pricing purposes, will increasingly be determined by digital health data. Regulatory authorities and HTA institutions should therefore advance common standards for the use of digital health data. The goal should be to audit health data according to consistent standards so that they can be mutually considered. In the recent past, for example, the regulatory authority EMA has already taken into account health data in form of virtual controls on several occasions, although the G-BA (Federal Joint committee) has only partially accepted it. These sporadically positive developments must be consolidated and further improved and expanded, respectively.

The currently discussed European HTA process can be helpful to drive this forward. In the current legislative project on EU-HTA, the additional benefit assessment of a pharmaceutical should be Europeanised without restricting the sovereignty of the EU member states in the price

negotiation of pharmaceuticals. Since an EU HTA assessment should be available at the time of European approval, synergies can be used to discuss and define common standards for the use of digital health data while maintaining two separate processes.

Conclusion: Harnessing the opportunities of health data for research and patient care

Digitisation will fundamentally change our society both nationally and internationally. This does not only bring changes for each individual. The healthcare system will undergo sustainable changes and take advantage of the positive stimuli it needs to improve patient care and actively shape medical progress.

Europe goes ahead and in the course of the German EU Council Presidency, work is being done on the prerequisites for a European health data area. However, more is needed to harness the opportunities of health data for patient care in Europe:

(1) Development of decentralised databases, structures and standards for real world data across Europe,

(2) Harmonisation of European data protection and ethics law,

(3) Regulated access of private research to health and treatment data, and

(4) Jointly defined standards for the use of digital health care data in regulatory approval and HTA

This calls for cooperation, because smart ideas can only be developed together.

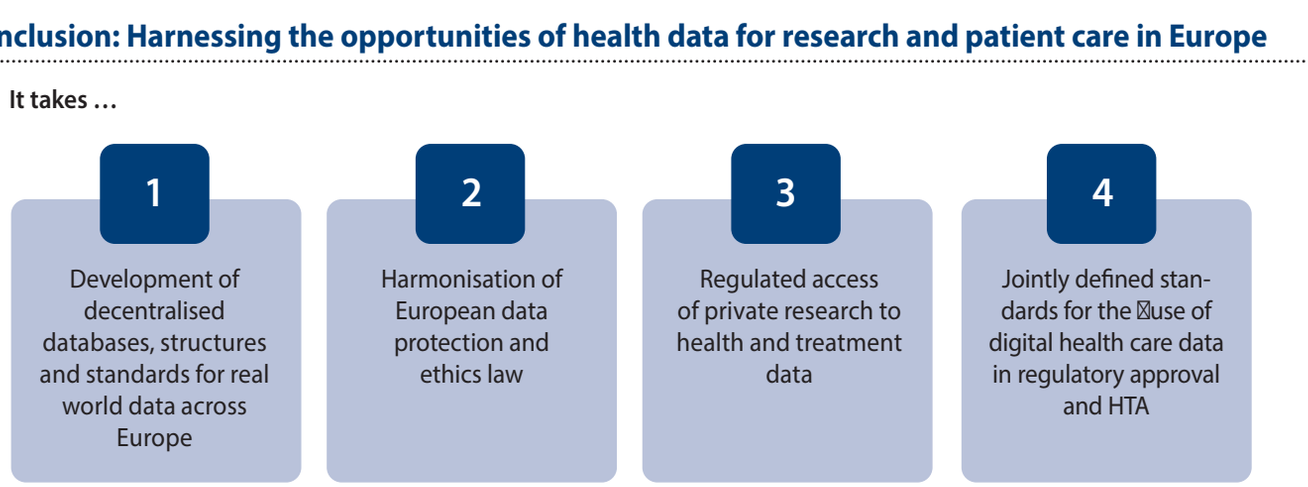


Figure 5: Harnessing the opportunities of health data for patient care across Europe will require more than the establishment of a European Health Data Space.

Digital health data: standardisation and utilisation

Professor Karl Broich, Dr Wiebke Löbker, Dr Stefanie Weber | Federal Institute for Drugs and Medical Devices (BfArM)

The digital transformation of the healthcare system in Germany and internationally is rapidly advancing. Expansion of the telematics infrastructure, introduction of the „app on prescription", electronic patient file, and interaction of these structures pave the way for a digitally networked eHealth infrastructure in Germany. The Corona pandemic has given impetus to this trend, so that the increasing acceptance of digital health offerings will presumably result in a growing volume of data. In order to efficiently use this data for regulatory and healthcare-relevant questions, these offers should be interlocked and networked. An essential prerequisite for this, but also for the use of health data, is semantic and technical interoperability. The BfArM wants to help drive digital development – and takes a key position in this process: The article takes a closer look at the role of the BfArM in the digital health market with the provision of classifications, nomenclatures, terminologies, expansion of the data transparency office into a research data centre, and the evaluation of digital health applications.

Digitisation: A changing healthcare ecosystem

The topic of digitisation has also become a determining topic and trend in healthcare. Particularly as a result of changed framework conditions, the path for a digitally networked infrastructure has been paved for two years now by the Appointment Service and Care Act (TSVG), the Digital Health Care Act (DVG), the Patient Data Protection Act (PDSG), and the draft for a Digital Healthcare and Nursing Care Modernisation Act (DVPMG). The amendment to the Data Transparency Ordinance (DaTraV) will expand the provision of healthcare data from the statutory health insurance system by expanding the Data Transparency Office into a research data centre at the BfArM.

In parallel, a steadily growing market of a wide variety of digital offerings that accompany the daily therapy routing of patients, physicians, psychotherapists, and caregivers has developed over the past few years[1,2], so that the support of patients' health behaviour and the integration of the processes of service providers and patients is increasingly moving into focus – and can result in digital health applications (DiGA) becoming reimbursable for around 70 million statutorily insured persons after appropriate evaluation by the BfArM in accordance with section 139e Social Code book V („DiGA Fast Track procedure"). As the range of products grows, so does the need for information on the benefits and safety of these products. However, so far a systematic, transparent overview and evaluation of the quality, safety, and benefit of the numerous digital offerings in this area is still missing.[3, 4]

This growing range of products is also associated with an increasing merging of (digital) medical products with „classic" drug approaches to one ecosystem in which therapies will be increasingly patient-centred in the future

due to digital capabilities, and a steadily growing volume of (more individualised) health data will be obtained from the healthcare system („real-world data", RWD). With the increased volume of data, not only is the volume growing, but also the usability of secondary data that can be used for scientific and regulatory issues.

Thus, great expectations and opportunities are attached to digitisation in healthcare: A better understanding of therapy and disease progression, e.g. through digital health applications as continuous „therapy companions in the hand of the patient" (and the physician), easier recruitment for or use of „virtual study arms" in clinical trials, use of digital tools for outcome measurement, etc.

On the other hand, however, new challenges must be addressed to exploit the full potential of digitisation. These include aspects ranging from interoperability to cyber security, data privacy, information security, and technical „side effects" resulting, for example, from software errors that can pose a risk to patient safety if they lead to e.g. misinformation or incorrect dosing recommendations.

In addition to the tasks already mentioned by the DVG, the BfArM is actively involved at national and European level in promoting digitisation in the healthcare sector and thus the use of RWD. This will include supporting the activities of the HMA-EMA Big Data Steering Group to establish a European network of databases (Data Analysis and

Professor Karl Broich *is a physician (approbation in 1985, doctorate in 1986) with a degree in neurology and psychiatry (neurology in 1993); additional qualification in psychotherapy with emphasis on behavioural therapy (1999). 2000 to 2009 initially Department Chair Neurology/ Psychiatry, then Head of Approval Department 4 at the BfArM; from 2009 Vice President, since 2014 President of the BfArM.*

After her studies in pharmacy, **Dr Wiebke Löbker** *worked as a scientific associate at the Institute of Pharmacology of the Free University Berlin, Pharmacology & Toxicology Department from 2009 to 2011. From 2011 to September 2016 she was an adviser of the Department for Medicinal Products of the Federal Joint Committee (G-BA) and since October 2016 she works scientific associate at the Federal Institute for Drugs and Medical Devices (BfArM).*

After her studies in human medicine, **Dr Stefanie Weber** *worked at the DIMDI as head of the „WHO Collaborating Centre for the WHO Family of International Classifications" from 2008. In 2010, head of the unit „Medical Terminology Systems" and from 2015 to 2018 as chair of the WHO Task Force to finalise ICD-11. Since 2020, she is Head of the staff unit „Classification Systems, Semantics Centre" at the BfArM.*

Real World Interrogation Network, DARWIN) with appropriate technical and semantic standards, as well as other quality standards.[5]

The research department of the BfArM is currently working on the automatic recording and evaluation of risk reports using artificial intelligence, e.g. with the aim of being able to quickly spot the details in the increasingly complex overall picture in the interests of patient safety. BfArM's expertise is taken into consideration in central approvals to address the question of how RWD can support data from classic randomized controlled clinical trials for approval and vigilance decisions. In cooperation with the University Hospital Düsseldorf; Vodafone GmbH, Düsseldorf; RWTH Aachen; FH Dortmund; Brainlab AG, Munich; University of Wuppertal / SIKoM+, the BfArM is involved in the „5G: Giga for Health" project[6] to develop and evaluate a novel medical device incident reporting app using mobile technologies and 5G to support, among other things, fast, easy, and helpful reporting by healthcare professionals.

In all activities and tasks it is apparent that semantic and technical interoperability is an important quality factor for a meaningful interaction of digital components within the framework of a national eHealth infrastructure, interaction of the telematics infrastructure, electronic patient record (ePA), DiGA, ePrescription etc. and usability of RWD. Interoperability is becoming increasingly important for healthcare, because it is the only way to use digital applications appropriately and efficiently and to achieve network effects.

Importance of semantic and technical interoperability

Digitisation in healthcare involves increased communication of IT systems about health data, e.g. physician-to-physician communication about findings in the patient's treatment pathway, but also merging of data from different sources in the ePA, at the research data centre, or in the cross-border care environment of the mobile patient in Europe. As with the exchange of information in a personal conversation, two important elements are essential here: language and communication rules. In electronic communication, these important elements are semantic and technical interoperability.

Efforts and discussions to define IT interfaces, technical standards, and data definitions have become an increasing focus in recent years, and the establishment of rules and guidelines for technical interoperability in healthcare are a core element of the German government's digitisation strategy. In the current legislative period, therefore, several legislative initiatives have been launched and implemented to pave the way for smoother data exchange; not least through the expansion of the telematics infrastructure.

But the second important element is also addressed in the legislative initiatives: semantic interoperability.

Semantic interoperability

If technical interoperability addresses the „packaging" of information being exchanged, semantics defines the content. The German Duden defines semantics as „meaning, content (of a word, sentence or text)". Semantic interoperability in healthcare accordingly requires a common language so that in electronic communication both the sending and the receiving IT system can interpret the meaning of the transmitted information in the same way. Since IT systems can only inadequately evaluate language variants or dialects, standardisation of the common language is essential. And this is precisely where the role of the BfArM comes in: As the National Competence Centre for Medical Terminologies (and Classifications), BfArM is currently developing a platform for semantic standardisation tools.

Legal framework & tasks of the BfArM

For several decades now, the former DIMDI which is now part of the BfArM has been mandated by law to provide classifications. In accordance with Social Code book V (sections 295 and 301), classifications for diagnoses and procedures are updated and issued annually.

In particular, the International Classification of Diseases, ICD-10, is now firmly established in the German healthcare system and provides a yet only aggregated way of evaluating healthcare diagnosis data. In its modified form for Germany, it provides e.g. the basis for accounting systems and is also used in various prescriptions (reports of incapacity for work, prescriptions for remedies and aids, etc.) and is the basis for hospital statistics. In close cooperation with the World Health Organization (WHO), the BfArM, as a cooperation centre, is also responsible to coordinate further national development requirements that must be incorporated into international classifications. The advantage of ICD-10 for health data exchange is its widespread international use. For example, by analysing ICD-10 coded data from the OECD, comparative statements can be made about healthcare systems worldwide.

But the ICD-10 was developed long before the increasing digitisation and can hardly meet the requirements of semantic interoperability. For many years, the BfArM classification team has thus been involved in the revision of the ICD to ICD-11 and accompanied its further development to a modern classification with integrated terminology.[7] With ICD-11, a comprehensive, flexible classification will be available that can serve as a basis for electronic communi-

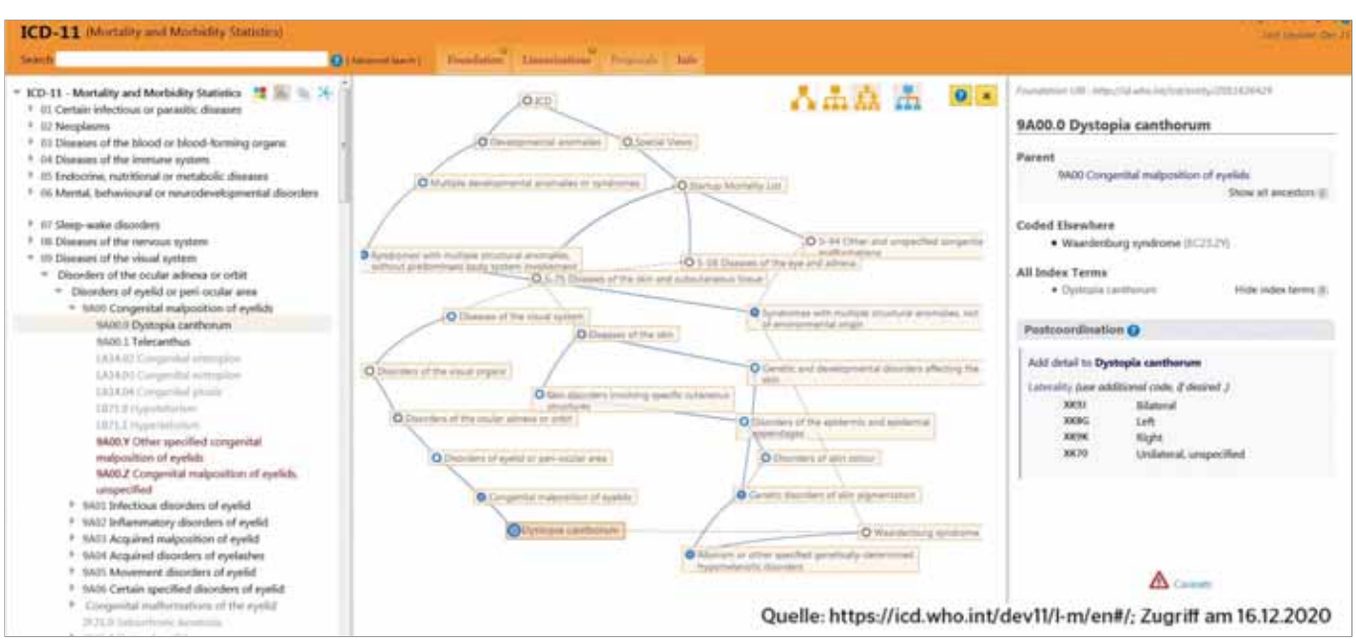


Figure 1: With ICD-11, a comprehensive, flexible classification will be available, which is suitable as a basis for electronic communication in the healthcare system.

cation in healthcare providing many structural and content-related advantages (see figure 1).

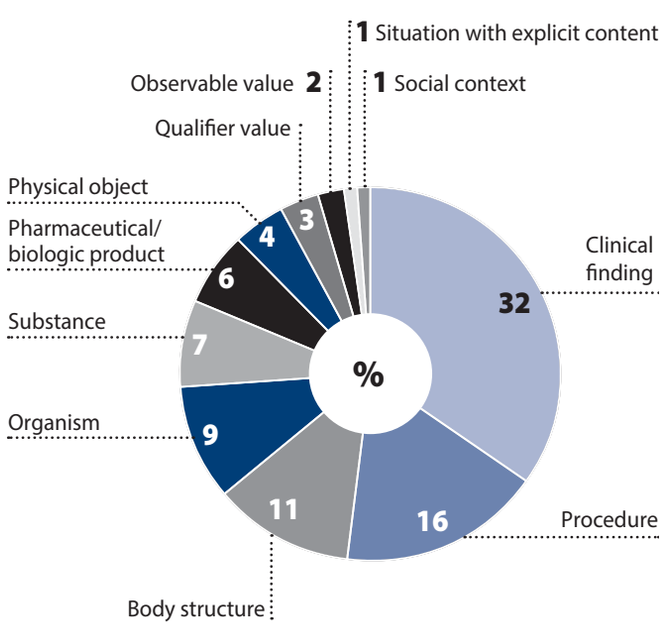
But comprehensive electronic communication requires more than a diagnostic classification: It should be possible to collect all areas of health data in a standardised form. The legislator addressed this in the PDSG and specified the provision of international medical terminology in Section 355 of the German Social Code, Book V (SGB V): On January 1, 2021, the free provision of SNOMED CT[8] for Germany is to be implemented by the BfArM. LOINC, a laboratory terminology, will also be made available to all users in Germany in accordance with section 355 of the Social Code book V. In the context of the introduction of the ePA for Germany, the provision of terminologies is a link in the chain and is reflected in the definition of the contents of the patient file by the Federal Agreement on Statutory Health Insurance Physicians. By defining the Medical Information Objects (MIOs)[9] and depositing them with corresponding subsets of SNOMED CT terms, the application of the terminology is defined (see figure 2).

Similar to the ICD, the SNOMED CT and LOINC terminologies will also have to be adapted, which will be further specified through implementation. The translation into German should be mentioned here, which will be adapted to the requirements step by step and in cooperation with other German-speaking countries and the users. However, the BfArM will also facilitate international further development by introducing Germany-specific requirements and required national expansion, similar to the ICD-10-GM. Building on many years of expertise in the field of classifications, a discussion platform for users is to be established quickly in order to bundle and channel national requirements.

Thinking out of the box

Thinking out of the box is another aspect of semantic standardisation in which BfArM has been active to date and will be increasingly so in the future: Patient mobility in the European Health Area and the patient's right to healthcare in Europe[10] have created the need to share health information across borders and languages as well. Within the framework of working groups at EU level, the BfArM has already been working for several years to establish semantic

Distribution of SNOMED CT concepts across different terminological areas



Source: https://browser.ihtsdotools.org/qa/#/descriptive-statistics; accessed 16 December 2020)

Figure 2: With its broad coverage of all areas of healthcare language, SNOMED CT provides a good basic terminology for defining Medical Information Objects.

standards and is also contributing the requirements from Germany here. One of the recent legislative initiatives addresses this point: In the draft bill of the DVPMG, section 219d SGB V defines the specifications for semantic interoperability required for cross-border data exchange as a task of the BfArM.

Cooperation as strength

The BfArM has placed great emphasis on coordinating requirements during its many years as a WHO collaborating centre and in other national and international network initiatives. In the most recent national initiative for semantic standardisation of COVID-19 research datasets, the cocos initiative[11], BfArM is part of the core team and regularly exchanges information with the other participating organisations. Interaction at national level, mirrored also in the European and wider international framework, is a core element of the successful work of the BfArM classification and semantics team.

Where should the journey go?

With the expansion of the activities of the BfArM within the framework of the current legislation and the merger of the BfArM and DIMDI, the National Competence Centre shall be established as the central point of contact in Germany for questions of semantic standardisation for routine data, research data and health data for cross-border healthcare. Users, developers and researchers will find a platform and advice on all questions concerning the terminologies and classifications provided.

Ideally, the individual user will not have any additional data entry effort due to the smart integration of the terminologies into IT systems and a linking of the terminologies and classifications with each other. On the contrary, it should be possible to automate the further use of data for various systems (ePA, digital communication as part of the patient care pathway, aggregation for billing systems or health statistics, etc.) through one-time standardised recording, and thus ideally even have less bureaucracy. By applying the same semantic standards, e.g. also in the context of digital health applications (DiGA), data can also be combined with an eye to future research questions and regulatory tasks and thus be used for the improvement of healthcare.

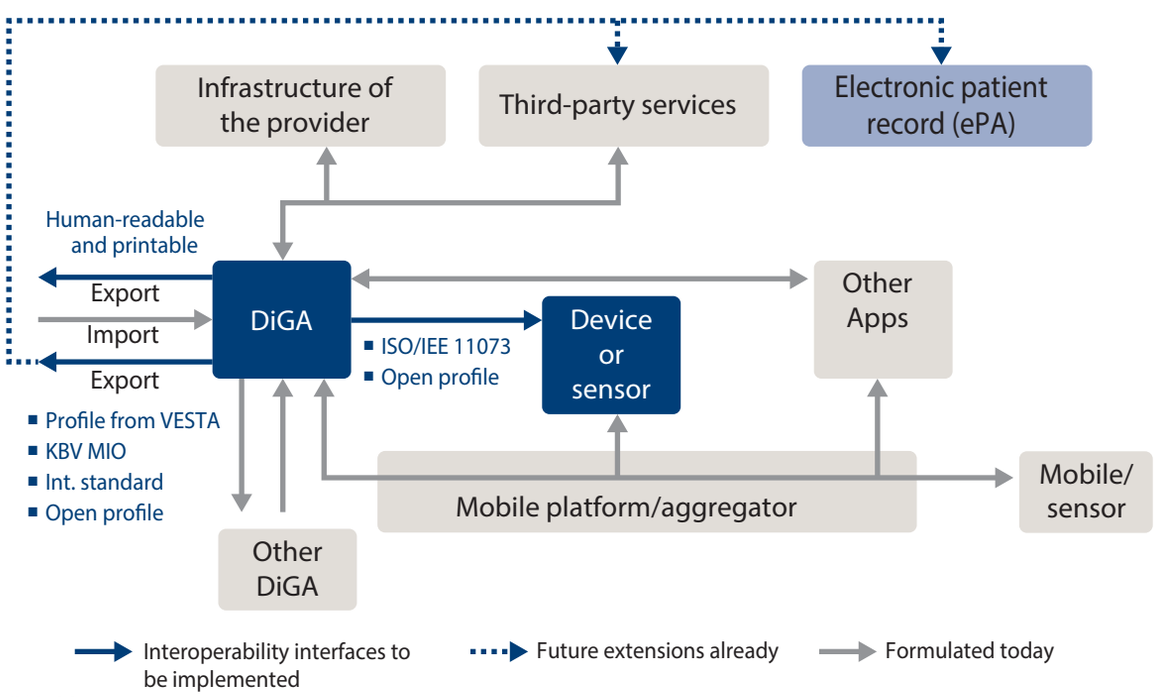
DiGA & the Fast Track procedure at the BfArM: An element of the growing national eHealth infrastructure.

DiGA should also communicate with each other in perspective, as well as interact with other services and applications in the national eHealth infrastructure, so that real added value can be achieved for (digital) healthcare (see figure 3) Interoperability is thus also an essential quality requirement for DiGA and thus falls under the requirements in Section 139e (2) Social Code book V for these products to be listed as reimbursable digital health applications. This is further elaborated in sections 5 and 6 of the Digital Health Applications Ordinance (DiGAV) and Annex 2 to the DiGAV („Interoperability"). This specifies which interfaces of a DiGA must be designed as interoperable from 2021 and how interoperability must be realised through the use of standards.

What is a DiGA and what are the requirements for inclusion in standard of care?

When the DVG came into force in December 2019, the „app on prescription" for patients was introduced. This means that approximately 73 million insured in the statutory health insurance system (SHI) are entitled to a provision of DiGA, which is prescribed by physicians and psychotherapists and reimbursed by the health insurance provider. Insured who submit proof of a corresponding indication to

Interoperability of DiGA interacting in a national eHealth infrastructure



Source: BfArM

Figure 4: If evidence of positive care effects is not generated and submitted to the BfArM during the trial phase of up to one year, DiGA will be removed from the list.

their health insurance provider receive the desired DiGA even without a physician's prescription.

DiGA are, in brief, low-risk medical devices according to section 33a of Social Code book V, whose main function is based on digital technologies and which shall be used by the patient himself or together with the physician or psychotherapist. Primary prevention approaches are excluded; they rather support the detection, monitoring, treatment, or mitigation of a disease or the detection, treatment, mitigation, or compensation for injury or disability.

A prerequisite for inclusion in the standard care of the SHI system is that DiGA have successfully undergone a review process at the BfArM and, as a result, have been listed as reimbursable digital health applications (DiGA list).[12]

The process is designed as a speedy „Fast Track" (see figure 4): The evaluation period for the BfArM is three months after receipt of the complete application. The core of the procedure is the examination of the manufacturer's specifications on the required product properties – from data protection to interoperability and user-friendliness – as well as the verification of a proof by the manufacturer the positive care effects that can be realised with DiGA.

The term „positive care effect" which has been introduced in this procedure, refers to a noticeable improvement for patients or users in the form of a medical benefit, e.g. an improvement in disease-related symptoms, quality of life, or an improvement in procedures and structures. These include characteristics such as improved health literacy, easier coordination of treatment processes between one or more healthcare providers on the one hand and the patient on the other, as well as adherence or access to treatment through the use of DiGA.

If sufficient conclusive evidence is not yet available for a positive care effect, but all other requirements for quality, security, interoperability, data protection and information security are fully met, an application for provisional inclusion of the DiGA in the directory can initially be submitted. A prerequisite for this is, in particular, the submission of an evaluation concept that contains a systematic evaluation of initial data from DiGA to substantiate the hypothesis of the positive care effect of DiGA and plausibly demonstrates that the necessary comparative data as compared to the non-use of DiGA can be generated and submitted to the BfArM within a trial phase of up to one year. If this evidence is not provided subsequently, the DiGA will be removed from the list. The BfArM has summarised details on the procedure and the required evidence and applicable assessment standards in a guideline (see figure 4).[13]

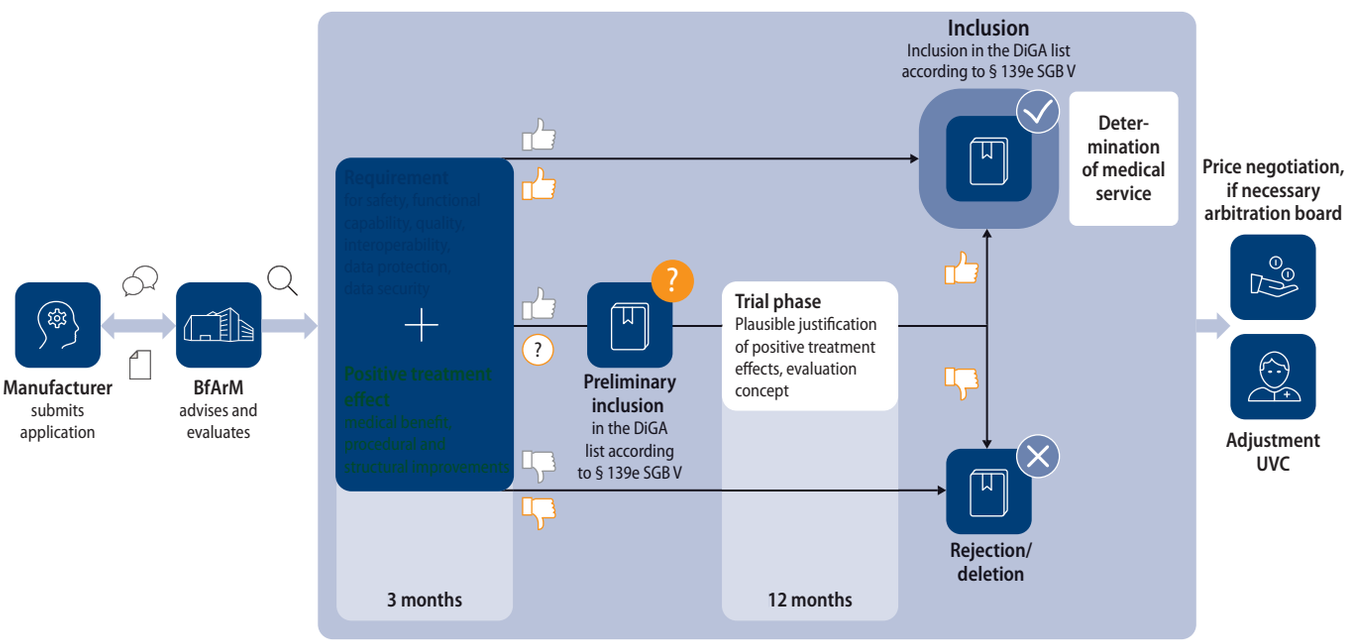
The requirements placed on the DiGA illustrate that these products should be seen less in isolation and more as an element of digitally supported healthcare in a secure and user-oriented interaction of a – technically and semantically interoperable – digital infrastructure of the healthcare system (see figure 3). This is also underlined by the current draft of the DVPMG, in which a directory shall be established for interoperable interfaces for the further processing of data from implants/auxiliary devices by DiGA, transfer of data from DiGA to the ePA, further development of the gematik interoperability directory into a knowledge platform, and the establishment of a coordination office for interoperability in the healthcare sector.[14] The respective requirements must be implemented in parallel with the evolving future national eHealth environment.

With DiGA the systematic evaluation of treatment-related data also gradually gains relevance. The BfArM procedure significantly contributes to the DiGA on the market with a systematic evaluation of aspects, such as data protection and interoperability on the one hand and added value for daily clinical practice based on treatment-related data on the other. In addition, data obtained with the DiGA and transferred to the ePA, for example, can contribute to a better overall understanding of disease and therapy processes in daily clinical practice. The publication of the evaluation results – together with extensive information on the DiGA features – in a directory on the BfArM websites provides a high level of transparency of these digital offerings.

Conclusio

In the increasingly growing and interconnected digital healthcare market, semantic and technical interoperability play a key role in many places to ensure that the digital transformation succeeds and the potential of digital healthcare is fully exploited. The provision of the terminology SNOMED CT for Germany, fulfilment of interoperability and other quality requirements for DiGA and other digital offerings, expansion of the Data Transparency Centre into a more agile RDC, establishment of a European Data Space („DARWIN") – to name just a few examples – significantly contribute to making the ever-increasing volumes of data from the „real world" usable for scientific and regulatory issues at national, but also at European level – for individualised, patient-oriented, effective and safe patient care.

Fast Track procedure according to Section 139e SGB V for inclusion in the list of reimbursable DiGA



Source: BfArM

Figure 3: DiGA should communicate with each other in perspective, as well as interact with other services and applications in the eHealth infrastructure to achieve real added value for (digital) healthcare.

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Digitalised clinical data – from the National Association of Statutory Health Insurance Funds' perspective

Dr Daniel Erdmann, Dr Antje Haas | National Association of Statutory Health Insurance Funds (GKV-Spitzenverband)

In the evaluation of the additional benefit of new patent-protected pharmaceuticals data plays a key role. In line with the original AMNOG motto of separating the „wheat from the chaff", pharmaceuticals should only incur additional costs if available data demonstrates a proven added value for the new pharmaceutical. Unfortunately, this principle is becoming increasingly less important. The authors therefore see the need to further promote both the quality and availability of study data, networking of different stakeholders, and to improve the processing of healthcare data for the benefit of patients and the insured community.

Benefit assessment of the Federal Joint Committee (G-BA) already provides a good understanding of the additional benefit of an active ingredient as compared to a specific comparative treatment at a very specific point in time (horizontal comparison), provided that suitable data is available. However, it is not yet able to quickly track the fast changing conditions within a therapeutic area with cluster innovations and reflect them in decisions. Moreover, it cannot provide clarity about the best treatment option or the best possible treatment sequence within an entire, potentially large therapeutic field (vertical comparison).

Malignant melanoma is one example for such an innovation cluster. At the end of 2020, 21 valid benefit decisions have been taken for a total of ten active ingredients in this indication alone. These are both monosubstances and combinations with other drugs that were regularly evaluated for their additional benefit as compared to the therapy considered standard at the time of the respective assessment. Keeping track of such complex developments is also a challenge for the attending physicians, emphasising the need for a modern electronic physician information system for knowledge transfer in the selection of a suitable pharmaceutical in daily clinical practice.

Such an improved physician information system could provide a real added value through the integration of horizontal and vertical comparisons. Formulated guidelines already pursue this goal today, but there is still room for improvement in terms of the methodology used, timeliness, orientation power, significance, and also with regard to conflicts of interest.

Neglected incentives, access and the consequences

In Germany, pharmaceuticals are generally reimbursable

from the date of their approval. Moreover, pharmaceutical companies are currently still completely free to determine their entry price. This combination makes an early entry onto the German market particularly attractive for pharmaceutical companies. Against the background of the external price referencing practised in many countries, the high German price helps them to establish an equally high price level. The respective pharmaceutical company can therefore – taking national regulations into consideration – enforce an optimal global strategy to maximise profits. This is regularly contrasted by often uncoordinated – and thus suboptimal – national cost containment strategies.

This power imbalance has been further exacerbated in recent years, particularly by the fact that the European regulatory authority is increasingly approving pharmaceuticals despite substantial evidence gaps. Neither a national nor the intended European HTA assessment can cure this lack of evidence. In order to break the cycle of less and less evidence for newly approved pharmaceuticals in indications with great suffering, the approval practice in Europe would have to change fundamentally.

Since national stakeholders cannot rely on such a change at the European level, what is needed – as a second-best option – is a strategy to generate the best possible post-approval evidence. Only in this way will it be possible to make appropriate decisions in future about the reimbursement and pricing of such pharmaceuticals. Moreover, only new evidence can be used to determine the place of a pharmaceutical within a therapeutic area, taking into account the information available at different points in time, and to provide valid information for attending physicians.

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Dr Daniel Erdmann *is economist. Since 2012, he has been working as specialist in the Medicine and Drug Division of the National Association of Statutory Health Insurance Funds and heads the Team for cross-sectional tasks in the AMNOG EBV Division.*

The German legislator reacted to this development within the framework of the Act for More Safety in the Supply of Pharmaceuticals (GSAV) by authorising the G-BA to request post-market data collection and assessments from pharmaceutical companies in certain submarkets to assess the additional benefit. However, this means that a considerable part of the burden of proof has been transferred from the pharmaceutical company to the society. Although the pharmaceutical company bears the direct costs incurred for the conduction of the studies, the required (staff) resources for post-market data collection at the G-BA, the Institute for Quality and Efficiency in Healthcare (IQWiG), and the coordination with all stakeholders should not be underestimated. Furthermore, there is concern that inconsistencies will arise in majority-bound decisions in the G-BA over time, which may ultimately stand in the way of the goal of a qualitative increase in evidence ranging from the active substance reference to the indication reference.

The (increasing) importance of the evidence gap problem has also been shown by Davis et al. (2017): According to them, 57 percent of all oncology products are approved without any proven benefit in terms of an increased survival or quality of life, and five years later 79 percent of these pharmaceuticals still lack evidence. It should also be noted that the proportion of patient groups evaluated by the G-BA for active substances with special approvals, i.e. pharmaceuticals with an orphan drug approval or an exceptional or conditional approval, has increased significantly over time. While the corresponding share was approximately 10 percent in 2012, it has now already reached almost 50 percent of the patient groups or subindications. A special feature of the evaluation of these pharmaceuticals is that they are about four times as likely to be granted a non-quantifiable additional benefit as compared to the other active ingredients.

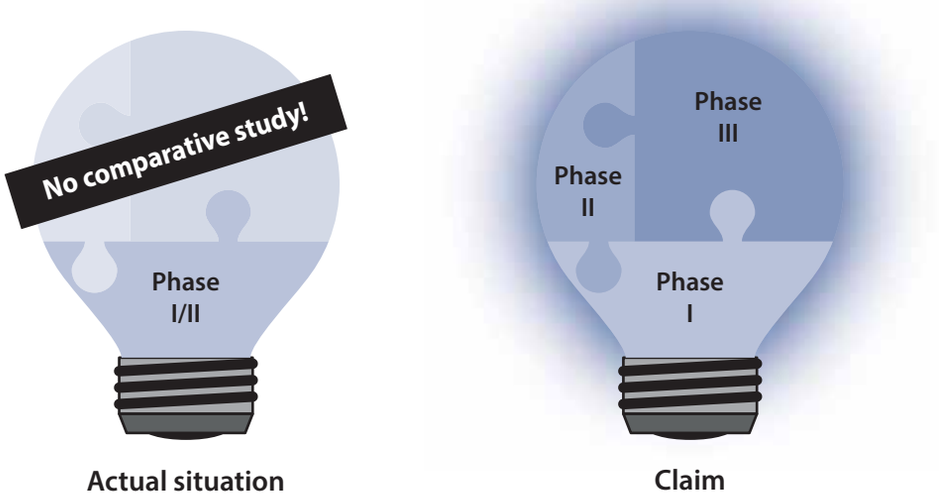
Against this background, it seems almost paradoxical that ever higher prices are demanded for new pharmaceuticals despite decreasing evidence. Between 2011 and 2019, for example, the annual treatment costs for pharmaceuticals with special approval increased by an average of 30,000 € every year and the number of cost outliers also increases significantly over time.

The combination of full reimbursement of new pharmaceuticals from the date of marketing authorisation, free pricing in the first year after marketing, and the newly created possibility for the G-BA to request post-market data collection reduces the incentive for pharmaceutical companies to voluntarily provide post-approval evidence for new pharmaceuticals (e.g. in personalised medicine) to a low level. At the beginning of the AMNOG, the focus was clearly on the principle of proof. The following graphic illustrates this contrast between target and the perceived actual situation (see figure 1).

When the AMNOG was introduced, it was clear that not the G-BA should investigate the quality of a product, but that it was the pharmaceutical company's sole responsibility to provide appropriate evidence. Thus, it was also within the sphere of influence of the pharmaceutical company to create the conditions for benefit-related pricing. This principle should now also apply in the opposite situation, in which more and more pharmaceuticals with uncertain data are launched onto the market, which should correspond to correspondingly low entry prices due to the unclear evidence situation.

In fact, the AMNOG process currently contains a false incentive detrimental to the patients and the members of the statutory healthcare system, since the principle of „hope" and thus the promise of a cure determines the price and no longer the actually proven added value. In view of the approval practice, there is a real reversal of the burden

"Principle of hope" vs claim of the AMNOG to good evidence



Source: GKV-Spitzenverband

Figure 1: With the authorisation of the G-BA to request post-market data collection from pharmaceutical companies, a considerable extent of the burden of proof has been transferred to the society.

of proof, as the examples of the new CAR-T cell therapies and tumour diagnostic approvals show.

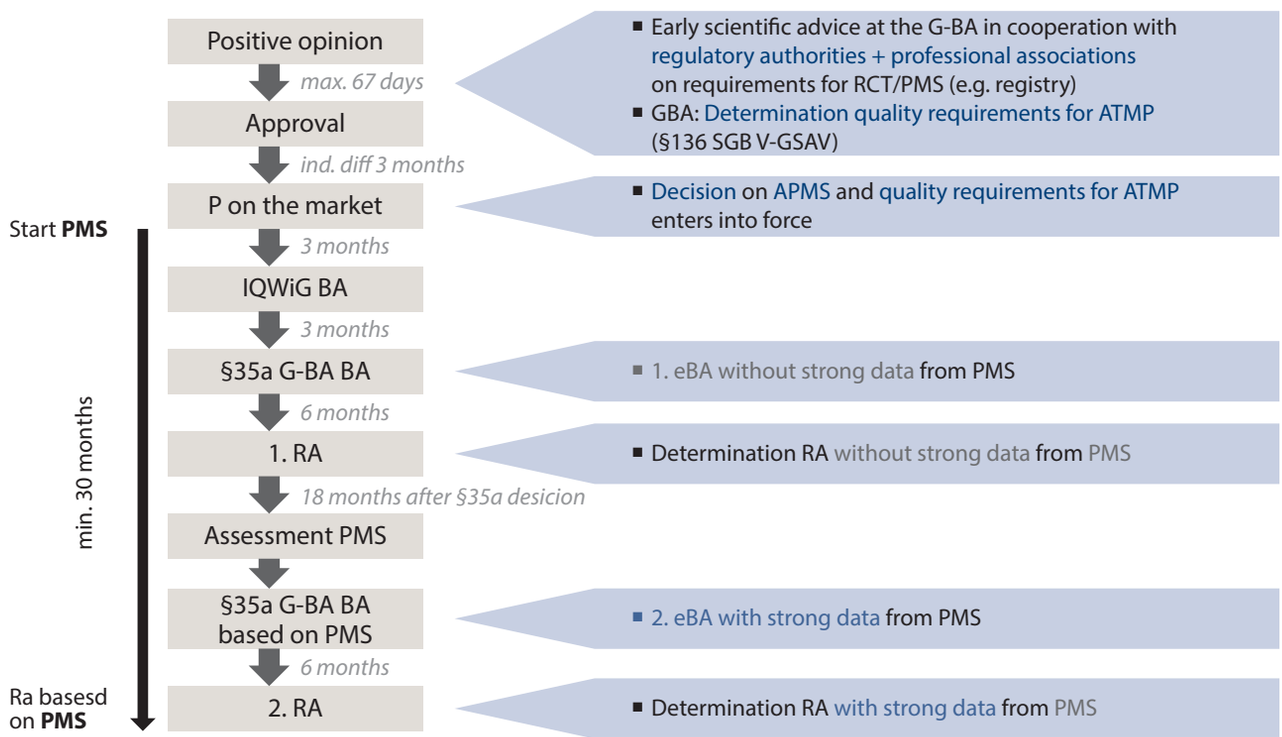
Therefore, it is currently hardly worthwhile for a pharmaceutical company to conduct open-ended research for a drug with a weak evidence base after approval, as it would expose itself to the economic risk that the exorbitantly high „hope price" could be reduced to an appropriate level if the therapy cannot prove the promised therapeutic effects after all. This actual situation is thus in clear contradiction to the original AMNOG guiding principle, according to which higher prices can be obtained with increasing data certainty and proven additional benefit as opposed to a situation with an uncertain data situation and no clearly proven additional benefit.

Compensation of evidence gaps and knowledge-generating care

Figure 2 introduces the tool for post-market data collection that has been implemented for Germany to help close evidence gaps in the submarket of conditionally, exceptionally, or orphan drug approved pharmaceuticals. Both the scope (too little) and effort (too much) required to carry out this national approach to collect post-market data have proven to be ineffective.

What is needed instead – besides better registration data – is a nationwide data or indication-based registry culture. Data bodies from post-market data collection are not only too small, they can also only be considered much too late in the AMNOG process. Only after two and a half years

The long road from market launch until a benefit-related price is set



RCT = randomised controlled study; PMS = post-market data collection; ATMP = advanced therapy medicinal product; P = pharmaceutical; (e)BA = (early) benefit assessment; RA = reimbursement amount; EBV = reimbursement negotiations

Source: GKV-Spitzenverband

Figure 2: Data bodies from the post-market data collections are not only too small, but they can only be taken into account much too late in the AMNOG process.

at the earliest can such data be incorporated into adjusted pricing.

The increasing importance of highly stratified pharmaceuticals also highlights the narrow limits of existing classification systems of medical diagnoses. For example, physicians currently still have to document increasingly complex multifactorial medical issues using monohierarchical and yet rather simply structured classification systems. The level of detail also proves to be an obstacle with the current ICD-10 classification. In some cases, the level of detail is too low, as can be seen in the example of hepatitis C, where the genotypes that are important for the treatment

decision are not documented. One example of a rather excessive level of detail is provided by „complex skin and soft tissue infections", which have a – mainly historical – differentiation of approx. 50 subgroups subdivided by localisation and germ structures.

Fortunately, there are also meaningful new developments in this specialist field, such as SNOMED-CT that can depict far more complex situations. One of the future challenges in this regard will be the expected parallel use of ICD and other novel coding systems. This requires good mapping between the respective systems, also to prevent costly duplicate documentation. Corresponding translations should be done automatically without involving service providers, project staff, third-party funded or any other additional staff. Such (technical) assistance would also additionally promote the success of electronic patient records and appropriate secondary use of treatment data (see figure 3).

The diagram shows that we are still a long way from smooth data-driven communication between the various stakeholders in the healthcare system. For example, there are still barriers between the service sectors with regard to morbidity documentation, also due to the use of different accounting systems. All data stored is used both for accounting purposes and purely medical documentation, what makes compromises necessary and can thus not provide an optimal solution for either purpose. Furthermore, there is a need for improvement both in terms of interoperability between different facilities/documentation systems and in terms of standardisation of collected data.

Moreover, there are large differences in coding requirements between the individual treatment sectors. Certification processes for practice management systems sometimes do not provide a guarantee that updates will be delivered to the user in a timely manner. Hospital information systems do not have an adequate quality assurance through appropriate certification. And all these challenges are multiplied turning an eye on Europe to enable data exchange across Europe.

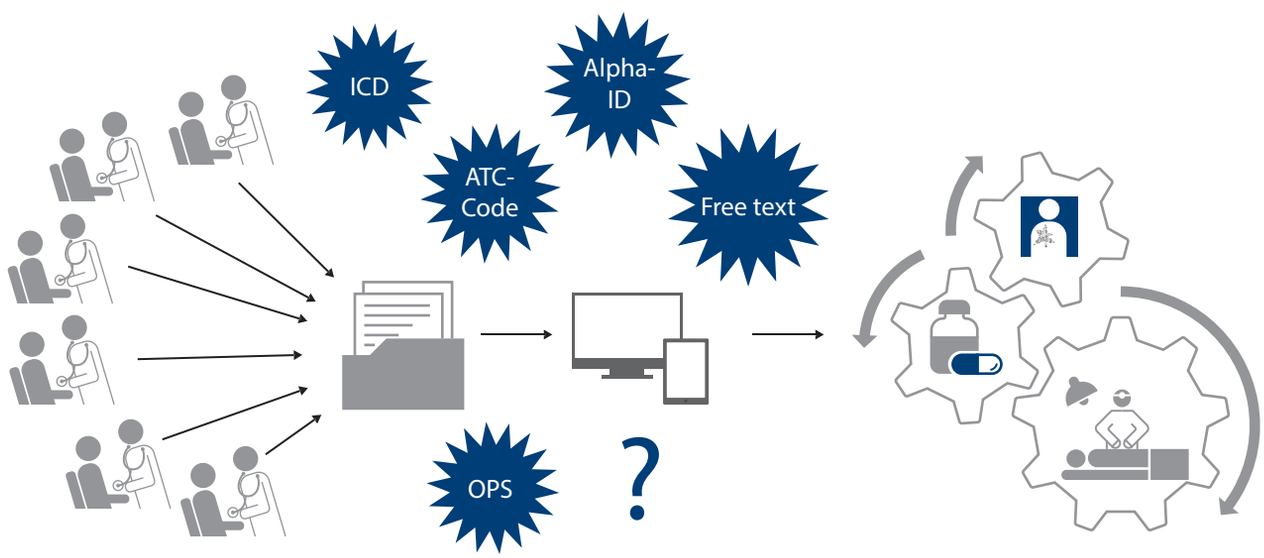
Provided we take an optimistic view of the future assuming that the currently prevailing challenges regarding methodological and technical issues can be satisfactorily resolved not only nationally but also at European level, there would still remain the question of how registry data should be dealt with adequately.

Should a registry culture for all morbidity become a normal state in future, or should we rather focus on specific indications? Positive examples of already well-functioning indication-based registries are the Rabbit Registry for rheumatological diseases and an established registry infrastructure in the field of cardiology in Sweden. Other questions requiring regulation include which institution will determine the data to be recorded in registers? And with what intended use? For whom and in whose service? Should data that are collected and stored in digital devices by patients also be taken into account? When users provide their data, will it be forwarded to the respective research data centre?

Above all, there is of course the question of the quality of this data and how – provided this data is suitable – it will find its way into a researchable electronic patient record. However, there are still some exciting technical questions to be answered, for example with regard to encryption and pseudonymisation of individual patients' data.

In order to meet the population's need for data protection, a self-reinforcing culture of trust is required between the population and the institutions that access pseudonymised data. Only if the insured can understand that their data is in safe hands and that the use of their data has a specific medical benefit for the respective individual and for the community, can the willingness to disclose data in-

Precision medicine requires precision data



Source: Dr. Antje Haas/GKV-Spitzenverband

Figure 3: At present, there are still barriers between the service sectors with regard to morbidity documentation, also due to the use of different accounting systems.

crease and, in turn, overall data quality be improved. The following figure shows this cycle of communication, data disclosure, and data quality (see figure 4).

A combination of data protection by means of pseudonymisation and thus transparent communication could become a kind of „enabler" or „supporter" of this culture of trust in Germany and across Europe. However, a situation in which data protection acts as an „impediment" must be avoided. Current discussions in the public with regard to the consistent use of data for research purposes are based on the assumption that data will be explicitly disclosed by the insured and that this will result in a comprehensive researchable patient record. If new developments in medicine continue to focus on small populations, e.g. pharmaceuticals against rare diseases, on diseases of personalised medicine with small patient groups, highly complex diseases, it is important that available data is as complete and accurate as possible and can also be used persistently.

Thus, there is a tension between voluntary data collection and the informative value of the data collected through this process. This challenge must be met by building a culture of trust that could accomplish this cultural change based on the voluntary nature of data disclosure as established in the Patient Data Protection Act.

Data evaluation for the benefit of people

Although, from IQWiG's point of view, the regulations on data transparency (section 303a – 303f of the German soci-

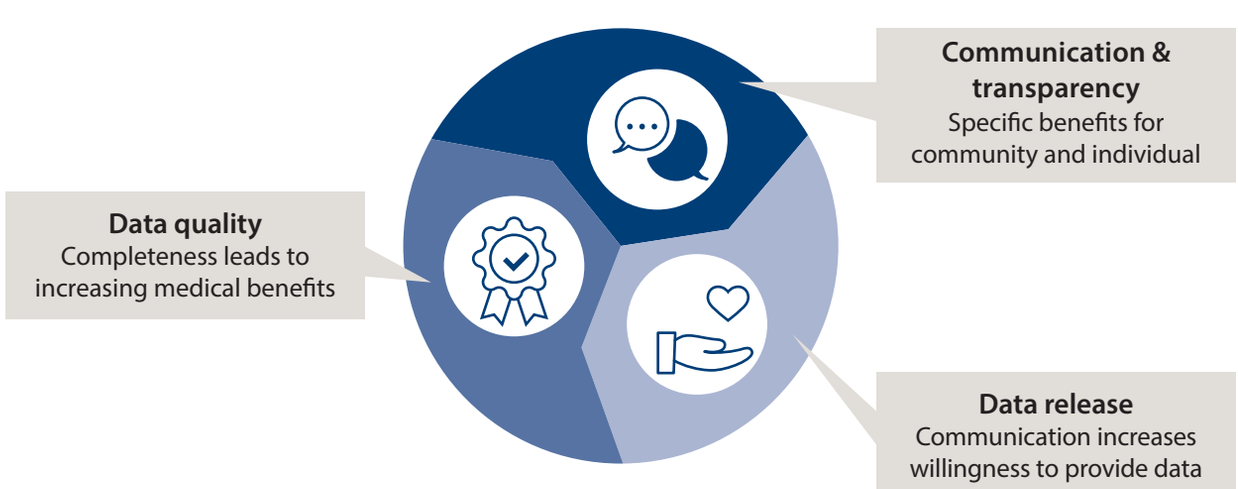
al code book V) most recently revised by the Digital Health Care Act (DVG) hardly result in the generation of suitable post-approval evidence with the data that can be retrieved in future, it is at least completely, fully and persistently available, since the DVG transfers this data body of accounting data to the research data centre without the right of deletion and the possibility of revocation. The Patient Data Protection Act (PDSG) presents a somewhat different perspective.

Despite the fact that patient treatment data collected in the electronic patient record is of good quality and suitable for research projects, with this body of data, the completeness, comprehensiveness, and persistent availability of data primarily depends on the willingness of the insured community to make their data appropriately usable.

The aim of politics – especially during the German EU Council Presidency – is to create a European data space. To make this ambitious project a success, solutions for a variety of issues, including standardisation of content tools (e.g. SNOMED-CT), need to be developed. Also a technical standardisation of the communication as well as the infrastructure, promotion of interoperability of the different (both new and old) national solutions have to be brought together in the European context. Uniform regulations on data protection, patient data sovereignty, rights of use, filling obligations, and financing issues must be established.

In addition to all these challenging tasks, however, there is the much more central question of who will benefit from all these efforts. Does this development really focus on people or is it ultimately associated with economic

Data that makes us healthy - building a culture of trust



Source: Dr. Antje Haas/GKV-Spitzenverband

Figure 4: In order to meet the population's need for data protection, a self-reinforcing culture of trust is required between the population and the institutions accessing pseudonymised data.

interests? In total, according to the EU Commission's data strategy, data rooms must be created for nine strategic sectors, including healthcare. It can be seen that abstractly formulated goals tend to focus on the specific benefits for people, such as improved data-driven health-policy making in the EU and at national level. The more concretely measures are formulated, on the other hand, the more likely it is that economic interests will shine through.

Taking the EU health strategy literally and putting people first

The basis of all research efforts should be the actual need of the European population for further medical developments. In future, this need should be determined independently of the industry on the basis of documented medical data. Research efforts would then no longer take place primarily in areas that are considered particularly lucrative, but where the greatest positive effects are expected with regard to the health of the population.

So this issue is also about value decisions and who will set the agenda in terms of European health policy. On the basis of a corresponding analysis, therapies could then be developed in a demand-oriented manner and access for European citizens could be ensured, also through local manufacturing facilities. Therapies thus made available could then be marketed in Europe at sustainable prices.

But: It is not yet clear from the previous drafts of the European data space which institution should be able to access which data. It remains to be hoped that – in the end – data will not merely be transferred from public agencies to companies and used only there. In the sense of a society-wide, partnership-based approach, access by public (research) institutions to data from private companies would at least also be worth discussing – or would this be prevented by competition law and the protection of secrets? May data from individuals be used by public institutions in future? If yes, for what purpose? Can data be exchanged between public (European) stakeholders? It would be conceivable, for example, to compare European treatment processes in the sense of best practice comparisons or a data-based further development of guidelines. Therefore, an EU-wide minimum content of the corresponding data and interoperability for exchange still needs to be worked out. Similar debates have been going on at national level for some time now, but the European level adds a variety of other stakeholders to this challenge.

Data collected nationally must be combined to meaningful data packages. Pooling care/research and study data across Europe would also allow the establishment of a better overview on research questions in smaller application areas, which couldn't be investigated so well when considered solely on a national basis with correspondingly small numbers of cases.

However, simply pooling the available data does not seem appropriate in this context, as the expected differences between the participating countries regarding the degree of implementation within the population and among healthcare providers alone may lead to distortions. Denmark and Estonia, for example, already play a pioneering role in the implementation of public e-health systems. Both countries already have electronic patient records, digital image and laboratory results archives, electronic prescriptions, etc. Other countries, such as Germany, are still in the development phase of these systems and will need several more years before they can catch up with today's pioneers.

Moreover, depending on the disease there are different morbidity burdens and structural profiles across the continent that must be taken into account in statistical analyses to avoid erroneous conclusions about the respective popu-

lation. In order to identify these differences, a high degree of transparency is needed regarding quality, scope, authenticity, and the like in the participating countries. For example, it must be clear whether the data used originates from studies, digital applications, or medical patient records, respectively.

This is the only way to approximate an overall picture for Europe. The pilot project is the program to generate data on genomes for at least ten million people by 2025, for which the legal framework still has to be finalised. Also more advanced is the establishment of a „Code of Conduct" to facilitate the processing of personal data in healthcare in accordance with the GDPR. Here, the friction between the question of whether „can" regulations are already sufficient to comply with data protection regulations and – at the same time – the need to avoid over-regulation that would slow down innovation becomes clear. One possible solution for this problem is to strengthen the autonomy of data subjects and to have recourse to a neutral data trustee.

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The EBMT Patient Registry: a pioneer for European clinical data?

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The European Society for Blood and Marrow Transplantation (EBMT) is an association of more than 500 specialised centres for blood stem cell or bone marrow transplantation from 57 different countries. Since its foundation in the 1970s, it maintains a registry of so-called „Essential Data" on every procedure performed at one of the – currently more than 600,000 – member centres. With the analyses of these „real-life data" trends regarding treatment methods and stem cell sources can be identified that are also relevant for health policy. In addition, it allows for benchmarking between different centres. Due to the size of the data pool, sufficient data of rare diseases can be collected to perform retrospective analyses and thus improve patient care. Finally, the EBMT registry is becoming increasingly important as a data source for regulatory processes related to FDA and EMA approvals.

The European Society for Blood and Marrow Transplantation (EBMT) is a non-profit organisation founded in 1974 by scientists and physicians involved in bone marrow transplantation to share their experience and plan and initiate cooperative studies. The background is that bone marrow or stem cell transplantation is a comparatively new treatment method in medicine that was clinically developed in the 1960s and 1970s replacing a diseased haematopoietic system with a compatible stem cell donor. Stem cell transplantation is a curative treatment option for a variety of systemic haematologic diseases. The complexity of the procedure, including the associated side effects, requires highly specialised expertise and high structural conditions for the institutions performing the procedure. In 1990, Professor Thomas was awarded the Nobel Prize in Medicine and Physiology for the development of stem cell transplantation. The EBMT was established in 1974 and promotes all aspects related to haematopoietic stem cell transplantation from different donor sources and types, such as basic and clinical research, standardisation of quality control, accreditation of centres, and continuous education of its members. The principle of the EBMT membership is based on centre members. In 2020, members of this European organisation included 558 transplant centres from a total of 57 different countries worldwide. The largest groups of members in Europe come from Italy, Spain, France, United Kingdom, and Germany. Currently, 84 German transplant centres are members of the EBMT. The 558 transplant centres employ 2,697 physicians, 747 nurses, 636 data managers, 124 technical laboratory staff, 201 quality managers, and other health care providers; thus, a total of > 5,000 individuals are member of the EBMT. In addition to the European countries, there are members in Asia, South America, North America, Russia, and Australia.

The EBMT Patient Registry

Already at the foundation of the EBMT, the decision was taken to establish a registry for stem cell transplantation and cellular therapy in order to be able to collect and evaluate sufficient data on stem cell transplantations. Established in the 1970s, this registry now represents the largest of its kind in Europe, with more than 600,000 documented haematopoietic stem cell transplant procedures from more than 500 centres in more than 50 different countries. Every year, more than 30,000 new haematopoietic stem cell transplant procedures are added.

The EBMT Registry is also affiliated with national registries, such as the German Registry for Stem Cell Transplantation (DRST). According to the membership statutes, EBMT member centres are required to report „Essential Data" of stem cell transplants online to the EBMT Registry using a so-called MED-A form. Centres are responsible for obtaining signed Informed Consent and relevant approval from the local ethics committee. For this documentation, no compensation is provided. Nevertheless, more than 90 percent of autologous stem cell transplants and approximately 98 percent of all allogeneic stem cell procedures performed in EBMT member countries are recorded in the EBMT Registry.

In addition to these so-called Essential Data, comprehensive data is collected for specific clinical trials from MED-B or MED-C forms on a voluntary basis.

The advantage of the centres is that they have continuous access to their own data in the registry and can thus create their own report to meet necessary accreditation or certification requirements with regard to quality management. Moreover, all members have access to so-called anonymised aggregated reports of the entire database. Data quality of the registry without on-site monitoring is safeguarded by:

- Exact definition and harmonisation of the definition with other registers
- Continuous education and training: regular education and training sessions for data managers
- Internal quality control: more than 4,000 so-called triggers control the correctness and the internal consistency of the entered data: regular follow-ups are performed in case of missing or incorrect data or missing follow-ups
- Continuous support from the Registry Office in the form of so-called help desks.

Benefits of the registry

Identifying developments and trends

Apart from prospective clinical studies, real-world data

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presentation shows activities and trends, e.g. with regard to different donor sources, but also with regard to indications in different disease entities, and thus also allows to support health policy decisions (see figure 1).

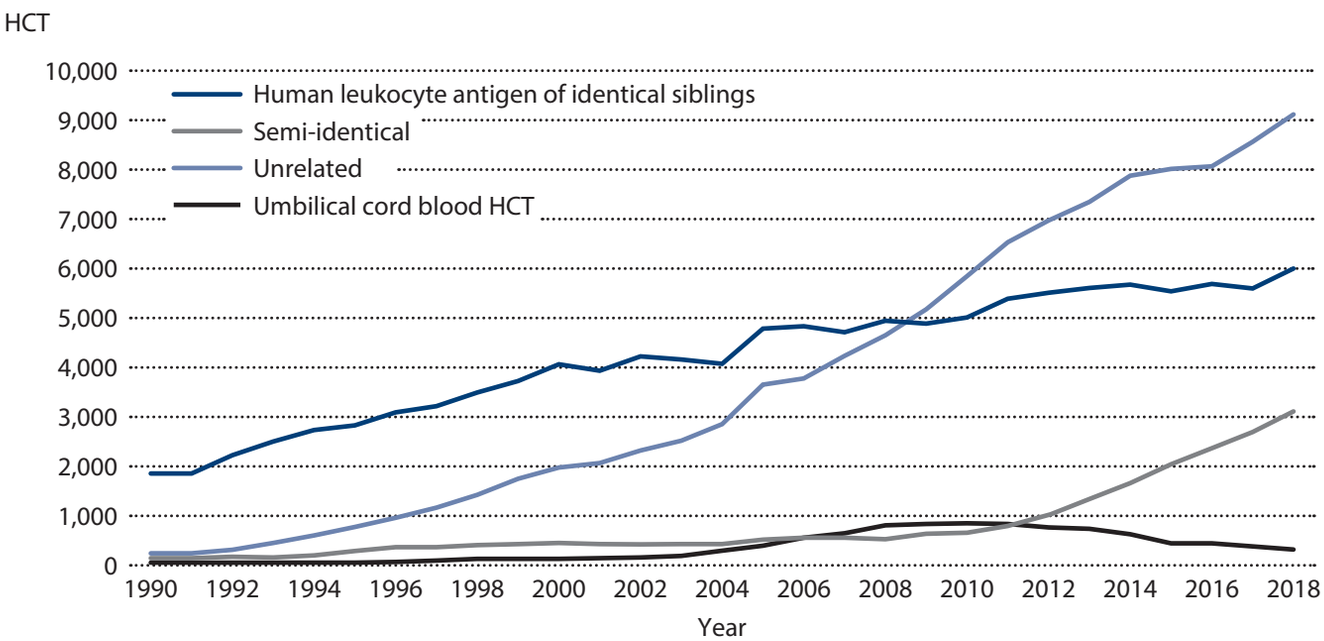
Benchmarking

In the Registry, every participating centre can compare their own results with other transplant centres for different indications and disease stages; this benchmarking is a prerequisite for internal quality assurance measures, but also for accreditation of internationally recognised quality assurance systems such as JACIE (Joint Accreditation Committee ISCT and EBMT).

Scientific findings and studies

The large number of so-called real-world data of stem cell transplantations and cellular therapies provides sufficient figures to allow scientific retrospective data analyses, even for so-called rare indications. This is performed within the EBMT in the ten different Working Parties working on either specific diseases or overarching complications of stem cell transplantation or cellular therapy. More than one hun-

Trends of different transplantation methods and stem cell sources in Europe



HCT=haematopoietic stem cell transplantation

Source: https://www.ebmt.org/registry/transplant-activity-survey

Figure 1: Through real-world data presentation, the EBMT registry allows for the presentation of activity and trends with respect to e.g. different donor sources or indications in different disease entities.

dred different publications in peer-reviewed journals emerge from these Working Parties each year, resulting in „practice changing" and numerous guidelines and demonstrated outcome improvements over the past 40 years that powerfully underscore the value of real-world data as quality assurance and improvement (www.ebmt.org).

Non-interventional studies

Many prospective, non-interventional studies such as so-called post-marketing authorisation studies on rare diseases – where approval has been granted due to often low patient numbers based on results from phase II studies – can be conducted by means of the EBMT Registry and the existing network of transplant centres and cellular therapy centres. These PASS studies also capture and document rare complications or long-term side effects that have not been described in the pivotal studies with small patient numbers and short follow-up.

Cellular and gene therapy

In addition to haematopoietic stem cell transplant procedures, the EBMT Registry also captures various forms of cellular therapy. Cellular therapy has seen rapid growth, particularly with genetically engineered T-cell therapy through CAR-T cells, but also through genome editing, and numerous pharmaceutical companies now market cellular products, some of which are commercially available based on data of phase II studies, after receiving FDA and EMA approval.

The European Medicine Agency (EMA) has therefore launched an initiative to enhance the use of existing registries and establish new high-quality registries that might become an important source for regulatory decision-making. A CAR-T cell workshop held in February 2018 and the subsequent qualification steps ultimately led to the EMA issuing a so-called Qualification Opinion for Cellular Therapy Modules of the EBMT Registry in February 2019, so that the required post-authorisation marketing studies can also be conducted via the EBMT Registry and a close collaboration with the pharmaceutical industry has been established.

The advantage of a single European registry avoids fragmentation of different national and regional registries, which would ultimately make data exchange and thus valid real-world data representation impossible. However, uniform European coverage of e.g. CAR T-cell products and other cellular therapies requires broad inclusion of stakeholders. The advantage respectively the purpose of this Registry is:

1. Quality control of clinical treatment

Beneficiaries of this quality control are:

a) participating centres,

b) national registries,

c) accreditation and certification, and

d) benchmarking processing of the individual centres

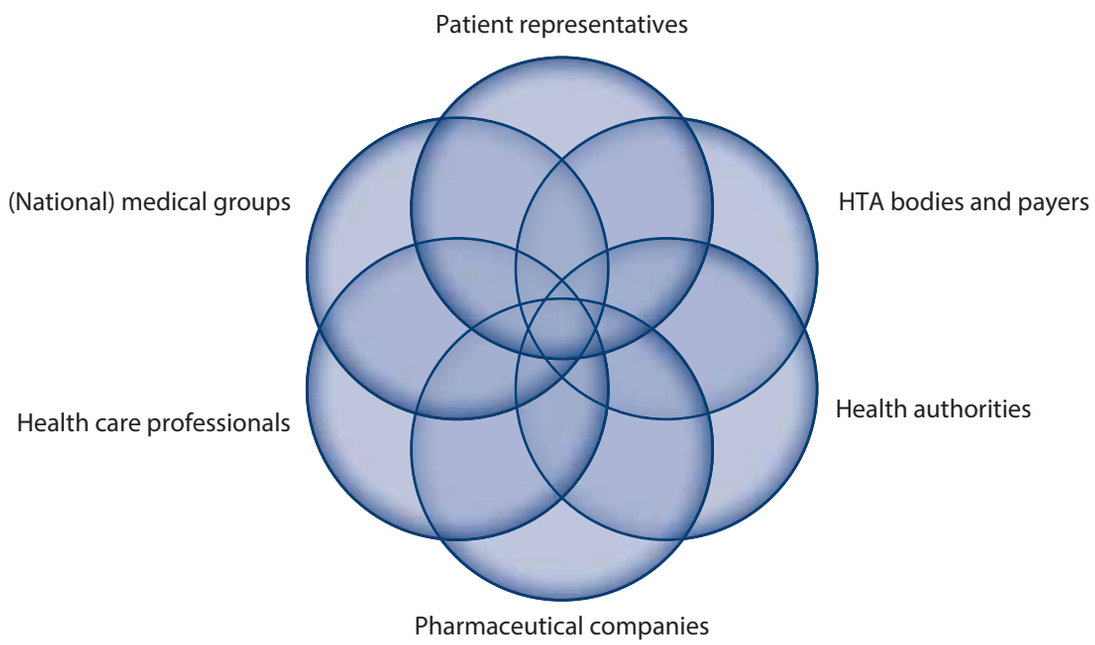
2. Science and education

Here, the scientifically operating groups such as the Working Parties of the EBMT, as well as international and national disease-specific study groups are particularly interested in valid results for retrospective studies.

3. Market surveillance

Market surveillance is primarily important for health authorities, sponsors and health insurers. In order to involve all stakeholders and ensure transparent data exchange and sufficient centre qualification in the context of CAR-T cell therapy, but also to ensure appropriate training and knowledge generation of healthcare professionals, the EBMT, has developed a so-called Governance Structure for CAR-T cells (GoCART) together with the European Haematology

CAR-T-cell-coalition (GoCART)



Source: Prof. Dr. Kröger

Figure 2: In collaboration with the European Haematology Association, the EBMT has developed a governance structure for CAR-T cells that brings together the various stakeholders.

Association (EHA), bringing together the different stakeholders to ensure different aspects of data harmonisation, centre qualification and regulatory process, and data evaluation (see figure 2).

In summary, the EBMT stem cell registry that has been developed over the past 40 years represents a valuable real-world data bank for scientific questions, quality assurance measures, and health policy issues. The steady increase of commercially available cellular products provides the opportunity to standardise data collection across Europe which is beneficiary for all stakeholders.

COVID-19: The first pandemic in the digital age

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The pandemic caused by COVID-19 has significantly accelerated important developments in the field of digital health research by pooling resources and expertise from a wide variety of stakeholders under one common goal. At the same time, an overwhelming amount of information must be handled, making it difficult to channel relevant insights to the different audiences. High-quality clinical data continues to require data collection strategies that go beyond electronically available information. Large national and international clinical, scientific and IT associations address these tasks and will be presented in this article.

Background

Political and economic systems are faced with extreme challenges through the SARS-CoV-2 pandemic. Due to the significant aerosol-mediated contagiousness and the comparatively high rate of severe courses, especially in vulnerable populations, strong measures to contain the spread are essential to avoid decompensation of the healthcare system with resulting shortage of medical care.

Although experts warned of a pandemic with dangerous pathogens for many years as a consequence of the steady increase in travel activities and exchange of goods in an increasingly globalised economy, at the beginning of the COVID-19 pandemic there were no overarching coordinated common strategies and action plans in most EU countries that would have been suitable for the management of this type of highly contagious respiratory disease.

In the initial phase of the pandemic, many European countries initially adopted concepts for containing the pandemic from the primarily affected countries (regulatory emulation). Only later were attempts made to coordinate containment measures across the EU, although these remained non-binding and to this day there is considerable heterogeneity regarding measures against COVID-19 among EU member states.[1]

The rapid development of support programs is remarkable. As of April 2020, at least 15 EU activities to comprehensively support COVID-19 research and control were launched within six months.[2] This created an effective context for European collaboration on COVID-19 prevention and therapy, albeit initially poorly coordinated – due to their short-term nature and simultaneity – with national funding programs such as the German Network University Medicine or the French national cohort FRENCH COVID.

Collaboration in the digital age and „infodemic"

SARS-CoV-2 is the first new and previously unknown pathogen to become pandemic in an era of global connectivity via social media and modern communication systems (chat platforms, video conferencing), posing a universal threat to health and prosperity. This led to an unprecedented accuracy in the monitoring of the virus spreading and its consequences, which – especially in the initial phase – sometimes made evaluation difficult due to the lack of references: Is this disease really particularly serious, or did we simply never look that closely before?

This also created uncertainty in scientific circles, which provided additional space for false reports and conspiracy theories. Prioritisation of news in social media by learning algorithms with a focus on user loyalty and profit made it extremely difficult for untrained readers to distinguish between scientifically based statements and political rhetoric, and often highly controversial and unsubstantiated statements stood on equal footing with important research findings.[3-5]

The global threat posed by the COVID-19 pandemic and focussing of hospitals on COVID-19 often inevitably led to a reduction of treatment options and also scientific activities in the field of other diseases. The resources released here, as well as the widespread commitment among physicians and scientists to contribute to averting the common threat, resulted in an unprecedented concentration of resources on one topic, resulting in more than 50,000 scientific publications in peer-reviewed journals in less than a year[6] – in addition to numerous unreviewed pre-publications of manuscripts, some of which are very popular on social media and medical blogs.

While numerous publications significantly contributed to identifying effective therapies and vaccines and selecting meaningful prevention and management strategies – with over 150 publications every day – it is clear that individual physicians and scientists cannot even get close to comprehend this amount of information. Paradoxically to the large amount of available information, this threatens that important news with possible implications for patient care might not be perceived or only with a delay.[7]

One positive aspect of digitisation has been the universal availability of modern communication tools, most notably the overwhelming triumph of video conferencing as the tool of choice for multi-party discussions, but also various other technologies such as chat platforms and cloud services with shared file storage and editing capabilities. This made an effective national and international collabo-

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ration possible.[8] In addition, there were several large-scale digital collaboration campaigns, such as the federal #wirvsvirus hackathons to engage civilians in the search for a solution[9].

Overall, digitisation has brought about very many positive aspects in dealing with the pandemic, but it has also created new problems, which manifest themselves in particular in a flood of information and also active involvement. Clever solutions are required here to help channel the oversupply at the beginning of a crisis situation and to structure the incoming volumes of information as it progresses, in order to avoid duplication and make essential contributions visible.

The European LEOSS Case Registry

In addition to specific clinical trials on vaccines and therapies, cohort studies have been initiated at numerous university medical centres worldwide to collect clinical data using methods of epidemiology and healthcare research, as well as precisely annotated biological samples. One of the largest European studies under German coordination is the Lean European Open Survey of SARS-CoV-2 (LEOSS, https://leoss.net) with currently more than 6,000 cases.[10]

LEOSS is an anonymous case registry and interested sites can provide their treatment data to enable analyses of clinical courses and disease management. Numerous contributions to the ongoing discussion, especially with regard to specific risk groups, have already been published. At the time of its establishment, there was no funding for LEOSS, so innovative approaches were sought to engage the medical and scientific community. In this context, a dedicated video service via Jitsi™ (8x8, Campbell, California, USA), chat platform via Mattermost™ (Mattermost Inc, Palo Alto, California, USA), Twitter channel and newsletter were set up for the LEOSS network.

The study is self-administered with transparent, performance-based participation in study committees and absolute control of the study by the participating sites. Some of the generated data is freely published in a so-called „Public Use File“ (PUF); detailed data sets are made available for use and approval by the study committees upon request as so-called „Scientific Use Files“ (SUF). Data flows and results can be examined directly on a web-based dashboard (established in cooperation with PROCON-IT, Munich) on the website (https://dashboard.leoss.net, see figure 1). To ensure anonymisation, a multi-stage procedure was developed that uses additional verification steps after anonymous data collection to find potential constellations that are usable for re-identification and – if necessary – further aggregates and reduces the data set.[11]

Data integration for clinical research

Shortly after LEOSS was created, the question arose as to whether it should be possible that a study like LEOSS is filled on a largely automated basis at the university medical centres in view of the increasing availability of electronic structured data in Hospital Information Systems (HIS) and Data Integration Centres (DIC) of the Medical Informatics Initiative (MI-I).

However, detailed analysis of the available data and comparison with the LEOSS dataset according to clinical epidemiological criteria revealed considerable differences between available and required data: In general, 50 to 70 percent of the variables maintained in LEOSS were available in some form in the DICs surveyed without further adjustment. But looking at the specific questions, it became apparent that a major part of the available structured data elements was not sufficiently usable and required manual re-entry.

This already applied to very simple questions: For exam-

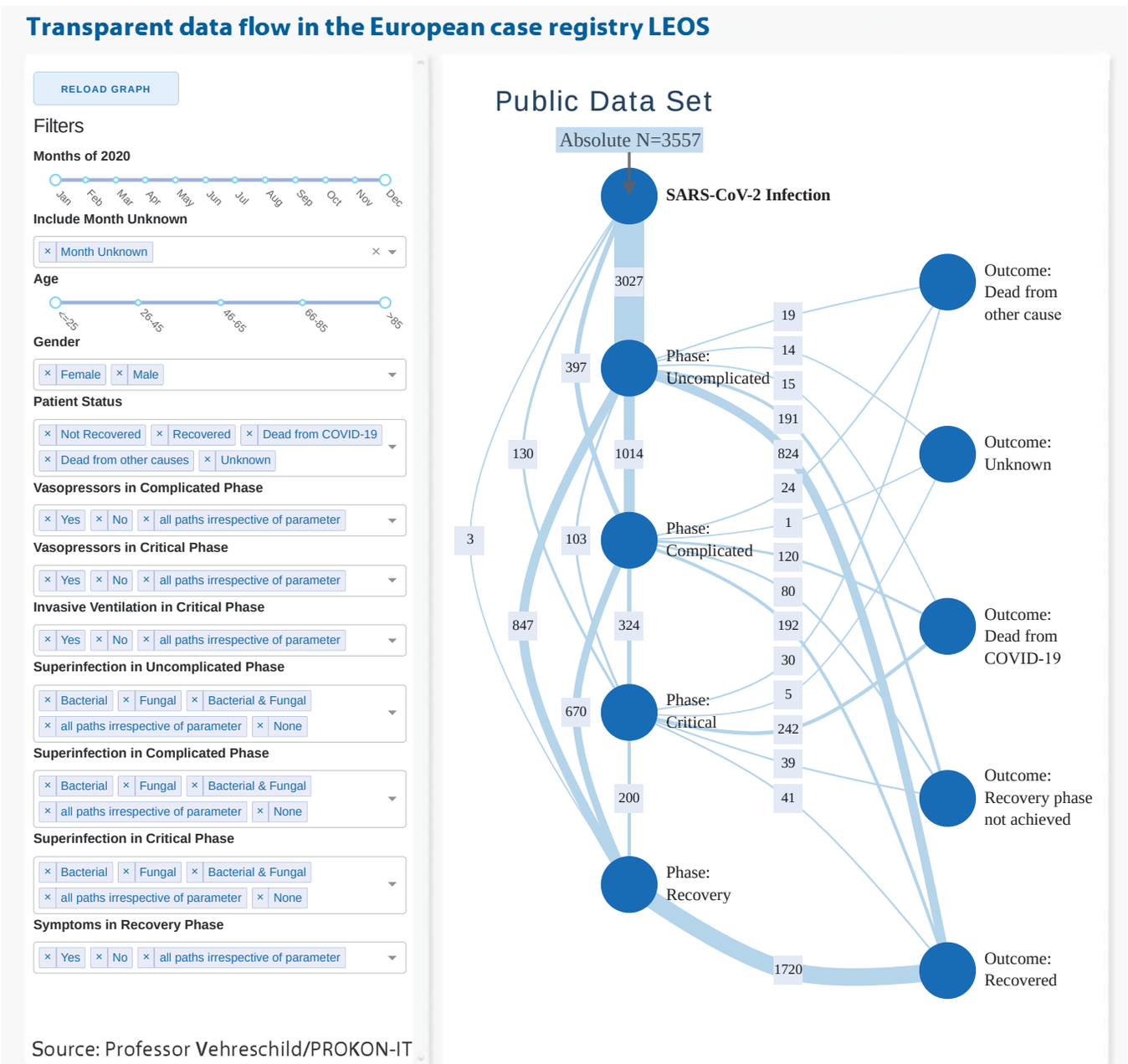


Figure 1: In the LEOSS case registry, datasets are partly published in a public use file. A dashboard then allows data flows and results to be examined directly on the website.

ple, the way a sample is collected, such as using a swab, is extremely important for epidemiological assessments. However, the extraction location is often a free text or is supplemented by a free text. In principle, such free text may also contain identifying characteristics („Ms/Mr XXX did not tolerate the nasopharyngeal swab"), which is why any unverified disclosure of such free text without the informed consent of the affected individuals is prohibited.

Furthermore, it became apparent that a number of relevant therapies are summarised with rough coding grids in the HIS. For example, in the context of populations with particular risks in the course of COVID-19 information on immunosuppressive and cytoreductive therapies was required. At many centres, however, these were only available as OPS codes, which only provide a rough classification of the expense of the respective therapy, but do not allow a general substance or dose reference.

There is still a major difference in the presentation of diagnoses. The ICD-10 codes which are often used by professional coders for accounting are available universally. This raises three problems for the scientific context: (i) sometimes there can be a significant time lag between treatment and accounting-related coding, (ii) coding is not primarily focussed on medical accuracy and completeness, but rather based on revenue criteria, and (iii) ICD-10 represents only a rough grid for recording comorbidities.

For example, a large proportion of myelodysplastic syndromes are pooled under D46.9; thus, aggressive diseases with a life expectancy of less than twelve months as well as chronic stable diseases with a life expectancy of more than ten years can be subsumed under the same digit. Here, additional structured data on cytomorphology, histology, cytogenetics, molecular genetics, and extramedullary manifestations should be available for haematological assessment and thus epidemiological comparability.

Furthermore, ICD diagnoses are not coded in most hospitals, if they occur transiently and are not revenue-relevant, example: A patient temporarily develops a symptom of nausea, dizziness, or exanthema, but this does not prolong hospitalisation. Although this information is highly relevant for a comprehensive clinical-epidemiological understanding the clinical picture, there is usually no coding and thus no structured recording in the electronic case record.

In 2020 (and today), all of this information still needs to be manual post-recorded by trained scientific documentation personnel. Nevertheless, digitisation may enable important innovations in cohort research: After all, a subset of the data, such as laboratory values and vital signs, can be collected in many clinics in excellent quality and in real time. On the one hand, the speed of collection enables use scenarios for pandemic assessment and control, and on the other hand, more complex studies can provide available data, thereby significantly reducing the documentation effort and at the same time significantly increasing the quality and quantity of the available data.

Furthermore, concepts for a kind of „meta-registry" emerged, where a very comprehensive data set is collected as an overlap of multiple studies through a mixture of electronically imported and manually documented data which are digitally transferred to different studies. However, this requires considerable preliminary epidemiological work and thorough evaluation on a case-by-case basis to ensure that the context of the data is correctly chosen. As a simple example of the conceivable problems, the temporal level of aggregation should be considered: One study might collect the highest temperature on the day, a second study the first temperature measured on a day, and a third study the most pathological value (i.e. also takes hypothermia into account). In this scenario, three different temperatures

would actually need to be collected in the meta-registry to avoid substantial bias in the analysis.

The National Pandemic Cohort Network (Nationales Pandemie Kohorten Netz, NAPKON)

The largest national cohort study on clinical COVID-19 cases, called NAPKON (https://napkon.de, see logo below), is currently being established within the framework of the Network University Medicine (NUM) with funding of the German Federal Ministry of Education and Research (BMBF). NAPKON includes 33 NUM sites and plans to involve a broad non-university sector, ranging from family physicians' practices to maximum care providers as academic teaching hospitals. More than 8,000 patients will be recruited in NAPKON to prospectively collect clinical epidemiological data and quality-assured biological samples. Digitisation plays a central role in NAPKON:

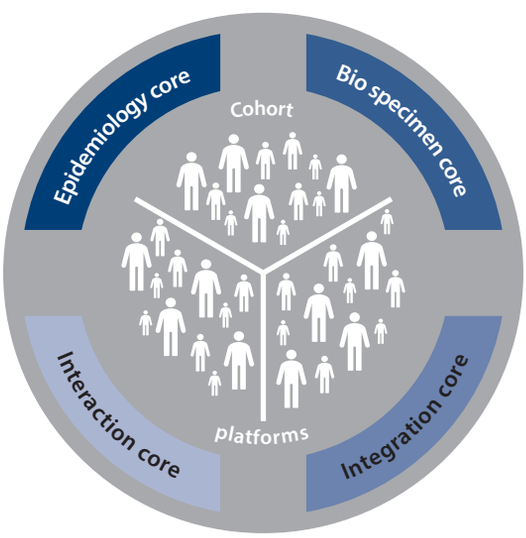
In the first of the four infrastructure modules (see figure 2) of NAPKON, the so-called interaction core, a comprehensive interaction platform was designed based on the experiences from LEOSS and with the goal of institutionalised broad collaboration and appreciative integration of all participating centres, physicians and scientists. It combines numerous online services such as forum, e-mail lists, file storage and project management in a harmonised web interface with single sign-on functionality.

Complex group assignments and rights hierarchies allow for adaptive distribution lists, through which contact persons at the study centres and among the participating scientists can be easily identified and addressed. Scientific participation in NAPKON is facilitated through the subject- and organ-specific task forces (Fach- und Organspezifische Arbeitsgruppen, FOSA) that have been established on more than 20 topics. Through the biological samples approach, quality audits of the collection and processing of biological samples are performed by means of video consultations. The Epidemiology Core Unit develops automated audit procedures to measure and improve data quality, while the Integration Core develops procedures to integrate existing studies and datasets into NAPKON.

Data is collected in three so-called cohort platforms: The Cross-Sectoral Cohort (Sektorenübergreifende Kohorte, SÜP) collects routine clinical data and biological samples from a broad patient group in all healthcare sectors and conducts individual long-term follow-ups. In the High Resolution Platform (Hochauflösende Plattform, HAP), deep phenotyping of severely ill cases takes place at selected university medical centres, with long-term follow-up and a comprehensive evaluation programme. In the third, population-based platform (Populationsbasierte Plattform, POP), comprehensive characterisation and long-term follow-up of recovered individuals after previous infection with SARS-CoV-2 will take place.

In the initial phase of the project, the German Corona Consensus (GECCO) – a dataset based on international standards such as FHIR and SNOMED – will serve as a common data core for the three cohort platforms. During the project, this shall be expanded and supplemented so that mapping of a complex clinical case history with information on all organ systems and clinical specialities is made

Infrastructure components in the National Pandemic Cohort Network (NAPKON)



AP1 Interaction core:
Project coordination, governance, data publication and community-outreach/FOSA

AP2 Epidemiology core:
Quality assurance and data analysis

AP3 Bio specimen core:
Quality assurance, audits, SOPs

AP4 Integration core:
Collaboration with existing projects

Source: Professor Vehreschild/NAPKON

Figure 2: The interaction core as the first of four infrastructure modules of NAPKON unites numerous online services, e.g. email lists or project management, in a harmonised web interface.

possible.[12] At the same time, as part of the COVID-19 Data Exchange Platform (CODEX), data integration centres of the Medical Informatics Initiative at the university hospitals across Germany will be equipped to hold data on COVID-19 patients in the GECCO format.[13] This is the first time that a uniform data set on the clinical treatment of patients with a serious COVID-19 infection can be effectively compiled for analyses across university medical centres.

The European perspective

Within the framework of Horizon 2020, among other things, the Connecting European Cohorts to Increase Common and Effective Response to SARS-CoV-2 Pandemic (ORCHESTRA) initiative is funded by the European Union (https://orchestra-cohort.eu/). This initiative aims at pooling data from a wide variety of COVID-19 cohorts into one central platform. In addition to clinically ill patients, patients with long COVID, healthy populations, healthcare workers, children, elderly people, pregnant women, and special risk groups with e.g. underlying haematological/oncological or psychiatric diseases will be considered. In addition to data from numerous European countries, international cohorts from Peru, Argentina, Venezuela, Ecuador, Brazil, India, Congo, Gabon etc. participate in ORCHESTRA. Prospective clinical trials, registries, and secondary use of electronic data sources are integrated.

In collaboration with the European Reconciliation of Cohort data in Infectious Diseases (RECODID, https://reco-

did.eu/) project, a concerted effort will identify common data elements and strategies of such international cohorts. Legal and regulatory hurdles for data pooling will be identified and solved using a multi-layered data integration concept. Here, a central search dataset of non-critical data elements will be established, while data requiring special protection (e.g. human genomes or other critical phenotyping elements) will be unified in national hubs and available for funded analyses or project-specific mediation.

Hence, strategic discussions go well beyond data integration: based on the harmonisation work, concepts for a harmonised collection of data and biological samples at the international level will be developed prospectively.

Beyond cohort and data mergers, other levels of collaboration have emerged in Europe through COVID-19, using digital tools to bring together large groups of partners and study participants. One example is the European Vaccine Trial Accelerator Platform (EUVAP, https://euvap.com/) that uses the VACCELERATE platform (https://vaccelerate.eu/) to connect interested subjects to international vaccination studies and coordinate study site resources to significantly reduce the time from study initiation to completion and save redundant recruitment and promotion efforts at study sites.

Discussion and outlook

The pandemic caused by COVID-19 has become a driver of digital health science across Europe. Collaborations and major harmonised projects have emerged and acquired a sense of urgency that would otherwise have taken several years to achieve. More data than ever is generated on a single disease in a very short time and much of it is available to the scientific community.

In addition to treatment and study data, a broad integration of other data sources, such as motion data and data from health and fitness gadgets, takes place, allowing complex modelling and prediction. To fully realise the potential of this new era for global health, it will be crucial to set a key course in the coming months and years through targeted funding:

1. Coping with the infodemic with its flood of information, data and also false reports, requires a comprehensive approach with broad involvement of politics, science, media and industry for the selection, testing, analysis, modelling, consolidation and target group-oriented communication of new findings. This requires targeted structural support to create incentives for sustained specialisation in these future topics. Interfaces between medicine, clinical and experimental science, and data science and/or computer science can play a key role. Such multi-specialised companies and scientists are crucial to close the translational gap between disciplines, identify key problems, and drive rapid development of accurately tailored tools for upcoming problems.

2. The urgency of the pandemic has brought together representatives from a wide variety of disciplines and interest groups and built valuable bridges. However, successes achieved cannot necessarily be applied to other groups and topics in what may be a post-pandemic era. Without continued support, new collaborations will be destroyed again. Instead, stabilisation followed by a smart and gradual expansion of the innovative pandemic concepts is required in order to secure what has been achieved for future tasks of a digital medicine.

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DiGA, ePa & Co: Governance at EU level is only emerging in outline

By Florian Staeck

SARS-CoV2 is the first pandemic that can be tracked virtually in real time in the digital age. As if under a burning glass, the treatment of COVID-19 patients reveals the problems and challenges of making digital data available and accessible to scientists and physicians.

The Longitudinal European Open Study on SARS-CoV2 (LEOSS) can show new ways and opportunities. In October 2020, this anonymous case record that was set up shortly after the onset of the pandemic included some 4,000 records of COVID-19 patients. It is characterised by the fact that all data collected are available to the scientific community for shared analysis. The registry is based on a broad involvement of research associations and professional societies and has an open governance structure – self-administration of the study takes place at the participating centres. More than 850 registered individuals from 215 sites feed data into the registry.

Experience gained in LEOSS provides insight into the challenges of automated reading of data from heterogeneous sources. On the one hand, digitisation has created unprecedented real-time observation capabilities. On the other hand, it has now become clear that less than 20 percent of the relevant data for COVID-19 is actually available in an interoperable form. Less than 50 percent of the data could be transferred from electronic sources in sufficient quality. For the next years, LEOSS will rely on manual post-structuring to collect essential data for the assessment of disease progression.

Thus, the registry highlights the importance of interoperability and need for common standards for electronic documentation using a highly topical example.

This was a widely shared view among participants at the 12th Interdisciplinary Platform on Benefit Assessment in Fulda, Germany, on 9-10 October 2020. The general title of the meeting, at which speakers met online, was „Availability of digital clinical data in a European context".

Learning from the flagship registry EBMT

Using the example of LEOSS, the participants of the meeting emphasised the importance of the sustainability of a registry and at the same time the danger of fragmentation into too many small registries. The value of a registry usually only became apparent after many years. This could be illustrated by the example of the European Blood and Marrow Transplant Registry (EBMT). This registry dated back to an academic development in the 1970s. Today, the registry was organised globally with 600 centres from 60 countries participating. Participants reported that although stem cell transplantation was still a rather rare procedure in haemato-oncology, the registry currently recorded approximately 600,000 transplant procedures at European level increasing by 30,000 records every year.

They outlined that participation in the registry was voluntary without any compensation being paid for data submission, and yet about 90 percent of all autologous and nearly 100 percent of allogeneic transplants were recorded. One of the many advantages for participating centres was the possibility of benchmarking, so that a centre could understand its own performance as compared to other centres. In other European countries, participation in the benchmark was already mandatory for reimbursement of transplantation costs while Germany was still more lenient at this point. By means of this treatment data, late effects of a transplantation could also be recorded which was not possible in clinical studies. Participants reported that a large number of high-profile studies had originated from the data pool.

In the meantime, the interest of research-based pharmaceutical companies in the data pool had also grown due to

EMA's initiatives to integrate new data into regulatory processes after approval so that several post-authorisation safety studies (PASS) have emerged from it. Moreover, the interest of national health authorities in the registry was also increasing. They said that the next development step of the EBMT was a discussion with stakeholders to organise a transparent sharing of data and emphasised the special importance of the EBMT registry in the two G-BA (Federal Joint Committee) procedures on CAR-T cells.

In focus: digital health applications

Regulatory mechanisms for reimbursement of digital health applications at the expense of the SHI are still at a different development stage. By the time of the October 2020 event, two digital health applications (DiGA) had been added to a list at the Federal Institute for Drugs and Medical Devices (BfArM) for the first time, enabling their prescription and reimbursement under SHI. Some 20 additional applications are already in the BfArM's review process, and consultation meetings have taken place for 75 to 80 additional DiGA to date. Participants reported that so far eight providers had withdrawn their application for approval.

The aim was to use these applications to lower the threshold for the use of digital assistance in medicine. They outlined that a wide range of applications were in the pipeline, many of which were for the monitoring of chronic conditions, e.g. for migraine patients. Other apps, they said, had the potential to help with diagnostics, such as recording cardiological and pulmonological measurement results in patients with sleep disorders. DiGA, they argued, could help to solve certain treatment problems more easily. These were always additional offers to supplement conventional diagnostics and treatment in order to improve it if necessary without replacing it.

The participants controversially discussed the procedure for the determination of the benefits of DiGA, which differs from the AMNOG process. Their approval was based on an application procedure in which additional benefit experience should be generated through the actual use by patients. In this Fast Track procedure, comprehensive data on the benefit of a DiGA was generally not available at the time of approval – the application by patients was initially based on a benefit hypothesis. Accordingly, the approval of an app was initially limited to one to a maximum of two years.

This application process encountered massive criticism from individual participants. The level of evidence required to obtain reimbursement resembled that of homoeopathic products, they outlined. Section 12 of the German Social Security Code (SGB V) stipulated that treatment in the SHI system had to be necessary, appropriate, economical, and in line with the state of medical science.

DiGA reimbursement: a political course setting

On the other hand, the establishment of the Fast Track procedure was a political decision. DiGA was one puzzle piece of digital medicine that had to be continuously reviewed to determine whether it actually improves care. It was not just a question of the medical effects of DiGA, but also of the organisational and structural effects on care. A sceptical response was that it was still unclear what energy DiGA providers would have to invest to furnish proof of positive care effects. Here the advisory discussions with the BfArM would be of great importance, participants said. They noted that currently the level of evidence required for SHI reimbursement differed significantly from that required for drugs and new medical services.

Critical comments were also made about the assumption that through the CE marking of an app it could

be assumed that the DiGA was actually safe. However, this was not a seal of quality, but only a confirmation by the manufacturer that the product meets the European requirements for safety, health and environmental protection. Participants reported that, in the past, there had been several examples where the CE marking was not a guarantee that harm to users was actually avoided. This was countered by the fact that a conscious decision had initially been taken to limit the apps to risk classes 1 and 2a.

The discussion showed that for DiGA an „adaptive approach" to evaluating the benefits becomes apparent. For example, for a digital headache diary, the regulatory agency will not require a clinical study from the provider. They noted that this would be different for closed-loop systems in diabetology, for example, where the provider was expected to present data with sufficient evidence of benefit from a randomized clinical trial (RCT). However, the regulatory authority was dependent on data from the provider according to a predefined checklist. If data protection problems became apparent during this review – such as the outflow of data from an app to a third country – the agency would not hesitate to remove an app from the list of approved DiGA, if necessary, participants said.

An iterative learning process

In the discussion, it was emphasised that an iterative learning process was associated with the – in global comparison – first-time reimbursement of digital applications. It was argued that the model based on drug approval, in which the pharmaceutical manufacturer develops a finished product that generates a return on investment until patent expiry, could not be transferred to DiGA in this form. Since in many cases these applications were not finished components, but rather subject to continuous further development, for example through updates, regulatory authorities would also have to manage this iterative process.

It was concluded that this learning process also needed to be understood and organised with regard to DiGA reimbursement. The participants agreed that future digital applications would have more relevance in clinical and outpatient patient care in the foreseeable. German and European developments were urgently needed here in order to avoid becoming increasingly dependent on China and the USA.

Taking Europe into account for the electronic patient record

The challenges of regulating and implementing elements of digital medicine become apparent on the example of the electronic health record (ePA). Participants emphasised that the ePA was not a digital record about the patient, but of the patient. This presented the challenge of recording data in a structured form. Participants emphasised that this was expressly not about an even more differentiated documentation, which would be associated with additional bureaucratic work for physicians, but rather about the automatic extraction of data that already exists. The ePA was associated with the perspective to fully record and understand all of a patient's health-related events for the first time. For this purpose, the ePA would be further developed step-by-step after its launch on 1 January 2021. Thus, the National Association of SHI-Accredited Physicians was currently working on converting 300 of the most common laboratory parameters into a medical information object so that they can be integrated into the ePA.

Gematik's vesta project was of central importance in this initiative, i.e. the interoperability directory for the German healthcare system. In the future, gematik – as host of the vesta board – would not only list the standards for inter-

operability, but also define them in order to guarantee a fair competition between large and small companies offering their products and services. In this context, the implementation of binding IT standards should also be a condition for SHI financing. It was thus be crucial to avoid creating new isolated solutions in order not to repeat past mistakes.

As things stand at present, as of 2024 the ePA will be embedded in a broad research context. From then on, data from care across sectors will also be made usable for research purposes. In ePA 3.0, accounting data from health insurers will be merged with treatment data from ePA in the future Research Data Centre (RDC). This could then, for the first time, create a comprehensive data basis on the course of diseases and recoveries in Germany. For patients, informed consent and the right of revocation would be central to the voluntary and pseudonymous release of data from the ePA.

The discussion made it clear that – in the view of participants – this project was still associated with many uncertainties. So far, it was completely unclear how data from risk structure compensation can be merged with provided data. Participants warned of a potentially large selection bias in data collection as compared to the overall population. They argued that the extent of this bias would depend on who will use the ePA, who will provide data, and which physicians these patients will consult.

A long way to the research data centre

Participants described it as constitutionally problematic that 2 according to the current status – only data of SHI-insured persons should be incorporated into the Research Data Centre (RDC), but not those of PHI-insured persons. Moreover, the question of data transfer to the RDC caused a great deal of uncertainty in the public debate and could impair patients' trust, they said.

Participants identified another factor that could influence the representativeness of the research dataset in the question of when patient data release should take place – „before" or „after" the planned trust centre. Politically, this question was answered in the Bundestag's Enquete Commission on Artificial Intelligence that the release should precede the transfer to the trust centre. During the discussion, it became apparent that Germany's connection to the European data space would be equally challenging. It was argued that up to now, telematics in Germany was still at the „Sütterlin" stage, i.e. the historical form of German handwriting, and the telematics infrastructure had not yet been aligned to the European standard. However, a common European data exchange format was of fundamental importance, and corresponding support programs had already been launched by the EU. For example, the X-eHealth project, which was launched in September 2020 for a period of two years. The aim was to create an EU-wide framework for the exchange of laboratory data, medical image data, and hospital discharge letters.

European Joint Action programme

In February 2021, a further step will be taken with the Joint Action Program on the European Health Data Space. This three-year project focuses on interoperability, data quality and the use of data from electronic patient records and disease registries. Some participants criticised that 36 months were far too short for such a project. This was a legislative programme that would have to run for years. This was countered by the fact that funding programmes for interoperability had existed at EU level for years, and the same applied to electronic patient records that had long been established in many EU countries. Against this background, 36 months was a realistic time frame to establish the technical standards.

Other participants expressed scepticism with regard to the necessary EU-wide consensus procedure to achieve a uniform morbidity documentation. In Germany alone, there were major differences between the individual treatment sectors. Moreover, Germany, for example, had introduced the medical nomenclature SNOMED CT with a pilot license, while the WHO preferred the ICD-11 for the classification of diseases. They warned that it was still unclear how and according to which procedure – unanimity or majority principle – a reconciliation process could take place here.

Challenges for both industry and payers

Participants went on to debate challenges of digital clinical data availability from a European perspective for the research-based pharmaceutical industry and payers. Digital data needed to drive research forward. They said that there was still a high risk that a molecule will fail in clinical phase 3. Big Data could help reduce the error rate here. Moreover, clinical studies became increasingly complex, because the number of patients to be recruited was steadily declining as a result of stratification. In view of the global nature of studies, it was essential to be able to work with uniform data standards.

The fact that – according to the current legislation – the pharmaceutical industry should not be given access to the research data centre could prove disadvantageous for Germany as a research location. Participants noted that it was not about a factual disadvantage for scientists in Germany – the research databases were not even operational yet – but about the political signal that research was not welcome in Germany. They were also concerned about the trend that Germany had been pushed out of first place in the EU as a location for clinical studies by European competitors since 2016, i.e. first by the UK and then by Spain in 2019.

Representatives of the payers reported about various – in their view – questionable developments in the benefit assessment of new pharmaceuticals. The AMNOG procedure made it possible to relate new active substances to the respective appropriate comparative treatment. What the treating physician lacks for a therapy decision was, however, an overview of the treatment sequence in an indication area.

Critical reference was made to the role of the EMA, which in the view of individual participants was increasingly accepting evidence deficiencies during the approval process. The current governance structure in Germany did not offer incentives for manufacturers to generate additional post-approval evidence after the early benefit assessment. They said that the „principle of hope" was being applied leading to false incentives. It was argued that at the same time, the importance of special approvals, e.g. orphan drugs or conditional approvals, was steadily increasing – active substances for which the probability of a non-quantifiable additional benefit was statistically increased by a factor of four. This was countered by the fact that the methodological tools available for assessing the additional benefit of innovative therapy methods were not suitable for the peculiarities of e.g. gene therapy products or tumour diagnostics.

The Act for More Safety in the Supply of Pharmaceuticals (GSAV) only provided inadequate answers to these challenges, they reported. Moreover, they criticised that the regulation of post-market data collections was „very narrowly defined" only reflecting laboratory conditions. Knowledge-generating care could not be established on this basis. In addition, the results of registries commissioned by the Federal Joint Committee would not be considered in reimbursement negotiations for at least two and a half years. Meanwhile, the annual treatment costs for new active in-

gredients from special approvals are currently increasing by around 30,000 € each year, they emphasised.

Participants also underlined the fact that the use of digital clinical data was welcomed by many stakeholders in the healthcare sector. However, the question arose as to how a balance could be achieved in future between profit and public interests. With data disclosure by the insured and automatic extraction of patient data, the question of who shapes the agenda in research and who prioritises the need for action in the development of pharmaceuticals is being raised with new emphasis. These central questions of governance formulated with the claim „to make healthy" had so far remained unanswered.

The same applied to the way towards a culture of trust, without which digital health data were unlikely to become sufficiently available. Participants reported that new survey results indicated a declining acceptance among German citizens to share their health data. Against this background, participants requested that patients should be involved in the development and implementation of new digital offerings from the beginning. One essential point for patient acceptance was the clear communication of the patient benefit. Experiences with ePA and ePrescription brought some valuable learning experiences.

Participants requested that the establishment of decentralised health databases should go hand in hand with voluntary data collection combined with the possibility of voluntary release as well as retrievability of data.

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