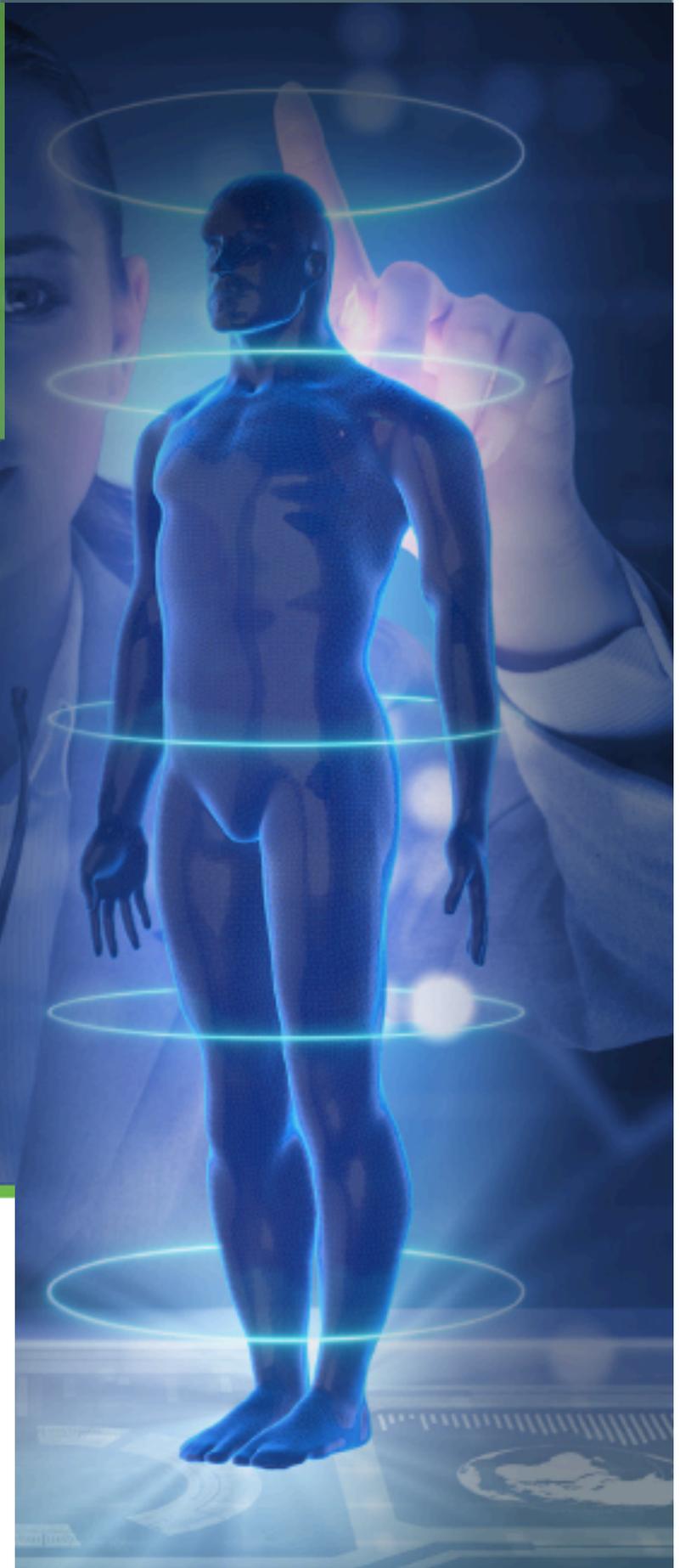




28TH-29TH JUNE 2017 TALLINN, ESTONIA

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## Report of EMIF Conference Tallinn, Estonia 28–29 June 2017

### EMIF – Digital Citizen, Digital Patient

The [European Medical Information Framework](#) (EMIF) programme 2013–2017 has laid the foundations of an EU-wide ecosystem that is enabling the reuse of existing health data. These foundations cover technical issues and governance, creating a trusted, federated system from which all stakeholders can benefit.

Via EMIF, researchers have connectivity to an unprecedented volume of data relating to 40 million subjects. The challenge now is to reuse the data to drive a new wave of patient-centred research.

Following two earlier meetings of EMIF participants in Barcelona and Budapest, it was particularly appropriate that the third meeting was held in Tallinn, just as Estonia, a world leader in e-Services, took on the EU Presidency for the first time.

In a day of high-level discussion and debate exploring each dimension of patient data and the work of EMIF forward to real-life applications that can maximise the benefits of data reuse for the good of patients, healthcare systems and the economy.



## Executive Summary – Key points for successful deployment

1. Build an inclusive ecosystem that is conducive to health-data-driven research.
2. At an EU and member state level, legislators must look to create a trustworthy environment that fosters data sharing.
3. There must be active participation of all stakeholders and especially of citizens, both in sickness and in health issues.
4. Digital literacy must be taken to a higher level to promote equity and encourage participation.
5. Patients have rights but they also have duties.
6. There must be active collaboration – no stakeholder can go it alone, especially not the pharmaceutical industry.
7. Start by understanding each other's needs and use this understanding to engender trust.
8. Collaborations needed to combine cohort data to increase the power of their analyses.
9. Successes must be leveraged faster to spread the benefits, and failures should be communicated in full to avoid duplication and to ensure that the same mistakes are not made again.
10. Remember that trust and trustworthiness are gained slowly but can be lost in an instant.
11. There should be a push to make data more mobile, easier to find and access, interoperable and reusable.
12. As with the rigour of randomised controlled trials, there must be robust methodologies for turning real-world data into real-world evidence.

**Building on EMIF, now is the time to debunk the mantra that data is the new oil and demonstrate that it is an infinite reusable resource.**

## Session 1

### Supporting a Data-Driven Patient Journey in Europe – How Can Member States Help Drive Results?

At the third meeting of the European Medical Information Framework (EMIF), held in Tallinn, Estonia, at the end of June, researchers and contributors put patients and the role of patient data in driving improvements in healthcare centre stage.

Given the title 'Digital Citizen, Digital Patient', it was particularly appropriate that the meeting was held in Estonia, a country widely held to be a leader in e-government and e-health.

Soon after taking on the mantle of the EU Presidency for the period July to December 2017, the Estonian government put the EU Digital Agenda at the heart of its programme.



“Estonia is a digital leader and many people have come here to learn how Estonia did it, and how they are using it to improve healthcare”, said **Bart Vannieuwenhuysse, Quantitative Sciences, Janssen Pharmaceutica and coordinator of EMIF**, welcoming delegates.

The central aim of EMIF is to allow for the secondary use of patient data by creating a catalogue of data repositories and putting in place standards for their access and use.

The objective is to speed up the development of new, effective treatments. Such a patient-centric approach is becoming ever more important. “The patient role is expanding; patients want to get involved, and they are actively involved”, Vannieuwenhuysse said. “The patients are the partners.”

The pharmaceutical industry is also waking up and directing more attention to patients, not as passive subjects, but as active participants; for example, involving them in designing trials.



This increased level of patient engagement creates an ever-greater imperative to extract value from the data that is generated, e.g. by allowing its secondary use.

Over the past five years EMIF has brought together patient groups, pharma companies, academics and others to establish mechanisms for doing this.

“The vision is to be the trusted European hub for healthcare data intelligence, enabling new insights into diseases and treatments”, said Vannieuwenhuyse.

EMIF underpins the continuum from cataloguing data resources, to individual assessment to ensure a dataset is right for a particular project, to access and use of data in an ethical way.

There are three components set up to provide practical demonstrations that the framework established by EMIF is functioning effectively and supporting the secondary use of data, namely the underlying platform for managing data access and two targeted projects around Metabolic Diseases (EMIF-Metabolic) and Alzheimer’s Disease (EMIF-AD).

These two projects also demonstrated that applying real-world data advances knowledge, Vannieuwenhuyse said.

It is clear that every encounter between the patient and the healthcare system should be an opportunity to learn and EMIF is an important building block in making this a reality.

Member states can help by creating an ecosystem that is inclusive and conducive to data-driven health innovations.

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The Estonian Government has put advancing the EU’s Digital Agenda at the heart of its programme for the EU Presidency, which has provided a unique opportunity to showcase the country’s leading position in public e-Services and to promote new applications for the data these services generate.

“Data will drive innovation in as yet unknown ways”, said **Ain Aaviksoo, Deputy Secretary General on e-Services and Innovation at Estonia’s Ministry of Social Affairs.**

In health, big data will fuel artificial intelligence and machine learning, sparking conceptual and methodological changes in how clinical research is performed and how care is delivered.

Rather than being subject to the system, citizens will be “truly in control” of their health and data, and healthcare can become “an asset, not a cost” for public budgets, Aaviksoo said.



Member states should work together to create an ecosystem that gives people control over their data and that enables its secondary use.

That Estonia is ahead of the field in making use of data from e-Services rests to a large extent on the high level of trust that people have in digital government services. This trust is “unique”, Aaviksoo said. “It rests on the fundamental principle that I as a citizen have control of my data.”

Individuals have access to all the data held on them in government databases, can control who uses the data and when, can delegate access and control, and can monitor individual requests to use their data.

The system of checks and balances means there is no possibility of systemic failure, said Aaviksoo.

There have been concerns that the EU Data Protection Regulation, with its tighter rules on the handling of personal data, could hold back digital healthcare when it comes into effect on 25 May 2018.

However, Aaviksoo said, “It won’t spoil the party. Having clear rules will make doing these things easier in Europe”.

He noted also that member states agree there should be collaboration on a pan-European data infrastructure to allow the secondary use of data for broad impact research between academia and industry. “This is a boost for EMIF”, he said.

### Digital Society Trust Recipe

Even given clear and consistent regulation, trust comes over time, and depends on good communication and transparency.

As one example, public support for the Estonian Genome Foundation rose from 18 per cent in June 2001 to 61 per cent in April 2017. Trust increased even though there were more and more instances of the data being used by third parties.

From this, Aaviksoo proposed a “digital society trust recipe”, with the ingredients of technology, a specific legal framework and strong data governance. The exact recipe will vary country by country, but in all cases, it should be predicated on “the understanding that we serve the people and they are part of the game”, Aaviksoo said.

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### **How data helps in responding to profound changes in the world of healthcare – the view from the Innovative Medicines Initiative**

EMIF is self-evidently about facilitating reuse of patient data, and indeed the themes of patients and data run through all the research backed by the EU’s two Innovative Medicines Initiative (IMI) programmes, under which € 2 billion went into 59 projects from 2008 – 13, and now, in IMI2, with a further EUR €3.3 billion to be is being invested in IMI2.

Half the money comes from the EU’s Horizon 2020 research programme in the form of grants to academics and SMEs, while the remainder comprises in kind contributions from pharmaceutical companies that are members of the European Federation of Pharmaceutical Industries and Associations.



IMI’s research aims to accommodate and capitalise on four issues that are driving profound changes in healthcare: the shape and rise of genomics and the digitisation of biology; the epidemiology of disease and the rise of international outbreaks of infectious disease; the role and behaviour of patients as the consumers of healthcare; and the unsustainable costs of healthcare systems as they currently operate.

“We all have to adapt to these four drivers”, said **Pierre Meulien, Executive Director, IMI.**



By creating an environment where pharma, academics, patients' groups and health bodies can collaborate, IMI is providing the means both to manage the impact and to capitalise on the outputs of these changes.

"IMI is unique for its unprecedented sharing of data, not only among companies, but also among public sector partners", Meulien said.

In particular, there is a focus on high unmet needs, with Alzheimer's Disease being a good example. In addition to the €250 million invested in its own projects on the disease, IMI has created links to another EU Flagship project, the Human Brain Project, as well as to the UK's Dementias Platform and to the Global CEO Initiative on Alzheimer's Disease.

As EMIF-AD has demonstrated, pooling clinical cohorts is bringing the power of numbers to Alzheimer's research, and as Meulien noted, IMI has developed a comprehensive data strategy to underpin all its work in Alzheimer's research.

The aim is to improve understanding in four key areas:

- What are the underlying causes?
- Who is at the greatest risk?
- How can clinical trial design be improved?
- How can brain scans improve diagnosis and treatment?

"There is a lot to be linked up," Meulien said. "Data is everywhere, not just research and clinical data, but environmental data, as well as data from biosensors, mobile devices, patient-reported outcomes and wearable devices."

The opportunity to generate new insights by merging data from clinical research and healthcare creates the requirement to scale-up access to combined data sources across Europe.

In support of this, as part of its Big Data for Better Outcomes programme, IMI is about to launch a call for a European Health Data Network – a five-year project to improve interoperability by converting datasets from across Europe to a common format and standard, so that they can be used within a federated network.

As an example of the value of data sharing, Meulien referenced the PROactive project in patient-reported outcomes in chronic obstructive pulmonary disorder. The project developed patient-reported outcome tools for measuring the level of physical activity and difficulties experienced during exercise, which ultimately encouraged patients to be more active.

The tools have since been used in six clinical studies, involving thousands of patients.

Similarly, the €25 million Radar CNS (Remote Assessment of Disease and Relapse in Central Nervous System Disorders) project is developing wearable devices to help prevent and treat depression, epilepsy and multiple sclerosis.

In terms of applying such digital technologies to healthcare, “We are just at the beginning”, Meulien said.

In addition to the matter of how technologies are applied at scale and how healthcare systems must be reshaped to respond to alerts from digital health systems, there is no comprehensive regulatory system as yet.

Questions to be answered include: Who validates devices and on what basis?; What are the data quality requirements?; Who has stewardship?; Who develops the standards? and What is the business model?, said Meulien.

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### Supporting a data-driven patient journey in Europe – How can the Commission help member states?

The European Commission takes a ‘health in all policies’ approach to healthcare, which helps to explain why its Directorate of Communications, Networks, Content and Technology has a unit dedicated to e-Health, Wellbeing and Ageing.



The unit contributes technical knowledge to overall health policymaking and also works to show how healthcare can benefit from the application of various technologies such as robotics, artificial intelligence, high performance computing and big data, **Terje Peetso, Head of Sector, e-Health and Ageing Policy**, told delegates.

In Horizon 2020, ICT for health secured €1 billion of funding for research, including into the use of big data to inform public health policies, digital security in healthcare, patient empowerment and in silico clinical trials.

Peetso's unit is now pulling together the work plan for Horizon 2020 for the period 2018–20 and is starting to scope out its successor, Framework Programme 9.

Among other initiatives through which the European Commission is helping member states to drive the digitisation of healthcare, Peetso cited the 2012–20 e-Health Action Plan, the Directive on Patient's Rights in Cross-Border Healthcare, work on setting standards to promote the implementation of mobile health devices, the Data Protection Regulation and the Digital Single Market strategy.

An important aspect of the Commission's work is in helping member states to avoid duplicating research and to ensure projects are able and encouraged to cooperate with each other. Another role is to promote digital literacy and health literacy, in order to encourage appropriate and safe uptake.

"Fewer than 50 per cent of citizens are sufficiently health literate, so there is a lot of work to do", Peetso said. "If you look something up on Google but don't understand what you found, it is a risky business."

Further supporting deployment, the Commission has put the spotlight on interoperability and the requirement to raise awareness of the benefits of digital health for doctors, patients and governments.

"We're not doing things in the same way", said Peetso. "[Digital health] changes things and that's why there is resistance."

As a recent offshoot of the digital revolution, m-Health is a field in which member states have little experience as yet, either in applying the technology to drive improvements in their healthcare systems or in regulating these products to ensure they are safe.

Currently, m-Health apps are not regulated. A lot of such apps tend to be downloaded but not used, or maybe used for a short time only, implying that the quality of the apps is low and that the potential m-Health holds to improve health and wellbeing is far from being realised yet.

As an example of the possible dangers of the regulatory void, Peetso cited a study involving melanoma apps in which four apps failed to spot harmful lesions.

In terms of unmined potential, fitness apps that count steps are a good way to track activity levels, but in patients with depression these can also provide important information for clinicians that is not available otherwise. For instance, the app might reveal how "you were feeling well on the day you

went to see the doctor, but not the day earlier, when you only did 100 steps in your house”, Peetso said.

Building on its Green Paper in m-Health, the Commission has set out a code of conduct for the use of apps that is currently under review by member states.

An update of the Commission’s Digital Single Market strategy, published in May, highlighted patient access to data, the creation of a data infrastructure to facilitate research and clinical practice, and better ways of getting patient feedback, as three areas where progress is needed in e-Health.

The three are all equally important. The Commission wants to encourage member states to work more closely in this area. Given this, “the Estonian EU Presidency digital health priority is very timely and very welcome,” said Peetso.

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## **PANEL DISCUSSION**

### **1. How can digital health apps be linked to drugs to provide real-world evidence of efficacy to inform marketing authorisation applications and reimbursement decisions?**

Before the idea is taken forward, there must be clear evidence that the drug/app combinations provide better data. There is a programme of testing and adoption of health apps in Germany, while in the UK there are apps that are reimbursed. Meanwhile, Estonia is also carrying out an assessment of how digital health apps can support a move to value-based healthcare.

However, the field is at an early stage and the value of apps can vary widely, from one that gives a prompt to the user to take a medication, to one that gathers data and actively makes a diagnosis.

### **2. What does it mean for patients to be in control of their data?**

This means providing a system that supports people and allows them to decide what happens to their data on an ‘as and when needed’ basis. There may be broad consent, for example on joining a biobank, or it may be about giving consent to use data in specific projects, but the key point is that citizens, not companies or governments, decide what happens to their data

### **3. If the patient is at the centre, who pays if they ask for the most expensive treatment? Or if they choose a specific treatment and die, who is responsible?**

The question misses the point – which is that control in this sense is about giving permission to use data. Clearly, sharing data to generate new knowledge cannot harm anyone.

Sharing will increase understanding of the profile of patients who are likely to respond to particular drugs. This could lead to those who are likely responders getting access to expensive drugs.

That in turn would lead to outcomes-based reimbursement systems, in which pharma companies are only paid for successful treatments.

#### **4. Is there a possibility of sharing specific types of data without permission?**

That is a question that would only be posed in the absence of trust. Rather than singling out categories of data that can be used without consent, the focus should be on getting consent beforehand.



#### **5. What influence do patient groups have in reality? Is the patient perspective truly being factored in?**

There is a feeling that signing up a patient group to contribute to a study is a box-ticking exercise. Patients groups report not feeling part of the team. However, the situation is evolving as academics and industry begin to see the value in factoring the patient experience into research and using it to inform them of the choice of endpoints.

When you integrate patients into projects and listen to them, that changes how things get developed.

## Session 2

### Patient-driven Data Generation – What Are the Evolving Trends and Opportunities?

The Connected Health Cluster in Tallinn brings together more than 70 partners from universities, pharma companies, biotechs, medical equipment SMEs and user groups to capitalise on Estonia's digital resources, to develop new products and services, and foster the creation of start-ups.

“We are helping companies to develop products and to export, and are making Estonia a great place to found and grow healthcare businesses”, said **Külle Tärnov, Connected Health Cluster Manager, Tallinn Science Park Tehnopol.**



To promote e-Health exports and their application within Estonia, the Estonian EU Presidency will be promoting the adoption of the free movement of data as the fifth freedom, to add to the EU's existing fundamental freedoms of free movement of people, goods, capital and services.

This would give all member states common access to digital services, including e-Health products.

Within Estonia, the Connected Health Cluster is involved in creating a framework to allow doctor-to-patient telemedicine to be reimbursed. The effort includes motivating doctors to implement telemedicine systems,

building the IT and service development skills of healthcare professionals and the healthcare know-how of IT people, developing a certification process and integrating data from telemedicine into broader healthcare.

“The idea is not to work case-by-case, but rather to open up the data for companies, with patient consent, so that the state does not have to be in the way”, said Tärnov.

As a potent example of how the cluster is promoting commercialisation and improving healthcare, Tärnov described a project that aimed to cut Estonia's high rate of HIV infection.

Following a workshop in June 2016 that identified the reasons for the high infection rate, the causes were outlined to tech companies, which were then given access to patients and doctors to explore the issues further.

By August, a number of possible solutions were put forward, of which seven were validated in a hackathon. Following this, three of the possible solutions received three months' funding to move from idea to prototype.

From these, Diagnostic Match was the overall winner for its automated decision support platform that helps general practitioners identify patients who may be HIV positive through indicator diseases and symptoms. This allows doctors to suggest to people who are unaware of their status that they should take an HIV test.

In second place was hINF, which involved development of a digital appointment system that allows people who are HIV positive to consult their doctors from home.

The power of both these solutions lies in the fact that they are based on actual problems experienced by the doctors and patients, who were also involved in development of the two products. "We worked with all the users", Tärnov said.

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Patient-driven data generation does more than joining the dots between consultations, it fills the data void too, as **Elin Haf Davies, Founder and CEO of aparito Ltd., UK**, told the meeting.



Her experience of nursing paediatric patients taking part in clinical trials has made her acutely aware of the episodic nature of traditional data capture. "Patients go from consultation to consultation and their doctors usually don't know what has happened in between. Parents say doctors don't see the good and the bad days", Davies said.

The limitations of episodic data capture moved Davies to found Aparito to develop

wearable devices connected via smart phones, enabling real-time remote monitoring and data collection. Working with patients and doctors, these are tailored to specific needs and an understanding of what needs to be monitored in particular conditions.

In an ongoing study sponsored by the US National Institute of Health, 77 per cent of patients continued to wear their Aparito devices seven months into the trial. Of these, 87 per cent also responded to quality-of-life questions.

“The value of recording data in this way is that you move from outputs to outcomes”, said Davies. Clinical study endpoints are often irrelevant to day-to-day life. “The technology empowers patients, who can voice what is important to them.”

The leap from paper-based records to digital data capture and real-time analysis offers huge potential benefits for healthcare systems and the conduct of clinical trials.

As a result of filling the data gaps, it has become possible to bridge the efficacy demonstrated in randomised trials to the effectiveness of a drug in a real-world setting.

Aparito is trialling its device in the US, India and Europe. Having a global product will make it possible to smooth out the variation that occurs between clinical trial centres. “You can eliminate the doctor bias”, said Davies.

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**Melanoma Patient Network Europe (MPNE)** is a potent example of how social media can help patients and advocates gain access to accurate and timely information about the latest developments in a fast-moving field.

Its founder, **Bettina Ryll**, was moved to set up the network following the death of her husband Peter from melanoma. Following his diagnosis in 2011, Ryll was able to apply her expertise as a medical doctor, with a PhD in molecular biology, to understand the state of play in clinical research. Peter joined two clinical studies but died in 2012, just months after the initial diagnosis.

At that point, no targeted therapies or immunotherapies were approved for treating melanoma. Now there are six. But these represent an entirely new class of treatment and there is little experience in their use. “It is hard to get the right drug and also often they may be difficult to access in Europe; it’s not fair”, Ryll said.

Patients need information, but as Ryll appreciated, this can be hard to source and interpret. “I wanted to transform access to medical information across borders and culture, so you don’t have to sign up for English lessons when you get a diagnosis”, she said.

While the core content of MPNE’s website is in English, there are country and language-specific groups as well as groups that reflect the concerns of patients at different stages of disease.

Ryll has identified a number of ‘social media connectors’ who are very active and have many followers and who act as nodes to spread information across Europe very rapidly.

This makes it possible to follow problems such as drug shortages and also to collect information from the network to paint an accurate picture of what is happening on the ground.

“We are sentinels: we are very good at picking up problems and trends, for example, pharmacovigilance and access issues”, Ryll said. This is now driving new insights. In pharmacovigilance, the network now has the numbers needed to highlight any rare side effects that may not have come to light in trials.

In one project, MPNE worked with the European Medicines Agency to assess the patient view of the risk versus benefit of experimental treatments. In a pilot study involving stage IV (advanced) melanoma patients, carers and advocates, patients had a higher risk acceptance of risk than carers, while advocates were more risk-averse than regulators.

When incorporating patient preferences into drug development and regulatory decision-making, it is important to have this level of granularity, Ryll believes. “In the end, we treat patients, not regulators or carers.”

MPNE also comments on trial designs and is becoming influential in promoting patient recruitment.

It is frequently the case that patients are not asked what they want. As a network, it is possible to articulate the patient voice and to make it heard. “I

can put issues on a forum and find out what patients want – it's impactful", said Ryll.

One of the most important attributes of MPNE is it being proactive. "If you're not going to do it, no one will. Citizens are taking power into their own hands, not sitting around saying governments should do this", Ryll said.

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**Dainius Pavalkis, Professor at the Lithuanian University of Health Sciences and former Minister for Education and Science in Lithuania**, describes the work of **RISE HL (Research and Innovation Strategic Expert – High Level group)**, a body that gives direct strategic advice to R&D Commissioner Carlos Moedas.



RISE's brief is to suggest how best to use research, innovation and science policy to promote smart, sustainable and socially inclusive growth. It is divided into three subgroups to reflect the policy priorities of Open Innovation, Open Science and Open to the World, which will underpin the next EU R&D programme, Framework Programme 9.

In relation to Open Innovation, RISE has recommended the introduction of a 'Seal of Excellence' for research that is of high quality, but, due to intense competition, cannot get funding from Horizon 2020, where funding

application success rates are a lowly 13 per cent, compared to around 20 per cent in the preceding Framework Programme 7.

The seal will be a marker that the research has been assessed by the European Commission as meriting funding. That will enable researchers to look for other funders, who will be saved the effort of making a full evaluation themselves.

"In Europe, we have a lot of excellent science, but we can't fund it all. The Horizon 2020 budget can only back research at the top of the pyramid", said Pavalkis. "A lot of disruptive innovation is not getting funded."

RISE has also made inputs into the formation, with funding from Horizon 2020, of the European Innovation Council. The Council will take a riskier, venture capital-style approach to awarding grants when it launches in pilot form later this year. "This will bridge research, innovation and business", Pavalkis said.

Pavalkis is a member of the Open Science Advisory group of RISE, which is working to create a culture for Open Science to flourish, namely by removing barriers and promoting incentives in research funding, career progression and science publishing.

“The aim is to open up the research process”, said Pavalkis. A first move would be to remove the extreme competition for limited resources by enabling a Europe-wide view of grant submissions, so they can be assessed by any funding body, while avoiding the duplication of research at national and EU levels.

“Opening up submissions will save money and time”, for both researchers and assessors, Pavalkis said.

The RISE Open Science group has also recommended that funding success rates for highly qualified early career researchers should be increased.

Open science cannot flourish without open access to data and indeed, more and more funders require the researchers they back to publish in open access journals, even allowing them to include the cost of publishing fees in their grants. However, said Pavalkis, while there has been progress in other disciplines, the situation in terms of open access is not so good in healthcare, where too much data is hidden behind paywalls.

In academia, journal publication typically equals career advancement. That can motivate scientists to salami-slice their research. The result is an output of 2.5 million scientific papers per year.

However, quality not quantity should be the driver, Pavalkis said. “We should limit the number of articles you are required to have to get European Research Council funding.” That would remove the perverse incentive to publish as many articles as possible and would help deliver “steak not salami,” he said.

Requiring data to be open for reuse raises many questions, not least how to change the mindsets of scientists who have devoted long hours to its acquisition, and how to make them see there is a return from sharing.

There are also challenges related to data management and curation, creating an infrastructure – in the form of the European Science Cloud – for accessing data, ensuring the supply of skills and setting out career tracks for scientific data and software specialists.

To promote open science, RISE has recommended that the criteria to be applied for assessing researchers should reward openness in reagents, protocols and data sharing.

A potentially very important development in terms of fostering an open science approach to health research is the proposal to establish a European Health Research Institute. This would increase the opportunities for translating basic research, promote its societal and economic benefits and create a platform for member states to perform interdisciplinary science.

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## PANEL DISCUSSION

### 1. How much hostility is there to the idea of open science?

Everyone likes to keep their research in their own pockets, so there is not much support from researchers yet, but there is from funders and governments.

### 2. There is often a redundancy of investment, so how do you balance streamlining against the opportunity to promote disruptive innovation?

While there are three times more researchers in Europe than the US, their output is similar. If productivity was not measured solely by the number of papers, but on getting involved in translational research and moving into applications, more innovation would be sparked.

At the same time, peer review militates against novelty, because the known quantities tend to get funded. This cycle needs to be broken.

Another avenue is to reclaim the 3 per cent of science funding that goes to private journal publishing companies by cutting the number of publications needed to get grants and by changing the rules of career advancement.

### 3. How much sharing of data are patients prepared to do?

This varies according to the disease areas. Those involved in rare diseases obviously have a huge motivation to share data and ensure the patient voice is heard. There is evidence that patients who share data live longer, with a recent study showing that patients with advanced cancer being treated at home suffered fewer serious side effects when they had the means to communicate any problems directly to their healthcare providers.

Patients want to be able to generate and share data according to their needs. Depending on the stage of disease, they may want to know about ongoing clinical trials or to share information about their quality of life to feed into reimbursement decisions

#### **4. Who owns the data – the citizens as patients, the healthcare providers or the government?**

That may be an irrelevant question. What matters is not ownership but control. In nearly all other spheres, it is possible to get access to data, but not in healthcare. The priorities for access to healthcare data should be set out from a societal perspective, with the aim of helping healthcare systems to become sustainable and to break out of the current vicious circle of doing research on cohorts that does not reflect the real-world patient population.

#### **5. There have been pockets of success in digital health, but how can this be scaled up to a system level?**

With so many initiatives across Europe's healthcare systems, one barrier is the 'not invented here' syndrome. Researchers trialling digital health applications want to ring-fence their work until after publication, creating a barrier to openness and scalability.

If patients had greater understanding of the potential benefits, this could generate the impetus to scale. Rather than worrying about whether it is safe to share their data, they would appreciate that doing so reduces the risk of medical errors and would help them to get the best treatments.

Medical professionals too must be ready to change. They hold the keys that could unlock the doors to digital health, but they tend to be conservative.

Progress in making more, trustworthy, sources of information available to patients and helping them understand what information they can rely on is starting to generate a virtuous circle. There will be further change as the age profile of the medical profession shifts to younger professionals, who were brought up in a more digital age. For example, there are some doctors now discussing individual cases with virtual colleagues on closed Facebook pages.

A further incentive to scale digital health applications would be to stop rewarding doctors and hospitals for activity, and instead to use the analytical power of digital health to reward them for outcomes.

## Session 3

### Incentivising the Sharing of Stakeholder Health Data – What works?

Decisions about what medical data to share may be personal, professional or competitive, but the fact that data sharing affects all of us as individuals is brought into sharp relief by the example of how EMIF-AD is advancing research in Alzheimer's Disease.

With so many unknowns, large clinical datasets are needed for studies on the aetiology of the disease, for understanding its prevalence and the effects of experimental therapies, and for the selection of subjects for clinical trials.



As **Pieter Jelle Visser, Clinical Epidemiologist at Maastricht University**, explained, Electronic Health Records are of limited utility because they date from the diagnosis, whereas there is now known to be a 'predementia' period of 20 years, when the pathology is in train, but there are no overt symptoms.

That leaves researchers hugely dependent on a relatively small, geographically scattered population of patients who have taken part in research cohorts.

The good news is that in Alzheimer's Disease, as in rare diseases, researchers are incentivised to share data because it means they get access to a far bigger pool of shared data.

However, there may be constraints in the form of ethical approvals and appropriate consent needed for data sharing, the perceived validity of the research third parties want to do, and the fact that data owners often receive little recognition for their contribution.

"Participants on the other hand – both patients and those who are cognitively normal – want to contribute to advance medical science", Visser said.

Researchers should ensure there is no barrier to that happening, e.g. by asking for broad consent for reuse in bigger studies, to get more data from national registries and to re-contact patients to take part in further studies.

However, just having data available does not make it usable and EMIF-AD has put significant effort into the technical aspects of sharing data, e.g. by creating a common data model and setting out minimal dataset definitions, such as clarifying which memory test was used in assessing a particular cohort.

To guide researchers to appropriate resources, EMIF-AD has produced a catalogue of cohorts that details what information has been collected. It is possible to search for specific patients, for example to find individuals carrying particular genes. EMIF-AD also provides central data storage.

As an example of the kind of analysis that becomes possible as a result of this activity, Visser referenced a meta-analysis of 8,000 subjects from 51 cohorts that was used to assess the prevalence of predementia.

“This shows there is 20 years between being amyloid positive and developing dementia. It would have cost far more to get this data without EMIF”, he said.

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While most of us are taught from an early age that sharing is a good and valuable thing to do, usually that does not lessen the pain when it comes to sharing data. With the ownership of data comes the right to exploit it and to control its flow. At the same time, ownership confers a responsibility to ensure that the data is not misused.

“By digitising information, you increase the scope of ownership, and here the rights and responsibilities may conflict, depending on who is the stakeholder”, said **Alison Bourke, Scientific Director, Quintiles IMS.**

For example, a doctor who makes a diagnosis ‘owns’ it. But if that doctor was supplied with inaccurate information and as result makes the wrong diagnosis, who is at fault?

The motivation for sharing differs from one stakeholder to another. Data donors and data collectors, such as patients’ groups and medical research charities, are driven by altruism, whereas some data collectors and data aggregators do it for financial reward. Data users meanwhile may be seeking career advancement and validation. A common theme is that people share information to get access to more information.

“To promote data sharing, you need to know what motivates people to share”, Bourke said.

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From the perspective of **the Council for International Organizations of Medical Sciences (CIOMS)**, the rise of big data means the research environment is changing at a faster pace than the understanding of the ethical issues that this change presents, said **Lembit Rägo, Secretary General of CIOMS**.



Ethics in healthcare, especially clinical research in humans, is a major focus for CIOMS, a body founded by UNESCO and the World Health Organization in 1949 and that now represents 44 biomedical research member organisations.

In 2016, CIOMS updated its 'International Ethical Guidelines for Health-Related Research Involving Humans' to bring them into line with modern research practice. “These are not specifically tuned to big data, though some of them are relevant to it”, Rägo said. There probably needs to be

more fine-tuned attention to the ethical considerations as clinical research expands from the sole focus on randomised controlled trials to real-world settings.

While most people can agree, it is rational to share, decisions on whether to share personal data are not necessarily made on the basis of rationality, but can involve fear or other emotions. People may be afraid of losing privacy, or that their data will be misused. “Fear is not rational, so how do you deal with it?”. The answer is by using appropriate communication, said Rägo.

It is amazing how much data is being collected from real-world sources, and people are under pressure to put it to use as speedily as possible. However, said Rägo, the application of big data is still at an early stage. “We are sitting on a huge potential”, he said.

In CIOMS' second major area of focus of pharmacovigilance, digital health offers the prospect of huge improvements. To date, most pharmacovigilance is based on the passive reporting of adverse events, which usually says nothing about what happened in the run up to the event or after it occurred.

In future, electronic health records will provide richer and more mature feedback about interventions. “You can’t guarantee safety before launch. If you had electronic health record data you could spot problems faster”, Rågo said.

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The lifecycle of a drug goes hand-in-hand with an associated data lifecycle, with different types of information being generated, collected and analysed at the different stages of discovery, development and deployment.



Pharma companies driving the product lifecycle cannot amass all this data alone, said **Nigel Hughes, Scientific Director, Quantitative Sciences, Janssen Research and Development**. “They need access to external data”, along the continuum from early discovery, where information about the biology of a particular condition is central to shaping the product profile, to pharmacovigilance data that is reported for as long as a drug is registered.

During clinical development, having access to external real-world data can inform a more strategic approach to inclusion/exclusion criteria and patient and site selection. “There is competition for resources in conducting clinical trials and you could use real-world data to expand the space here”, Hughes said.

Although the product lifecycle encompasses a huge variety of data – from target biology to pharmacovigilance – in the end, data is of only two types. “There is the data you own, and the data you don’t own”, Hughes said. “The issue is to get connectivity between the two.”

Quite naturally, for pharma, the focus is on data it owns and on which it also has intellectual property rights. But real-world data not generated by the industry is crucial too. “How do you interact with it, connect to it, work with it?”, said Hughes.

The data you do not own creates the greatest challenge, both in terms of societal issues around allowing the industry to have access and the technical hurdles to doing so.

“All use of data has to be around a quid pro quo: what’s in it for me; what’s in it for you”, Hughes said. People can be persuaded to do things when it is in their self-interest. “You need to understand the drivers.”

The nature of the beast of big data creates its own imperative to collaborate, Hughes believes. “It is expensive to pull big data together – no one organisation can do it themselves. We have recognised that in pharma and that is one reason IMI is so important.”

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## **PANEL DISCUSSION**

### **1. Is it right to think that patients are only motivated by self-interest and that they only share data because they have a concrete need?**

It is true that people are incentivised to share data if they are ill, but there is also a need to appeal to altruistic instincts to incentivise them to share data for other reasons; for example, drug safety or public health.

Those wanting to use such data must show they are trustworthy. It then becomes possible to persuade people to share sensitive personal information; for example, in studying sexually transmitted disease.

To earn trust, there must be good governance – a lot of public health problems are a result of poor communication of the messages and a lack of good governance.

### **2. Would it be easier to incentivise patients to share data if industry was excluded from access?**

You cannot say research is less ethical by default because it is funded by industry – academics are open to conducting unethical research – and if you are ethical it should not matter who performs the research.

If industry were to be excluded, the full benefits of big data would likely not be delivered. Everyone shares the same purpose of achieving better therapies for patients.

### 3. How should we respond if the media misrepresents the objectives and motivation for aggregating and sharing patient data?

At the heart of this is the need to communicate the reasons for allowing the secondary use of data. Governments play a critical role here. Failure to educate the public often leads to mistrust. In a number of cases, governments have decided data sharing would be good for people without asking them. However, here the data is owned by patients and they should be involved in any decisions about how it is used.

To prevent inaccurate media reporting, communication should be built into product development. There should be a consideration of how to communicate the research beyond what is published in a journal and also how to manage any new findings.



## Session 4

### Harnessing Health Data for Managing Patient Benefit–Risk What New Processes Are Needed?

In the drive to improve the collection and use of patient data, the only way to succeed is to work with patients as partners, said **Nicola Bedlington, Secretary General of the European Patients' Forum**, a body representing 74 patients' groups.



“Meaningful patient involvement in the development of services and in decision-making about health data is essential for the digital age and the big data era”, Bedlington said.

Patients' expectations of digital healthcare are that it will be patient-centred not disease-centred and will offer a better integration of different services. Patients will have the means to become involved in their care as equal partners with providers, and outcomes and value will be assessed from a patient's perspective. This will improve chronic disease management and lead to a better quality of life.

All of which begs the question, “What is patient-centred data?”, said Bedlington. It means that any data which is gathered should take account of patients' preferences and perspectives. Metrics, such as patient-reported outcomes, experience or incident measures, must be co-designed with patients, based on patients' priorities.

“Outcome measures should include measures defined by patients themselves of what really matters”, Bedlington said. EPF is currently working with the OECD on the PaRIS Initiative (Patient Reported Indicator Surveys), helping to define the right indicators.

In terms of the reuse of their data for health research, Bedlington said patients are generally willing to share data to help peers, the wider society and future generations. But, she said, there must be a trusted environment. “We can never be cavalier about data security. There can be bad repercussions if data gets into the wrong hands.”

For meaningful patient involvement, there must both be better health literacy and a greater understanding of how the patient perspective of benefits and risks can best inform decision-making. “Patient involvement matters – it is needed for the determination of the true value/added therapeutic value of treatments”, said Bedlington.

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Even as the 50,000th genome-wide sequence was being added at the end of June, the Estonian Biobank was already on the way to opening up the potential of ‘omics’ data in healthcare and public health.

The power of the Biobank lies in the numbers – it will include sequence data and associated plasma and cell samples from 52,000 volunteer participants, around 5 per cent of the adult population of Estonia – and in its connectivity to other sources, including cancer registries, three major hospitals and mortality records.



The Estonian Human Genes Research Act allows subjects to get feedback by right, and the broad informed consent and clear access rules mean the Biobank is operating in line with open research, said **Lili Milani, Senior Scientist at the Estonian Genome Centre, Tartu University.**

The Biobank has demonstrated its worth in genome-wide association studies looking for genes involved in common chronic disease. “We are now using these genetic associations to make risk predictions”, Milani said. One example is in Type II diabetes, where, although obesity is the strongest predictor, genetic factors are also involved. The difficulty is in

teasing out how these factors can be applied to identify an individual's risk of developing Type II diabetes.

By polling data from subjects with and without the disease in the Biobank, "we can now predict who will get Type II diabetes", said Milani. This is important information because the onset of Type II diabetes can be postponed or even partially prevented by changes in the lifestyle of high-risk subjects.

Similarly, the Biobank has been used to determine genetic risk scores for cardiovascular disease and to pinpoint individuals at risk of suffering a heart attack.

Ninety eight per cent of Europeans carry at least one or more mutations that influence how they respond to drugs, and the Biobank is thus being used for pharmacogenomics studies.

Genomics data is now being actively applied in healthcare in Estonia, feeding back information to participants via their general practitioners. This includes informing people if they are at risk of common chronic diseases and about incidental findings, such as identifying carriers of BRCA1/2 breast cancer mutations.

To date, 49 cases of BRCA1/2 mutations have been uncovered. "Of 20 women contacted so far, only four knew they had BRCA", said Milani. "We are now reaching out to family members to test them too."

Milani said, "We are piloting personalised medicine on a national scale and using genomics data for the public health prevention of common diseases, getting [participants] to take control of their own health."

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The EMIF project – with its 58 partners in 14 countries and €56 million of resources – has opened access for researchers to an unprecedented volume of data relating to 40 million subjects.

"That is a huge volume of data sources we are trying to unlock", said **Johan van der Lei, Head of the Department of Medical Informatics,**

**Erasmus MC, University Medical Centre, Rotterdam.** New processes are



urgently needed to extract value from these databases. “We have moved quickly from data starvation to data overload, without a period where we had just enough data to work out how to use it”, van der Lei said.

The challenge in this morass is how to find the best data to answer specific research questions. To be able to do this, it is necessary to understand why any particular dataset was collected.

Within EMIF, data stays local, and that is where governance occurs and data is de-identified. There is a common ontology and data model and information from data owners on how their systems work.

There are some technical issues, but IT is not the limiting factor in combining databases, said van der Lei. However, he said, EMIF is facing a reordering of the socio-technical construct of how data is used, what is driving the agenda behind the scenes and how roles and responsibilities are changing. “This affects everybody across the piece”, van der Lei said.

The aim should be to foster the development of a “learning healthcare system” that promotes continuous improvement and innovation and where knowledge is captured as an integral as a product of healthcare delivery. It will take a considerable amount of homework to develop the processes required to reach such a state of grace.

Patients, as the owners and controllers of their data, must recognise that rights come with duties. For example, anyone who is HIV positive must disclose this if they visit an accident and emergency department. There should be no free rides, such as people opting out of vaccination programmes, because that puts society as a whole at risk, said van der Lei.

In addition, new processes are required for a better analysis of data and how to promote the acceptance of evidence by regulators and payers. They are under increasing pressure to use real-world data but as yet are not convinced the processes for generating and interpreting such data are stable enough, van der Lei noted.

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Europe's health technology assessment (HTA) agencies are currently making recommendations on whether or not therapies should be reimbursed on the basis of randomised controlled trials of efficacy, whereas what they really need is real-world evidence of effectiveness in their patient populations.

“There are often uncertainties about therapeutics”, said **Wim Goetsch**, **Director EUnetHTA JA3 Directorate of the Zorginstituut, The Netherlands**, when

discussing the practicalities of applying real-world data in effectiveness research.

The question is how real-world data can be gathered across the life cycle of technologies and applied to bridge the efficacy–effectiveness gap. One of the first hurdles to overcome is that there is no agreed view between different stakeholders on what constitutes real-world data. Rather than getting hung up on the broad definition, Goettsch suggested it is more appropriate to identify the specific information that HTA agencies need to make their assessments.



A study involving six HTA agencies found that currently they are using real-world data in different ways, such as to support initial reimbursement decisions, in pharmacoeconomic analyses and in conditional reimbursement schemes. As things stand, there is no systematic approach to applying real-world data for HTA for decision-making and also access to such data remains low.

There has been little opportunity to conduct sophisticated analyses to demonstrate the value of real-world evidence in comparative effectiveness research and in general there is limited trust in the validity of real-world evidence among decision-makers.

“There are problems in moving forward”, said Goettsch. Collaborative effort is required to promote better governance. Real-world data will become important, but first there must be more clarity and insight on its use.

At the same time, the quality of real-world data is a crucial issue, Goettsch said. “We need transparent reporting of real-world data studies and guidelines for the interpretation of such data and to ensure acceptability for decision-making, there must be more interaction with the final decision-makers.”

## PANEL DISCUSSION

### **1. Can behaviour changes be instilled in people who are told they have high genetic risk factors?**

There are a number of studies that indicate people would change their behaviour, and the Estonian Biobank is tracking whether this is truly the case in participants who are given such information. There has been some positive feedback; for example, in the case of a deletion that causes slight mental retardation, some people told they had the deletion expressed relief because they finally understood why they could not cope with higher education.

In another example, the mother of a woman who died at 40 years of age from breast cancer found out via the Biobank that she was a carrier of BRCA mutations, allowing her granddaughter to be tested.

Also, it is not just a case of making people change their lifestyles. The Estonian Biobank is working with the Ministry of Social Affairs and with hospitals to incorporate their findings into treatment schedules, if intervention is required.

### **2. How is HTA interacting with the European Medicines Agency in the application of real-world data?**

For products that are being fast-tracked through the EMA, there will be more questions to answer post-marketing approval, and real-world data will then become more important in demonstrating safety and effectiveness. HTA therefore needs to be aligned with EMA. There are issues around how the use of real-world data will be funded; one approach is to charge pharma for access to registry data.

### **3. Is it possible to link different real-world data sources to get a 360-degree view of an individual patient?**

Linkage per se is not technically difficult, the problem lies with the rules and regulations – linking up different sets of data relating to a single individual would mean that, de facto, the data was no longer anonymous because you need the name to link the sources. And as things stand, it is not feasible to go back and get detailed informed consent to allow linkages to be made.

## Conclusion

The work the European Medical Information Framework (EMIF) has been performing in promoting interoperability, agreeing a governance structure and compiling a catalogue of relevant data repositories has both opened the way to data sharing among researchers and established a role model of open science in action.

EMIF has made data resources visible, created a centralised system for granting connectivity and put in place interoperability standards.

All this helps makes the data usable, allowing researchers to pull together information from diverse data sets, and to answer questions that could not be answered before.

Pulling together and analysing historical data from diverse data sets can generate new insights and provide the foundation for future research, in which real-world evidence from wearables, patient reported outcomes and so on can be captured and fed into analyses, providing the building blocks for patient-centred healthcare.

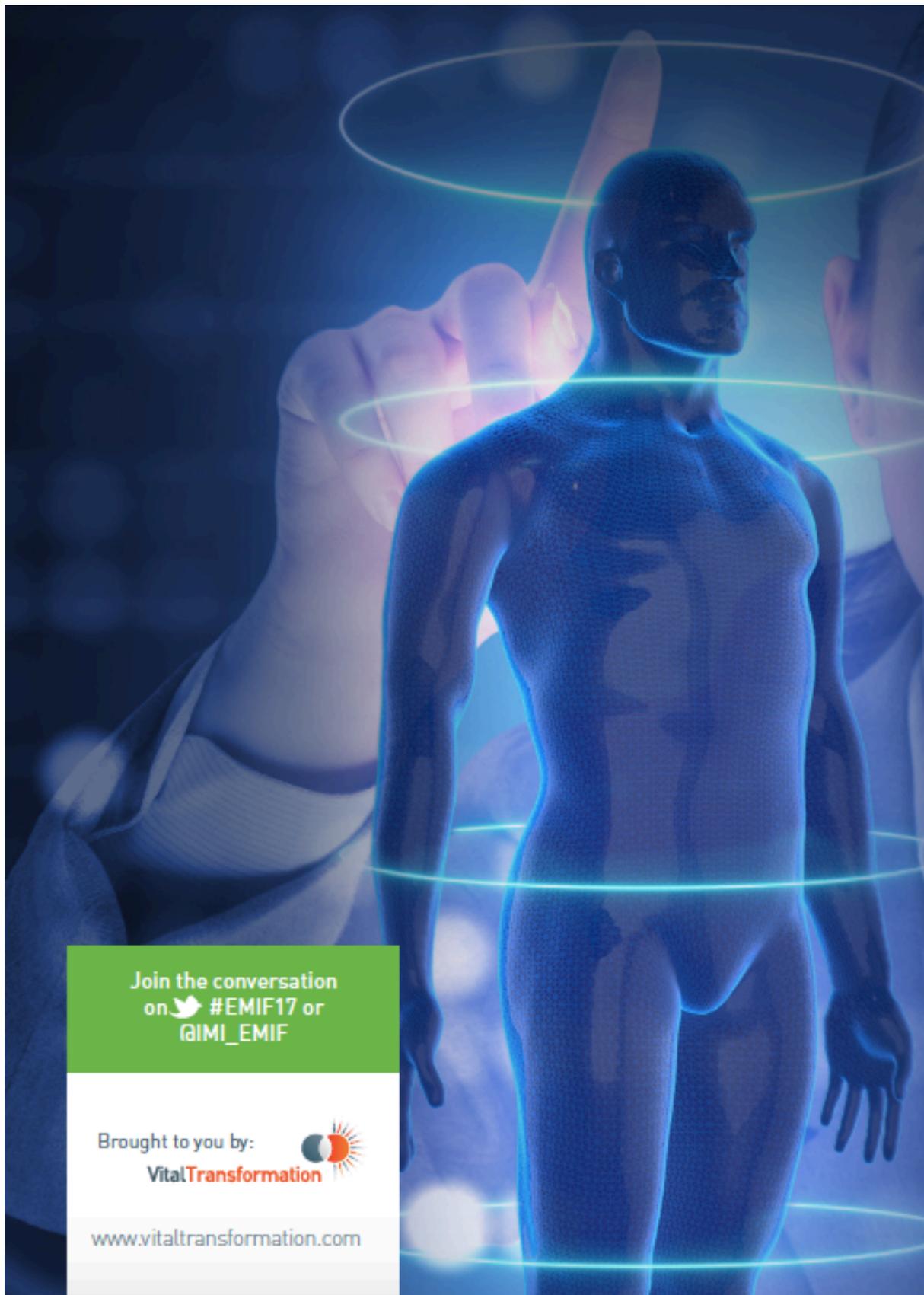
At the same time, EMIF-AD and its counterpart EMIF-Metabolic have created model frameworks for data sharing in other fields, demonstrating how EMIF can be applied to other disease areas. Informed by such analyses, researchers can request stored biological samples relating to specific research cohorts.

The principle of open science is laudable, but it can be hard to put into practice. Researchers who have spent an entire career creating and curating a data repository may understandably be reluctant to give others access. Even for the willing, sharing is time and resource consuming.

EMIF is significant then, in providing a means for data sharing and also for demonstrating the value of sharing.

In addition, EMIF has created a space for collaboration between academics, clinicians and pharma, which is promoting the translation of publicly-funded research.

Now it is time to take the work of EMIF forward to real-life applications that maximise the contribution data reuse can make to the development, assessment and uptake of new, effective treatments – and to make healthcare truly patient-centred.



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