**innovative
health
initiative**

IHI 2023
In Focus

Annual Report
Summary

COCIR
Advancing Healthcare

efpia

EuropaBio
The European Association for Bioindustries

MedTech Europe
from diagnosis to cure

Vaccines Europe

Co-funded by
the European Union

Contents

Foreword

In 2023, IHI's ambitions became reality as the first projects got underway. Grant agreements were signed for 16 of them, launching the IHI portfolio.

As a true partnership of public and industry actors, the IHI programme is unique globally. Each of IHI's interdisciplinary project teams are composed of diverse experts, including medical researchers, healthcare practitioners, patients, and health industry representatives.

IHI's ambition to foster truly cross-sectorial research for the long-term sustainability of the European health industry can be seen in the calls launched during the year: in addition to topics on novel methods for combining diagnostics and treatment and patient-centric care, we also launched two exciting topics on sustainable-by-design solutions for healthcare products and new manufacturing methods in the circular economy.

We must now turn our attention to creating partnerships that ensure the long-term uptake of project outcomes. In 2023 the IHI Patient Pool was established and as we move forward, they will be an important part of IHI — both in discussions on individual projects and for the shaping of the overall programme. We are also looking to deepen the connections with other important actors: regulators, health technology assessment bodies, and national and regional healthcare systems to help embed project outcomes in European healthcare.

Over the next few years, I am excited to see how our community grows and evolves. There are a lot of intriguing topics in the pipeline where we can expect to see innovative projects made up of strong public-private collaborations emerge. The future is bright — if we work together, we can tackle these cross-sectoral challenges to improve the European health sector and benefit patients' lives.

Niklas Blomberg
IHI Executive Director

Highlights of the year

2023 marked a significant milestone – the launch of the first IHI projects. We're excited to see these new projects kick off – the IHI portfolio covers key challenges in health research that will benefit from our public-private, cross-sector approach.

Our new projects are investigating the use of big data, imaging and diagnostics to advance cancer diagnosis and treatment, creating new digital platforms to improve the care of people with neurodegenerative diseases and other health problems, and developing screening platforms to identify people at risk of or in the very early stages of a disease.

During 2023, we also launched two more calls, searching for innovative proposals that aim to:

- reduce the environmental burden of the health sector
- cut down on the number of animals used for research
- improve the care of stroke patients
- increase the involvement of underserved patient populations
- speed up the development of treatments for rare diseases
- improve the experience of blood tests
- advance the potential of synthetic data in health research
- explore theranostics (in which a diagnostic test and therapy are twinned)

A warm welcome to our new Executive Director, Dr Niklas Blomberg, who was appointed in summer 2023. With experience in both the public and private sector in leadership and research roles in Europe's life sciences sector, he took the helm of IHI in January 2024.

Involving patients in health research leads to better and more patient-friendly innovations, and IHI set up a patient pool composed of 120 people that can be called upon to share their knowledge for various activities. Members of the pool may be invited to participate in project meetings, scientific events, webinars, or trainings organised by IHI, and IHI will turn to the pool if patient / caregiver expertise is needed in core activities such as the evaluation of proposals, reviews of ongoing projects, and discussions on future funding opportunities.

Working better means working together, and IHI signed a Memorandum of Understanding (MoU) with EIT Health in 2023 that will facilitate collaboration and allow the two organisations to leverage their strengths, networks and expertise to create a platform that supports healthcare entrepreneurs, researchers, and professionals across Europe.

IMI's projects are continuing to deliver strong results that highlight the value that public-private partnerships deliver when it comes to health research in challenging cross-sectoral areas. The benefits derived from our collaborative partnerships last beyond the project's end, as demonstrated by many of our successful sustainability stories.

For example, the ITCC-P4 project has developed a spin-off company to make its results available to the wider research community over the long term, and similarly the conect4children project has launched a non-profit foundation to continue delivering services that will support the conduct of paediatric clinical trials.

In terms of administration, we continue to perform well, with good results on budget execution and achievement of all key targets relating to the management of calls and payments.

IHI's first projects

2023 marked the first year that IHI projects started, so here's a brief overview of our new projects and what they set out to do!

The IHI portfolio, by subject area and SRIA objective (So)

Subject area	SRIA objective	Projects
BRAIN	So 1 — Determinants of disease	AD-RIDDLE, PREDICTOM, iCARE4CVD, EDENT1FI, GRIPonMASH, LIVERAIM
CARDIO-METABOLIC	So 2 — Integrated solutions	CLAIMS, PROMINENT, COMBINE-CT, GUIDE.MRD, IMAGIO, SASICU
ONCOLOGY	So 3 — Patient-centricity	PaLaDIn
HEALTHCARE OPTIMISATION	So 4 — Digitalisation & data	IDERHA, IMPROVE
REGULATORY	So 5 — Value assessment	HEU-EFS

So 1
Determinants of disease

▶ AD-RIDDLE 🔗

The **AD-RIDDLE** project aims to revolutionise the way Alzheimer's disease is detected, diagnosed, prevented, and treated. It will do this by delivering a 'toolbox platform' of validated resources with resources designed for patients, caregivers and healthcare providers. This toolbox platform is designed to be modular and customisable, allowing health systems and healthcare providers to tailor component tools to the unique needs of different settings and practices. It will offer a digital community engagement portal including self-guided assessment tools for people concerned about their dementia risk, as well as an array of screening and diagnostic tools to support healthcare providers.

▶ PREDICTOM 🔗

The goal of the **PREDICTOM** project is to develop a screening platform capable of identifying people at risk of dementia, before the first symptoms appear. Crucially, patients would be able to start the screening process from the comfort of their own homes. They could collect samples of bodily fluids, and use digital technologies to gather results (e.g. smartphone-based eye tracking and cognitive tests).

Samples will be sent to the **PREDICTOM** partners' laboratories, and then to the **PREDICTOM** platform for processing of the data. Algorithms based on artificial intelligence (AI) would then assess the person's risk of developing dementia and their prognosis. In this way, the platform will facilitate the early diagnosis of a wider range of people, enabling earlier intervention and hopefully slowing progress of the disease.

▶ EDENT1FI 🔗

Many people are only diagnosed with type 1 diabetes (T1D) when the disease has already caused significant damage. Research efforts to identify people with T1D earlier on in the disease have so far focused mainly on people with a family member with the disease. However, 90% of those diagnosed have no family history of T1D and so are not picked up by these efforts.

The aim of **EDENT1FI** is to change that by setting up a pan-European open platform to screen 200 000 children and adolescents for T1D. The project will assess the psychosocial, medical and economic impacts of screening for T1D in different health systems and populations. The team will also refine the biomarkers used to determine a person's risk of developing T1D, how advanced the disease is, and how the disease should be monitored in different patients. Another part of the project will focus on designing clinical trials of novel treatments that could stop the disease in its tracks.

▼ iCARE4CVD 🔗

The **iCARE4CVD** project aims to improve patient care for people with cardiovascular diseases (CVD) across the board, starting from those at risk of developing CVD to those with advanced disease. To allow a more personalised approach to patient care, biomarkers will be used to assign those diagnosed to clinically-meaningful subgroups – this will make it easier to pick up on which patients are in most urgent need of treatment. Tools based on artificial intelligence (AI) will also make it possible to predict how individual patients will respond to different treatments, and part of the project will focus specifically on people with type 1 diabetes, who are at risk of developing CVD. Over the course of the project, data will be gathered on more than 1 million patients from existing cohorts and anonymous access to this data will be possible via a blockchain-supported federated database.

So

1

**Determinants
of disease**

▶ GRIPonMASH 🔗

Metabolic dysfunction-associated steatotic liver disease (MASLD), which is characterised by a build-up of fat in the liver, affects 30% of the world's population. Many people with MASLD will have no symptoms, but some (around 1 in 5) will develop MASH (metabolic dysfunction-associated steatohepatitis), where the fat in the liver becomes inflamed and damaged. In the most serious cases, MASH can cause irreversible damage to the liver and can even lead to liver cancer. MASH is expected to be the leading cause of liver transplants worldwide by 2030. Yet all too often, patients only find out that they have MASH when they develop serious complications such as cirrhosis or liver cancer.

The aim of the **GRIPonMASH** project is to design and set up a platform capable of diagnosing people who have MASLD, so that they can take steps to protect their liver and stop their condition from evolving into MASH. **GRIPonMASH** also plans to develop non-invasive alternatives to liver biopsies based on imaging and organ-on-a-chip technologies, as well as providing patients with personalised lifestyle advice via the platform to help patients to boost their liver function.

▼ LIVERAIM 🔗

The **LIVERAIM** project's overall goal is to set up a screening platform to detect cases of liver disease early on, so that patients can take steps to protect their liver before it's too late. As the silent phase of the disease can last for two decades, there is a clear window of opportunity to take action here. Previous research has found a number of biological markers of liver damage, but they have not yet been tested in large numbers of people in the general population. **LIVERAIM** will take biological samples and data from earlier projects (including the IMI project LITMUS) and use them to evaluate the ability of these biomarkers to detect which patients have liver damage and which do not. The results of this work will be analysed using standard statistics and artificial intelligence (AI) with the goal of developing a biomarker platform.

The platform will then be validated in a randomised clinical trial to prove the benefit of a screening programme. People diagnosed with liver disease will receive personalised advice designed to halt the progress of the disease. For the majority of patients whose liver disease is linked to factors such as obesity and alcohol use, the advice and support will focus on helping patients to change their lifestyle.

So
2
Integrated solutions

▶ CLAIMS 🔗

CLAIMS will develop an AI-based platform for multiple sclerosis (MS) patients that will help to predict the course of the disease and identify the best treatments for them. Diagnosing MS and selecting the best treatment is extremely challenging, because patients experience a range of different symptoms, and a treatment that works well for one patient may not work at all in another, or may result in serious side-effects. Around a third of MS patients also have other physical health problems, which can make it even harder to select the right treatment. Today, developing a treatment plan for each MS patient is largely based on a trial-and-error approach – **CLAIMS** hopes to prompt a switch to a personalised medicine approach which could see patients receive a treatment that works for them much sooner and so significantly boost their quality of life.

▶ PROMINENT 🔗

PROMINENT aims to set up a digital platform that will improve the diagnosis and personalised treatment of people with Alzheimer's disease coupled with other diseases. It will draw on existing artificial intelligence tools to create an open, interoperable platform capable of interacting with multiple systems to integrate diverse data from sources such as medical records, mobile devices and imaging repositories. Advanced analytical tools embedded in the platform will highlight the most likely outcomes for individual patients, along with personalised, evidence-based suggestions for the most appropriate ways of managing the patient's health.

While the platform will focus on Alzheimer's disease, the project hopes that it could ultimately have an impact on the care of patients with other neurodegenerative diseases.

▼ COMBINE-CT 🔗

According to current clinical guidelines in the EU, UK and US, patients suspected of having coronary artery disease (CAD) should first have a scan called a coronary computed tomography angiography (CCTA). CCTA is non-invasive and uses X-rays and computer processing to create a detailed 3D image of the coronary arteries. In practice, challenges with interoperability across systems, devices, and geographies mean that CCTA is not being used to its full potential. As a result, an estimated 60% of patients still undergo invasive tests for CAD unnecessarily.

The goal of the **COMBINE-CT** project is to deliver an automated CCTA-enabled workflow that will improve and connect the different steps in the care of CAD patients, ranging from diagnosis to treatment planning, treatment procedure, and follow-up. Artificial intelligence (AI) powered algorithms will make it easier than ever to definitively diagnose CAD, select the right treatment for the right patient, plan interventions, use this information during an invasive procedure, and ensure patients are followed up appropriately.

2 **So**
Integrated
solutions

GUIDE-MRD 🔗

After undergoing surgery to remove tumours, sometimes cancer patients have residual disease left in their bodies. The **GUIDE-MRD** project is investigating how blood tests could be used to identify which cancer patients might benefit from additional treatment to destroy any remaining cancer. Cancers usually shed fragments of tumour DNA into the patient's bloodstream, and while blood tests to detect this cancer tumour cell DNA (ctDNA) already exist, they are not standardised and the key details of how these tests work are not publicly available.

GUIDE.MRD will define standards and use them to benchmark ctDNA tests available now. The project will rank existing blood tests according to how accurate they are at correctly identifying patients as either ctDNA positive or negative. The most promising ctDNA blood tests will then be compared against clinical outcomes to treatments in a clinical trial. Finally, the most accurate ctDNA blood tests will be used as a tool to help doctors and patients select the right treatment for their individual situation.

IMAGIO 🔗

The **IMAGIO** project focuses on interventional oncology (IO), an approach that uses miniaturised instruments to target cancer cells more precisely, sparing healthy cells from the toxic effects of many cancer treatments. The project will explore and demonstrate how next generation IO imaging techniques can be applied to cancer research and treatment, from laboratory studies to clinical trials, focusing on lung cancer, liver cancer and soft tissue sarconas.

In the case of IO surgery, damage to, and scarring of, healthy tissues is dramatically reduced and there is a much lower risk of infection and bleeding. For IO radiotherapy, radiation damage to surrounding healthy tissues is much reduced, which means a higher radiation dose can be used, resulting in a faster response to treatment. Similarly, for chemotherapy, the precise delivery of the treatment means that higher doses can be used because healthy tissues will not be exposed to the treatment. Finally, IO immunotherapy results in a strong immune response in both the primary tumour and any metastases.

SASICU 🔗

Intensive care units (ICUs) are highly technical environments, with myriad machines monitoring patients' vital signs and keeping them alive by supporting their vital organs and delivering medicines, fluids and nutrients. These machines are equipped with multiple alarms which sound when they detect an issue. The problem is that alarms sound so frequently that it is increasingly difficult for ICU staff to pick up on which alarms require attention and which can be safely ignored due to the context. Moreover, the sheer number of alarms can induce 'alarm fatigue', when staff no longer notice them. On the patient side, the constant beeps and bells often prevent them from getting the rest they need to heal.

Studies have shown that the majority of alarms in ICUs are false or do not require clinical intervention, meaning that there is immense potential to reduce noise levels and make ICUs more peaceful places for staff and patients alike. The aim of **SASICU** is to use smart technologies to both reduce the frequency of alarms in the ICU and make it easier for staff to identify patients at risk of deteriorating or developing post-intensive care syndrome (PICS).

So
3
Patient-centricity

▶ PaLaDIn 🔗

Developing new treatments for rare diseases is highly challenging. Because there are, by definition, very few patients with each rare disease, there is a major lack of data on patients' needs, preferences and experiences of living with the disease, and what little data exists is often fragmented and hard to access.

The aim of **PaLaDIn** is to address this head-on by developing a state-of-the-art platform dubbed the 'Interactium' to drive innovative, real-world data collection from patients with rare diseases. The project focuses on rare neuromuscular diseases (NMDs), specifically Duchenne muscular dystrophy (DMD) and facioscapulohumeral muscular dystrophy (FSHD). The team plans to leverage the TREAT-NMD Global Registry Platform, which brings together over 60 NMD patient registries which collect patient data following a harmonised data model.

The project will test the feasibility of using data from the Interactium to influence health research and care via four use cases: on regulatory decision-making; monitoring patient care; creating standards of care; and facilitating clinical trials.

So 4
Digitalisation & data

So 5
Value assessment

IDERHA 🔗

The aim of **IDERHA** is to set up an open platform that will facilitate the integration and analysis of diverse types of health data, which will be fully compliant with current and forthcoming legislation for health data, including the European Health Data Space. The platform will link up multiple public and private data sources and put in place interoperable tools and services that will make it possible for key groups to use the data.

The **IDERHA** team will use lung cancer as a use case to design the platform and will use existing data to identify people who may be at high risk of developing lung cancer. **IDERHA** will also use remote technologies such as wearables and digital applications to monitor the condition of patients who have been diagnosed with lung cancer.

IMPROVE 🔗

Today, a wealth of information and data on patients exists, but is scattered across different platforms and systems. This makes it very hard to use this data effectively to improve patient care. The aim of **IMPROVE** is to develop an evidence-based, real-time framework capable of integrating information from patient reported outcome and experience measures (PROMs and PREMs) and patient preference information (PPI), including real-world data from m-health and e-health technologies such as wearable devices and mobile apps.

By drawing on this patient-generated health data (PGHD), the **IMPROVE** framework will deliver new insights into the real-life behaviour of, and challenges faced by, patients of all ages living with complex health problems. The **IMPROVE** framework will be integrated into an online platform designed to facilitate the smart use of patient inputs and evidence in the development of integrated healthcare solutions, which will be tested via 10 use cases covering five disease areas in different European countries.

HEU-EFS 🔗

The aim of **HEU-EFS** is to develop a harmonised framework and accompanying recommendations for conducting early feasibility studies (EFS) in the EU. An EFS is a clinical study conducted on a medical device in the early developmental stages, which typically involves a small number of participants. It primarily assesses the initial clinical safety and performance of the device, providing guidance for product modifications.

By facilitating EFS in the EU, the project seeks to bring Europe in line with the United States, which already has a dedicated EFS programme. **HEU-EFS** will therefore enhance the EU's competitiveness. Even more importantly, it will ensure that patients in the EU gain access to innovative medical technologies that are safe, effective, and aligned with their needs, and will improve clinical excellence for healthcare professionals in the EU.

IHI calls

IHI runs two types of calls – single-stage and two-stage calls. Here are the main differences between them.

Single-stage calls

DEFINING THE TOPIC

1 Ideas for single-stage call topics come from **a wide range of sources**

- such as the Ideas Incubator
- or from industry partners
- potential contributing partners
- and other stakeholders in the health community

2 The ideas are then discussed and assessed **by the Science and Innovation Panel**

3 The Science and Innovation Panel sends its opinions **to the Governing Board**

4 **The IHI Programme Office** then drafts the topic texts

5 Once at an advanced stage, **the States' Representatives Group and the Science and Innovation Panel** consult on the topic texts

6 **The IHI Governing Board gives the final green light**

APPLICATION PROCESS

7 **Applicants put together consortia involving public and private partners,** ensuring that 45% of their proposed budget can be paid for by industry partners or contributing partners

8 **Applicants** submit their proposal **in one stage**

The full proposal is evaluated and is either accepted or rejected

Two-stage calls

DEFINING THE TOPIC

1 **The European Commission and the industry partners** define the topics for the call

2 The topic texts are again sent for consultation to the **Science and Innovation Panel and the States' Advisory Group**

The topic texts are approved by the Governing Board **3**

In the published topic text, the industries that are willing to contribute to the project are already identified

APPLICATION PROCESS

4 **Applicants eligible to receive funding** develop consortia, but their consortia do not contain industry partners and they do not need to ensure that they have funding for 45% of the proposed budget at this stage

- from universities
- research centres
- patient organisations
- SMEs
- regulators, etc.

5 **The different applicant consortia** submit short proposals addressing the topics put forward in the call

> this is stage one

6 The applicant consortia are assessed, and the winner is matched with the pre-defined industry consortium. **These industry partners will contribute the 45% if the proposal passes the second stage**

7 For each topic, the final combined consortium then prepares a full proposal which is again submitted for evaluation

> this is stage two

Finally, if the proposal passes the evaluation, then the project can start

Calls

IHI's call 3 closed in January 2023, while calls 4 and 5 were launched in summer 2023.

Call 3

IHI call 3 was a single-stage call that searched for innovative solutions to diseases of unmet public health need, rare diseases, mental health, hospital efficiencies, and patient-generated evidence.

Topic 1 🔗 Screening platform and biomarkers for prediction and prevention of diseases of unmet public health need

Topic 2 🔗 Patient-generated evidence to improve outcomes, support decision making, and accelerate innovation

Topic 3 🔗 Combining hospital interventional approaches to improve patient outcomes and increase hospital efficiency

Topic 4 🔗 Strengthening the European translational research ecosystem for advanced therapy medicinal products (ATMPs) for rare diseases

Topic 5 🔗 Digital health technologies for the prevention and personalised management of mental disorders and their long-term health consequences

19 proposals were received in response to this call, and **9 were selected** to become IHI projects.
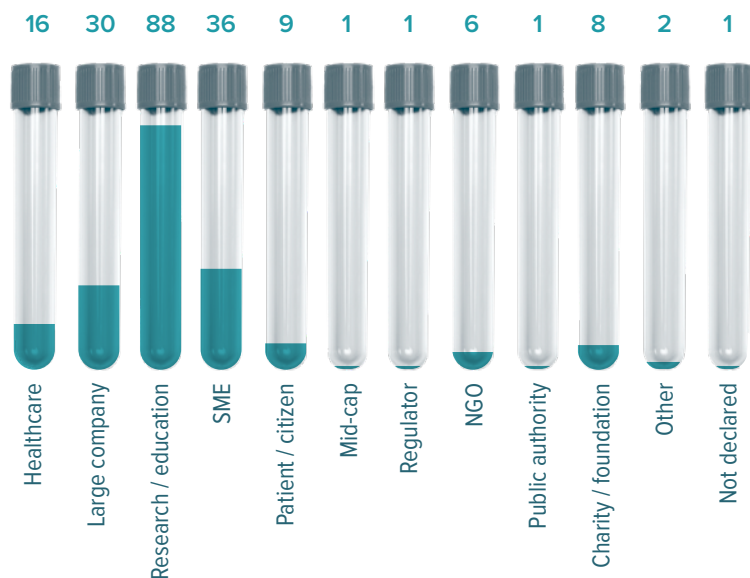
Participants in selected proposals

17% of the participants are IHI industry partners, and **12%** are IHI contributing partners.

The table below gives a detailed breakdown of the participants by both country and organisation type.

Distribution of the applicants by organisation type

Healthcare	Large company	Research / education	SME	Patient / citizen	Mid-cap	Regulator	NGO	Public authority	Charity / foundation	Other	Not declared
16	30	88	36	9	1	1	6	1	8	2	1

Call 4

IHI call 4 was a two-stage call with topics on the 3Rs, patient-centric blood sample collection, clinical trials, and the environmental impacts of healthcare.

Topic 1 🔗 Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment

Topic 2 🔗 Patient-centric blood sample collection to enable decentralised clinical trials and improve access to healthcare

Topic 3 🔗 Inclusive clinical studies for equitable access to clinical research in Europe

Topic 4 🔗 Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases

Topic 5 🔗 Safe & sustainable by design (SSbD) packaging and single use device solutions for healthcare products

Topic 6 🔗 Sustainable circular development and manufacturing of healthcare products and their quantitative environmental impact assessment

17 short proposals were submitted in response to this call. The short proposals were evaluated by independent experts and the top-ranked consortium for each topic was invited to join up with the industry consortium identified in the call text and submit a full proposal.
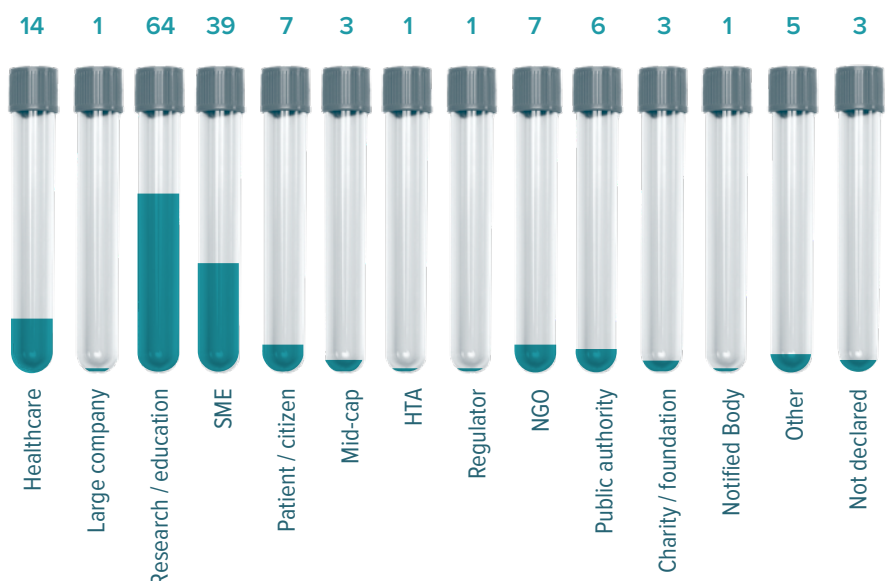
⧗ The deadline for receipt of full proposals was 23 April 2024.

Participants in selected proposals

1% of the applicants are IHI industry partners, and **16%** are IHI contributing partners. Industries appear to be under-represented because the pre-identified industry consortium members will join only in stage 2.

The table below gives a detailed breakdown of the applicants by both country and organisation type.

Distribution of the applicants by organisation type

Healthcare	Large company	Research / education	SME	Patient / citizen	Mid-cap	HTA	Regulator	NGO	Public authority	Charity / foundation	Notified Body	Other	Not declared
14	1	64	39	7	3	1	1	7	6	3	1	5	3

Research highlights

IMI projects – delivering results with impact

The IHI Programme Office continues to manage the large number of projects launched under the IMI1 and IMI2 programmes. Here's a selection of those outputs – between them, they demonstrate how our projects are delivering results that address major unmet health needs, including infectious diseases such as tuberculosis (TB), metabolic disorders such as diabetes, and more. The projects are continuing to deliver knowledge and resources that can be used by the wider research community. In addition, the many results in fields such as health data and medical devices demonstrate how IMI paved the way for IHI by launching projects with a strong cross-sectoral element. You'll also see a number of results from projects that actually ended several years ago. The fact that the consortia are still collaborating and publishing new papers is testament to the way IMI projects are creating long-lasting, productive networks.
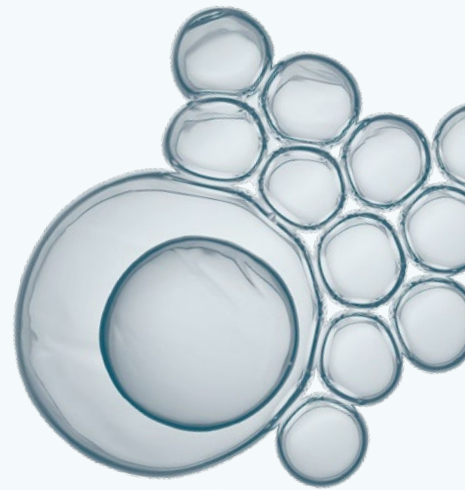
IMI projects deliver tools and resources for the wider research community

Many projects make their outputs accessible to the wider research community, thereby increasing their potential impact dramatically.

➤ EUbOPEN opens its gates to a library of chemical compounds 🔗

When developing new medicines, scientists need to understand the underlying causes of disease. To do that, they need to be able to study in detail the role of the different proteins involved in the disease, which requires chemical compounds capable of altering or blocking the action of individual proteins.

By end of 2023, the **EUbOPEN Gateway** sustainably provided scientists with access to a library of 2 300 very precisely annotated chemical compounds covering roughly 850 different proteins. The EUbOPEN team aims to create the largest and most deeply characterised open collection of chemical modulators of protein function. In addition, 88 probe compounds of very high quality co-developed between academics and pharmaceutical industries have been made available to the global scientific community up to now. Both initiatives will help researchers in academia and industry alike to use the tools to design drugs capable of blocking specific proteins involved in diseases, as well as identifying proteins that play a key role in disease development and deepening our understanding of disease mechanisms.
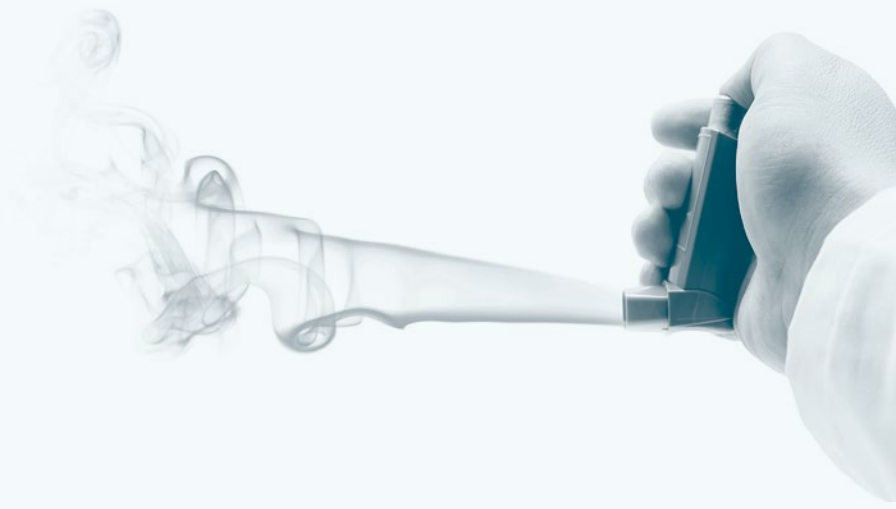
➤ 3TR project creates common standards to boost severe asthma research ⵀ

People with mild-to-moderate asthma can often rely on common inhalers to treat their symptoms. But those with a severe form of the disease find it more difficult to control, even with higher doses of medication.

Although researchers across the world are developing better treatments for severe asthma, they often use different tools to assess how well they work (the outcomes). This makes it difficult to compare or combine results of any research on the condition.

Until now, asthma researchers have not used a consistent, standard set of results (called core outcome measures) to understand whether or not certain asthma therapies work. To remedy this, a European multi-stakeholder working group has developed the 'core outcome measures sets for paediatric and adult severe asthma' (COMSA).

By having a minimum set of outcome measures for all future clinical trials, the hope is that COMSA will speed up finding which treatment works best for individuals with severe asthma.

The work on COMSA was led by IMI project 3TR, and the working group behind it included doctors, people both young and old living with severe asthma, patient representatives, pharmaceutical companies, and health policymakers. They looked at what individual outcome measures were being used in severe asthma research, for example ways of measuring changes in lung function during a clinical trial, and surveyed patients living with severe asthma and their carers across Europe.

The full COMSA set of core outcome measures includes measures of lung function, frequency and severity of severe asthma attacks, and regular steroid tablet use. It also includes standards for patient-reported outcomes, such as asthma control questionnaires and asthma quality of life questionnaires for adults and children.

The COMSA is described in a **paper** in the European Respiratory Journal and in a **video** prepared by the 3TR team.

➤ EBiSC teams up with the EIT Health project to facilitate access to cells for research ⵀ

IMI project EBiSC has developed a not-for-profit bank of almost 1 000 high quality induced pluripotent stem cells (iPSCs) for use by researchers in academia and industry.

Human iPSCs are mature adult cells that have been reprogrammed to make them 'pluripotent', i.e. they can be differentiated into any type of cell found in the human body. As such they are widely used health research. Meanwhile **R2U-Tox Assay**, a project funded by EIT Health, has developed a test for drug toxicity testing using heart and nerve cells derived from iPSCs. Now, the two projects have teamed up so that EBiSC can distribute the R2U-Tox Assay tests via their channels.

For R2U-Tox Assay, the collaboration is therefore contributing to the uptake of their product, while for EBiSC, the R2U-Tox Assay represents a useful additional product that they can offer to their customers. The collaboration also underscores the synergies between IMI/IHI and EIT Health, and the **Memorandum of Understanding** signed by IHI and EIT Health in 2023 makes future collaborations like this one more likely.

IMI projects are adding to our understanding of diseases of unmet need

IMI projects are adding to our understanding of a range of diseases, including heart disease, liver disease, and chronic pain, to name just a few. These results also highlight an important area of alignment between IMI and IHI; one of the specific objectives of IHI is to 'improve our understanding of the factors that affect our health and the development and treatment of certain diseases'.

➤ Examining data in new ways highlights genetic differences in psoriatic skin 🔗

Psoriasis is a skin disease that manifests in scaly skin patches. There is no cure and the treatments do not work well for all patients.

IMI project BIOMAP carried out an extensive analysis of a wide range of molecular data from people with psoriasis, and uncovered some previously unknown genetic factors that are associated with the onset of the disease. They published their findings in the journal **Human Genomics**.

People with psoriasis experience flare-ups — for example, if you have psoriasis on your elbow, it may appear scaly, red and sore for a few weeks — but then the skin will recover, and you'll experience another flare-up a few weeks later.

One thing that the data showed was that skin from a psoriatic lesion showed genetic differences to healthy skin from the same person. Even more intriguingly, the genetic pattern looked different again when you compared it to the healthy skin of someone who didn't have psoriasis at all.

Another aspect of the study was the discovery of "bridge genes" — a group of genes that form connections between genes that are known to be associated with psoriasis. These bridge genes were never described in scientific literature before.

Looking to the future, some of the genes identified could be investigated as a potential drug target or biological marker for psoriasis.
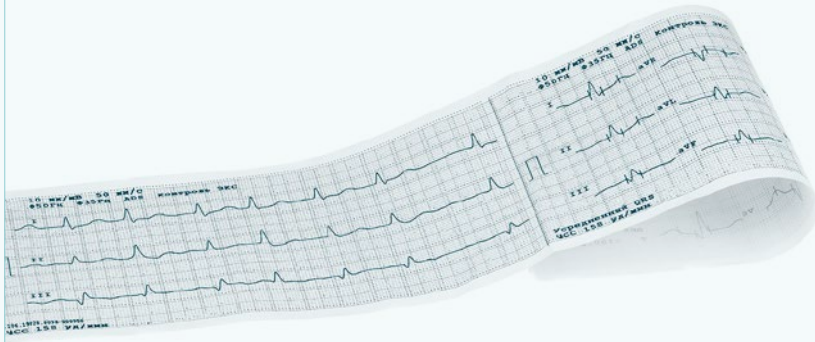
## ➤ Research shows the hidden biases in cardiovascular disease data 🔗

Heart disease is a major cause of death for both women and men, but it remains under-diagnosed and undertreated in women because they often have different symptoms, and this has not been taken into account in past research. IMI project **BigData@Heart** published two papers on this issue. The first paper, published in the **European Journal of Heart Failure**, draws on data from clinical trials on heart failure and a reduced ejection fraction (where a weakened heartbeat pumps out less blood) and observational registries on heart failure.

The project identified three groups of people: people who actually took part in a randomised clinical trial (RCT); people who were eligible to take part in an RCT but did not; and people who did not qualify to be included in an RCT.

Their results showed that generalising the results of RCTs towards all patients with heart failure and reduced ejection fraction is likely unwise, since females were under-represented in clinical trials. The women who did enrol in trials also had a lower-than-expected mortality rate (5.6%) compared to women in the registries who were eligible to take part in trials (14%) and those who were not eligible (28.6%).

There could be many reasons behind this. One is that cardiovascular symptoms show up later in women, which gives time for other health issues to also play a role in their health, which in turn might cause them to be excluded from some trials. Social factors may also play a role.
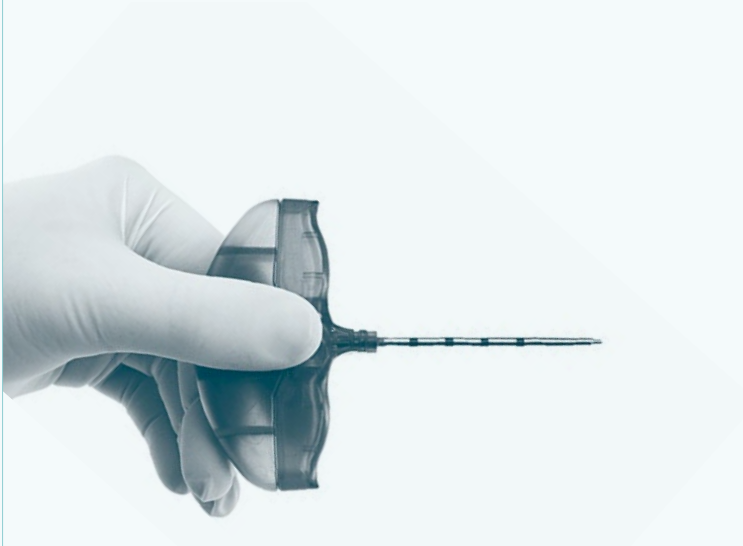
➤ Biomarkers, not biopsies, indicate who will fall foul of liver disease 🔗

Although most people will never have heard of it, MASLD (metabolic dysfunction-associated steatotic liver disease) is common, affecting around a quarter of adults. MASLD (which was known until recently as NAFLD, or non-alcoholic fatty liver disease) is characterised by a build-up of fat in the liver, and most of those affected will have little to no symptoms at all. However, a small proportion of people with MASLD will go on to develop a more serious condition called metabolic dysfunction-associated steatohepatitis (MASH), which places them at a greater risk of developing liver cirrhosis and liver cancer.

Today, a biopsy is needed to confirm which MASLD patients have progressed to MASH and to determine the severity of the condition.

IMI project LITMUS wants to revolutionise the testing process so that patients can opt for a simple blood test or scan.

The project team has already identified a range of biological markers that offer important clues as to the state of a person's liver. Crucially, they have also generated data that shows that these biomarkers may be as good as biopsies, or better at predicting long-term outcomes.

The project worked closely with regulators to ensure that their approach to biomarker identification and validation was sound, and in October 2023 they submitted a qualification package for certain key biomarkers to the US Food and Drug Administration (FDA). They also shared their lessons learned on working with regulators in an article in the Journal of Hepatology.

➤ Better understanding the genetic link between obesity and type 2 diabetes 🔗

Clinicians have long known that there's a link between obesity and type 2 diabetes (T2D), but the nature of the link is unclear, as evidenced by the fact that not everyone with obesity will develop T2D, while many people who do develop T2D are not obese.

Writing in **Nature Metabolism**, IMI project SOPHIA explained how they identified 48 genetic changes called single nucleotide polymorphisms (SNPs) associated with having both obesity and T2D, and 19 SNPs associated with having obesity but being protected from T2D. They also worked out some of the mechanisms behind T2D caused by obesity. For example, a person's higher capacity to expand fat tissue around the thigh area plays an important role in genetically-determined obesity without T2D. Other such 'biomarkers' include blood pressure, the cholesterol content of high-density lipoproteins, and levels of the protein HS6ST2.

Finding and understanding these biomarkers marks an important step to precisely identify whether a person with obesity is susceptible or resistant to developing T2D, while knowing the genetic background to these biomarkers can help when designing future medications.

➤ Getting to grips with pain management with IMI-PainCare 🔗

Pain is the leading cause of disability worldwide among adults but despite this, treatment options are limited. Furthermore, roughly one in five people that suffer from chronic pain have been diagnosed with depression because of it, and two-thirds were less able or unable to work outside the home. The IMI-PainCare project is delivering knowledge and tools to help in the development of novel painkillers.

Chronic pelvic pain affects more than one in four women, yet it remains difficult to treat and affects patients in a range of different ways. IMI-PainCare conducted a **study** involving 769 women which illustrated the negative effect that chronic pelvic pain has on a patient's quality of life, impacting their mental health and sexual relationships, and demonstrated the need for novel approaches to be taken to classify patients with pelvic pain.

It is not always easy to determine how best to measure how effective existing pain management strategies are. IMI-PainCare conducted a **trial** to evaluate how effective patient-reported outcome measures were at assessing changes in pain in patients who had just undergone a surgery. They found that using self-reported pain measures alone was not a good indicator of changes in pain, suggesting that a patient should report on a range of domains instead in order to reliably estimate the efficacy of pain management strategies.

To develop new painkillers, a specialised series of tools is needed, and the IMI-PainCare project is putting together a toolbox, including **biomarkers** and core outcomes sets, to help drug manufacturers develop more targeted treatments. 'Core Outcome Sets' (COS) are a minimum set of outcomes that should be measured and standardised in clinical trials for a specific health condition, and can then be used to develop better targeted drugs, and in 2023, the IMI-PainCare project was **the first to identify four COS** relating to pain.

Contributing to efforts to tackle infectious diseases

IMI boasts an extensive infectious disease portfolio, with projects addressing antimicrobial resistance, tuberculosis, and vaccines. Despite advances in research, infectious diseases remain a major threat to public health worldwide, meaning the results presented here are more relevant than ever.

➤ New treatment shows promise for combating dangerous drug-resistant bacteria 🔗

Antibiotic-resistant carbapenem-resistant enterobacteriaceae (CRE) are widely considered to be among the most dangerous drug-resistant bacteria in the world. They can cause infections in almost any body part and can be fatal. IMI project COMBACTE-CARE has been supporting the development of a combination treatment called aztreonam and avibactam (ATM-AVI). Aztreonam is an antibiotic, but it falls prey to beta-lactamases, which are released by the carbapenem-resistant enterobacteriaceae. Avibactam targets the beta-lactamases, effectively protecting the aztreonam so that it can do its job.

In 2023, a phase 3 study of ATM-AVI called REVISIT suggested that ATM-AVI was effective in treating serious bacterial infections due to Gram-negative bacteria, including metallo-β-lactamase (MBL)-producing multidrug-resistant pathogens for which there are limited or no treatment options. It was also tolerated well by patients, with no new safety concerns arising.

Data from the REVISIT study will enable the ATM-AVI combination to be formally submitted for marketing authorisation to health regulators across the globe, and in fact the EMA started an accelerated procedure to review the marketing authorisation application of ATM-AVI in September 2023.

Because of the urgent need for this new antibiotic, the ATM-AVI combination was approved under an accelerated procedure for marketing authorisation by the European Commission.
The green light means that this new treatment will soon be available for adult patients with life-threatening bacterial infections that are resistant to almost all currently available antibiotics.

TRIC-TB receives orphan drug designation for novel combination treatment for TB 🔗

The drug ethionamide (often shortened to Eto) is widely used to treat tuberculosis (TB). However, it can cause severe gastric-related side effects. IMI TB project TRIC-TB has been working to advance the development of novel compounds (boosters) that increase the activity of Eto and overcome resistance. If successful, this would allow clinicians to reduce the dose of Eto (and associated side effects) typically given to patients. In 2023, the US Food and Drug Administration (FDA) granted orphan-drug designation (ODD) to one of these boosters, alpibectir (BVL-GSK098), and ethionamide in a fixed-dose combination for the treatment of TB. The ODD reflects the urgent need for more research into ways to overcome resistance to TB medicines, and the potential for the alpibectir/ethionamide combination to improve treatment options for patients who have TB.

A phase 1 clinical trial carried out under TRIC-TB showed alpibectir to be safe and well tolerated.

Its further development in a Phase 2a clinical trial currently tests the combination in TB patients and is being supported by another EU partnership, **EDCTP2**, demonstrating the synergies between the two partnerships.

Research reveals characteristics of 'neglected' lung disease 🔗

Bronchiectasis occurs when the airways in the lungs permanently widen because of damage caused by inflammation and infection. This widening in turn makes it difficult for the lungs to remove mucus. The mucus lining the lung helps to clear particles and bacteria from the airways, and as the mucus builds up, it becomes easier for bacteria to multiply and infect the lung system. Bronchiectasis is growing in prevalence, but clinicians still do not fully understand the disease's causes, levels of severity, and treatment options.

One important output of IMI project iABC is the European Bronchiectasis Registry (**EMBARC**), which includes data on bronchiectasis patients from across Europe and Israel. The iABC team drew on EMBARC to analyse the characteristics of the disease in almost 17 000 people. Their findings are published in **The Lancet Respiratory Medicine**.

The results showed that the most common identified cause of the disease was a 'post-infective disease'; when patients contracted an earlier infection or disease that later caused bronchiectasis.

Bacterial infections causing the disease were most common in Southern Europe; *Pseudomonas aeruginosa* was prevalent in over 50% of cases, perhaps owing to the bacteria flourishing in warm, damp environments.

Perhaps most the most revealing result in the study is that the most severe cases of the disease seem to happen in countries in central and eastern Europe. One reason this might be the case is that public healthcare in these countries is not geared towards early detection of the disease, meaning it has time to worsen before being treated.

➤ ERA4TB gives the green light for first in-human trial in an academic centre 🔗

One of the goals of the ERA4TB project was to create a tool to validate sites selected for first-time-in-human (FTIH) clinical trials. Up until now, all initial clinical trials for tuberculosis (TB) treatments have been carried out by specialised contract research organisations (CRO), however the costs for running a trial through a CRO can be high and the waiting times for trials to take place are long because there are a limited number of facilities.

The criteria for carrying out first-time-in-human clinical trials are particularly stringent, because a certain level of quality assurance is required by regulatory bodies, and the risks are high: this is the first step from preclinical or animal studies to human populations.

ERA4TB has developed a feasibility tool for validating FTIH trials, and used it to validate five academic centres for clinical trials for TB, and the first trial will take place in 2024. Increasing the number of sites that are suitable for phase 1 clinical trials will lower the price that phase 1 clinical trials currently cost and reduce the waiting times for trials, which in turn will accelerate the timeframe that it currently takes for medications to reach the market. The tool and validation process are described in a paper in **Clinical and Translational Science**.

➤ Clinical trial for TB drug regimen launched by UNITE4TB 🔗

Tuberculosis (TB) is the world's second leading killer infectious disease after COVID-19, wiping out 1.3 million people in 2022. Unfortunately, more and more patients with TB are becoming resistant to drugs that are commonly used to treat them. Even when a person's TB responds well to treatment, patients still experience side effects and must undergo a lengthy medication regimen involving 3-4 different drugs over at least 6 months.

> Better solutions are needed, and in 2023 the IMI project UNITE4TB launched a brand-new clinical trial that will test 14 combinations of 9 existing drugs as well as 2 newly-developed candidate drugs.

The Phase 2B/C clinical trial takes place in Cape Town, South Africa, and tests multiple drug regimens and durations of treatment to find the best results. The research team will be searching for the right combination of drugs and the shortest possible treatment duration.

Developing completely new drugs is essential to overcome the increasing multidrug-resistant TB around the world, so the trial is examining the efficacy of two brand-new agents, GSK-656 and BTZ-043 in combination with bedaquiline and delamanid which represents a totally new combination / regimen.

While TB clinical trials usually focus on developing one drug at a time, a major advantage of the UNITE4TB trial is that it is investigating an entirely new drug regimen. According to the project, this could revolutionise the way TB drug development is done.

➤ Categorising people according to 'immunotype' could predict vaccine effectiveness 🔗

Not everyone responds in the same way to influenza vaccines. In fact, the variability in effectiveness of the vaccine among older adults ranges from 17-53%, leaving a significant proportion of the population unprotected even when vaccinated.

Researchers from IMI project VITAL analysed the immune profiles of more than 300 people aged 25-98, both before and after they received a flu vaccine. They identified two pre-vaccination immunotypes, one of which was associated with a weak response and one with a strong response.

> These results, published in the journal **Aging Cell**, highlight that age is not a good predictor of flu vaccine responsiveness, whereas baseline immune profiles are.

This work could help to identify those individuals who would most benefit from a flu vaccine, with a view to developing new vaccination strategies for those individuals who are not protected via current vaccines.

Advancing paediatric research

Developing new treatments for children is particularly challenging – they process, metabolise and excrete medications completely differently to adults. Moreover, the small numbers of children affected by some diseases mean that it is hard to find enough patients to carry out clinical studies and trials. Meanwhile their developing immune systems mean they can be more vulnerable to certain infectious diseases. A number of IMI projects are delivering knowledge, tools and resources that will ultimately help to advance the development of safe, efficient medicines for children of all ages.

➤ **RESCEU research sets the stage for the implementation of immunisation strategies for RSV** 🔗

Respiratory syncytial virus (RSV) is a common respiratory virus that causes cold-like symptoms. Although mild in most older children and adults, infants and older adults can develop severe RSV which can lead to hospitalisation or, in the worst cases, death. Every year, RSV is responsible for more than 100,000 deaths in young children and results in more than 3 million being hospitalised.

Last year, the world's first immunisation products against RSV were approved in the USA and Europe. IMI's RESCEU project conducted studies into the impact of RSV, developing tools to better predict RSV outbreaks and making recommendations for future immunisation regimes.
In 2023, the results from a birth cohort study carried out by RESCEU were published in **The Lancet Respiratory Medicine**.

They indicate that vaccinating pregnant women or healthy babies during their first winter season could reduce the healthcare burden caused by RSV.

In an article published by the journal **Vaccine**, RESCEU studied the cost-effectiveness of employing monoclonal antibodies (mAb) and material immunisation (MI) interventions against RSV in six European countries, while another **study** estimated RSV-associated hospitalisations in children under 5 years in the European Union over the period 2006 to 2018. The results of both studies are now being used to optimise public health responses to RSV and support planning for future RSV immunisation programmes.
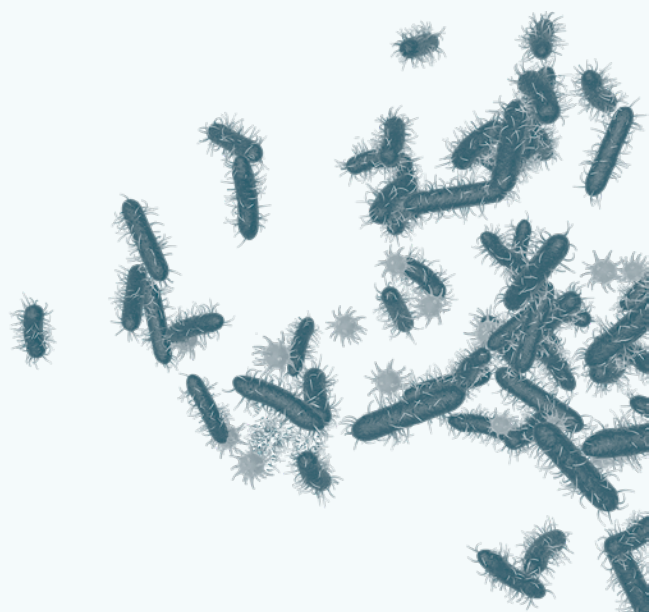
➤ **Game-changing trial for children with tumours being established thanks to EU-PEARL** 🔗

IMI project EU-PEARL delivered a range of resources including toolkits and plans to help in the operational planning and development of platform trials. In a platform trial, multiple organisations can test candidate drugs simultaneously against a shared placebo group, and it is relatively easy to add new treatment groups and drop candidate drugs that prove ineffective. The resources developed by EU-PEARL are **freely available online**.

To guide its work, the project focused on four disease areas: major depressive disorder, tuberculosis, the liver disease non-alcoholic steatohepatitis (NASH), and the rare disease neurofibromatosis. Project partner the Children's Tumor Foundation (CTF) has announced its plans to use the methodology and structure established by EU-PEARL to set up a platform trial for neurofibromatosis 1 (NF-1) and schwannomatosis (SWN). As of the end of 2023, CTF and the Global Coalition for Adaptive Research were working together to select sites and speaking to pharmaceutical companies who could want to test drugs via the trial.

According to the CTF, without the funding and the way it brought all stakeholders together, 'the design of this platform trial wouldn't have happened'.

➤ **Expert network works towards better drug development for children** 🔗

Setting up a clinical trial for children comes with a range of challenges. IMI project conect4children (c4c) sought to tackle many of these issues by setting up a Europe-wide network to make clinical trials in children easier to conduct whilst also connecting clinicians, academia, methodology experts and parents to ensure high-quality clinical trials for children's drugs.

One key project output is a pilot expert advice process, through which drug developers can easily access a wide array of important information directly from experts when designing clinical trials. The idea is that drug developers can come to c4c asking for advice in relation to the treatment of a particular childhood disease that they are targeting. An advice group is quickly formed which the drug development company can then consult. The experts include not only clinicians, researchers and methodology experts, but also parents and patients themselves. The network is described in a paper in the journal **Clinical and Translational Science**.

For example, if the experts can propose a clinical trial design that might be innovative, maybe reducing the sample size or reducing the need for a large trial, that can make paediatric drug development more feasible. And if an advice request was around a study design, the patient or parent perspective might say well this is unacceptable, I can't take my child out of school once a week to come for a clinical trial visit. Or they might say there's too many blood tests here.

Even on outcome measures, a clinician might find a specific blood value important whereas a patient might say well, I have a terrible headache every day so for me it's more important that my headaches are gone than that my blood value changes.

The c4c network also developed a standardised contractual system for the c4c industry partners and the experts, which greatly reduced the administrative burden for drug development companies.

> **AIMS-2-TRIALS investigates if sleep disturbance predicts autistic traits** 🔗

The AIMS-2-TRIALS project tracked babies that were born into families with a history of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) to see whether disturbed sleep in infancy was a predictor of ASD or ADHD onset later. Sleep was assessed according to day/night sleep duration, number of naps in the day, frequency of night awakenings and sleep onset problems, and the infants were assessed at 5-, 10- and 14 months of age.

They found that at 14 months of age, babies with a first-degree relative with ASD, but not ADHD, showed lower night sleep scores than those with no family history of ASD.

These lower night sleep scores were also associated with a later ASD diagnosis. The results, published in **The Journal of Child Psychology and Psychiatry**, indicate that interventions targeting infant sleep might be helpful for families with a history of ASD.

Dealing with data

The discussions on the proposed European Health Data Space (EHDS) mean that health data (and the question of who can access and use it) is rarely out of the headlines. Both the IMI1 and IMI2 programmes launched an extensive portfolio of projects designed to address the multiple challenges of gathering and using diverse types of health data for research, including ethical and legal issues as well as technical problems such as interoperability.

➤ EPND project opens up neurodegenerative disease research 🔗

There have been decades of research to find biomarkers relating to neurodegenerative diseases such as Parkinson's or Alzheimer's disease, but the samples and data from this research are spread across laboratories in multiple countries. Each of these may also have different rules and protocols for collecting, storing and sharing samples and data, which further complicates cooperation between researchers, and across borders.

To make things easier, the IMI European Platform for Neurodegenerative Diseases (EPND) project aims to bring these disparate sources together in a central hub.

In 2023, the project launched the first component of its platform: the **cohort catalogue**, which covers neurodegeneration research from 12 disease areas. This version already contains over 60 cohort studies, and users can filter them by disease area and the kinds of biological samples, imaging and other data available.

The catalogue also lets researchers filter these cohort studies by certain criteria to suit their own research. Researchers could for instance search for studies on Lewy-body dementia that are collecting serum samples, MRI scans, or a combination of other factors.

➤ An app for biomarkers offers speedier biomedical research 🔗

Recent decades have seen a boom in the discovery of biomarkers that are widely used in research and clinical trials. Information on their use in clinical studies can be found in **ClinicalTrials.gov**, a US-based registry of clinical trials, but the data is 'free text', meaning there is no classification or organisation of the information – only sentences and paragraphs. This means it is difficult for other researchers to further analyse biomarkers for use in other clinical trials.

In a paper published in the **Computational and Structural Biotechnology Journal**, scientists from IMI project eTRANSAFE describe how they developed a 'natural language processing' machine-learning algorithm to identify, extract and classify the information on biomarkers from ClinicalTrials.gov.

In total, the researchers found over 3 000 biomarkers being used in relation to around 2 600 diseases. The way the biomarkers are classified allows researchers to easily spot patterns in how biomarkers are being used in different therapeutic areas, the type of biomarker (e.g. certain genes being expressed, cell markers, or proteins in the body) and how specific they are to certain diseases.

This information has now been packaged into the **Clinical Biomarker App**, which the project describes as a 'proof-of-concept tool' to display the data generated by their approach.
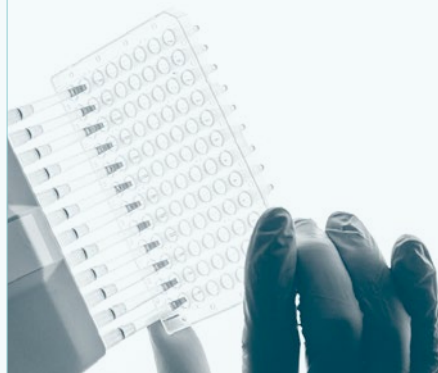
➤ IMI projects help bring urology big data hub to life

The clinical guidelines physicians use to treat diseases are often based on randomised clinical trials. Although this data shows the general efficacy of a treatment, it often cannot provide information on the longterm effects of treatments, how they work alongside other drugs, or how they affect certain subgroups in society such as the elderly or those with obesity.

To tackle these gaps in knowledge, a group of experts in urology, health services research, implementation science, artificial intelligence (AI), epidemiology, and data science have launched the **UroEvidenceHub** platform. The platform aims to better understand real-world urology guidance and practice across all subgroups within and across European countries. This can help optimise the treatment of patients with urological conditions such as prostate cancer, bladder disorders and kidney diseases.

The platform will use urology data from clinical trials alongside information from real world data analytics, including patient feedback.

The platform will also see how to best use AI to help develop new guidelines and treatment recommendations, especially where clinical trials do not exist.

The UroEvidenceHub platform was developed by the European Association of Urology and uses similar data techniques to those deployed by the IMI projects **PIONEER** and **OPTIMA** . PIONEER aims to format, standardise and integrate data from well-known prostate cancer studies, electronic health records and registries so they could be accessed on a single platform, while the OPTIMA project is working to create Europe's first platform for generating oncology data and evidence.

Meanwhile IMI project **EHDEN** is also providing expertise to the platform via its EHDEN Academy, which trains SMEs with the skills and tools needed to map and analyse reports from clinicians and patients about how effective medical treatments are outside the lab, in 'real world' use.

➤ Making data FAIR to all 🔗

Ideally, research data would follow four principles: being easy to discover (Findable); easy to obtain (Accessible); possible to combine with other data or systems (Interoperable); and Reusable. Together these are known as the FAIR principles. In reality, much data doesn't match up to these principles. IMI project FAIRplus set out to change that by creating resources and guidance to help organisations and projects to change their data management culture via a 'FAIR transformation'.

A core project result is the **FAIRification Framework**, a planning process that shows how to use available resources to adopt FAIR principles and expand organisational FAIR data management capabilities. This framework was developed alongside 17 other data-producing IMI projects, which allowed the project to apply the framework to datasets from clinical studies, lab experiments on molecular interactions, and real-world observational data.

The framework means that these and future organisations/projects have a template that is easy to apply, adapt and reproduce within their workflows. However, even these processes may need more specific guidelines to help organisations achieve a FAIR transformation. The project's **FAIR Cookbook** provides organisations with specific 'recipes' to keep the data FAIR.

For example, users of the cookbook can get specific guidelines on search engine optimisation, creating a metadata profile, or data licenses. Although the FAIRplus project has finished, the cookbook is being sustained by project partner ELIXIR as a service currently provided by four ELIXIR Nodes (UK, Luxembourg, Spain, Switzerland).

➤ ConcePTION resource aims to improve collection of data on medicines safety in pregnancy 🔗

The ConcePTION project is working to make it easier for people who are pregnant or breastfeeding to find reliable, evidence-based information on which medicines are safe for them and their baby. Today, data on the safety of using medicines during pregnancy is gathered in different ways by different organisations. This makes it much harder for researchers to combine data from different studies for large-scale analyses which could yield useful new results on this important subject.

> To address this issue, ConcePTION developed a reference framework of core data elements (CDEs) designed to standardise the collection of data on the benefits and risks of medications used in pregnancy.

The framework comprises 98 individual data elements, categorised into 14 tables covering issues ranging from maternal medical history and pregnancy medication exposure to details of the delivery and the longer-term health of the child.

The process through which the CDEs were developed is described in an article in **Drug Safety**, and the CDEs themselves are **publicly accessible** on the ENTIS (European Network of Teratology Information Services) website.

IMI projects result in long-lasting collaborations

From the beginning, IMI and now IHI have sought to foster long-term cooperation between industry, academia, and other stakeholders in health research. As the results below demonstrate, the networks formed in our projects often continue to collaborate and deliver results, sometimes several years after the project has ended. This demonstrates the lasting impact of PPPs like IMI and IHI on the health research and innovation ecosystem.

➤ New spin-off set to boost research into childhood cancers 🔗

Across the world childhood cancer remains rare, although around 15 000 children and adolescents are diagnosed with cancer in Europe each year. Sadly, around one in four of these patients cannot be cured with existing treatments and do not survive. Roughly two-thirds of those who do survive cancer in childhood will experience long-term side effects because of their treatment.

> IMI project ITCC-P4 has developed a platform of over 400 patient-derived models, based on cells and tissues obtained from patients covering more than 20 common childhood cancers such as acute lymphoblastic leukaemia, neuroblastoma, high grade glioma, and osteosarcoma.

These models are designed to facilitate research into these diseases and develop much-needed new treatments.

In 2023, the project set up a spin-off company, ITCC-P4 gGmbH, to make the models developed by the project available to the wider research community.

➤ Ensuring a future for a paediatric clinical trial network 🔗

Conect4children launched in 2018 to set up high-quality paediatric clinical trials for all disease areas and all phases of the clinical drug development process. It has created a pan-European clinical trial network to provide expert advice on all aspects of paediatric clinical trial design. The network also provides support for clinical trial conduct, education and training for researchers on paediatric drug development, and a platform for paediatric multistakeholder meetings.

Now, the project has created the conect4children Stichting, a Dutch non-profit organisation, to sustain the work started by the project.
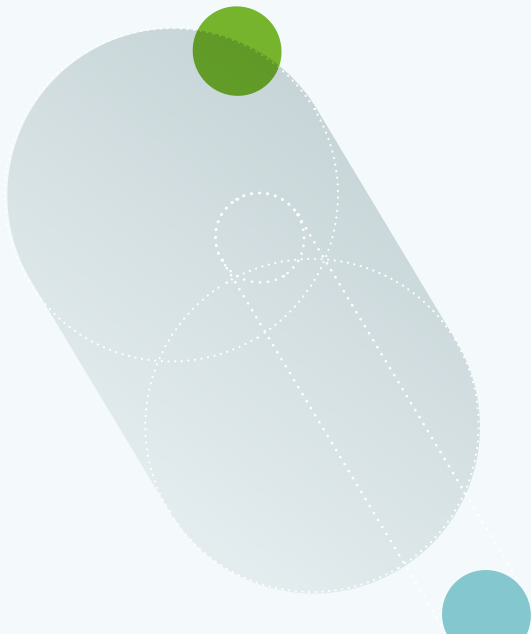
➤ PREFER Expert Network set to capitalise on pioneering project's output ⟠

IMI project PREFER delivered a wealth of resources on when and how patient preferences on benefits and risks should be incorporated into decisions on medicinal products. In 2023, the project set up the **PREFER Expert Network** to capitalise on the experience and expertise gained through the project and support its sustainability.

The voluntary network includes pharmaceutical companies, academic institutions, consultants, and patient representatives and its goals are to:

● exchange understanding, experience, and implementation practices of patient preference studies and their outcomes;

● discuss policy and methodological questions related to patient preference research;

● develop best practices of patient preference studies and identify knowledge gaps which may lead to new research topics.

➤ Molecules in diabetic patients could help personalise treatments ⟠

Although IMI diabetes project RHAPSODY ended in 2021, the academic labs and industry partners of the project continue to collaborate and deliver results. Writing in **Nature Communications**, the team explain how they carried out extensive analyses of thousands of blood samples to identify new links to molecules that could act as biomarkers for type 2 diabetes progression.

One protein, MIC-1/GDF15, was associated with the highest risk of diabetes progression, confirming previous research on this protein. Another protein called NogoR had the next-largest correlation with disease progression, leading the researchers to try to better understand its method of action. They first injected NogoR into mice fed a high fat/high sugar diet. This improved their glucose tolerance. In contrast, in mice with type 2 diabetes, injecting NogoR worsened their insulin sensitivity; in other words damaging their ability to regulate blood sugar levels.

> This result, says the paper, shows that the effects of NogoR glucose metabolism in animals are complex, and depend on the state of diabetes.

In the future, medication might be able to inhibit this protein, thereby preventing it from killing the pancreatic cells responsible for secreting insulin.

A final result from their analysis showed that that the biomarkers identified for diabetes progression are the same as those related to diabetes risk, which suggests that the same biological process happens in both cases.

➤ Creating sub-types of childhood asthma could lead to more targeted treatments ⟠

IMI severe asthma project U-BIOPRED ended in 2015, but the partners are still working together, thanks in large part to the strong involvement of patients in the project – this provided the researchers with inspiration and motivation for further collaborations. In 2023 the team published a paper in the **American Journal of Respiratory and Critical Care Medicine** exploring how the community of microbes living in the sputum (mucus and phlegm) contributes to childhood asthma or wheezing.

They took sputum samples from 131 preschool-age children diagnosed with wheezing and 140 school-age children with asthma and tracked how their condition changed over the following 12-18 months.

They then grouped the children with asthma or wheezing based on their underlying microbiome composition.

> They found four groups of children with distinct throat microbiome profiles, and these groups were linked to allergies, and how their lungs functioned. In addition, these groups could serve as a predictor for the risk of 'future' lung attacks.

According to the researchers, this could help clinicians to define subgroups among children with asthma or wheezing so they could monitor them more closely or provide personalised treatment options. Furthermore, sampling younger people before they show symptoms could mean that patients get treated even earlier and in a timely manner.

➤ **Patients with a specific gene could benefit most from certain diabetes drugs** 🔗

IMI diabetes project DIRECT resulted in biobanks comprising tens of thousands of samples for later use and a strong network of researchers keen to keep working together after the end of the project in 2019. This combination resulted in a 2023 paper in **The Lancet Diabetes & Endocrinology** that examined why the efficacy of diabetes drugs called GLP-1 agonists varies so much from one patient to another.

GLP-1 agonists work by interacting with the GLP-1 protein in the pancreatic beta cells and so encouraging them to produce more insulin. By studying genetic and clinical data from 4 500 people with type 2 diabetes, the researchers pinpointed two genetic variations acting together in 4 % of their study population who had a 30 % greater reduction in their glucose levels over three months when treated with GLP-1 agonists. Finding this correlation means that these drugs can be better tailored to those with the two genetic variations, where it is most effective.

➤ **ABIRISK identifies potential link between development of antibodies and poor response to RA drugs** 🔗

Biopharmaceuticals (BPs) are drugs based on biological molecules like proteins and monoclonal antibodies. They have revolutionised our ability to treat many serious conditions including some cancers as well as autoimmune diseases like rheumatoid arthritis (RA) and multiple sclerosis (MS). In some patients, BPs can cause the immune system to produce anti-drug antibodies (ADAs), which can change the concentration of the drug in the body or even neutralise it. IMI project ABIRISK, which ended in 2018, shed new light on the causes and consequences of ADAs.

Now, a new paper from the project team, published in **JAMA Network Open**, sheds new light on the influence of ADAs on how well certain BPs work for patients with RA. The researchers studied 230 people with RA who were starting treatment with a range of BPs and tracked which patients developed ADAs and how well patients responded to their treatment. Their analysis revealed that patients who had developed ADAs were less likely to respond well to their treatment. This suggests that monitoring ADAs could help to improve the management of RA, particularly those who do not respond to biological treatments.

Cross-sector collaborations deliver results

Cross-sector collaboration is embedded in IHI at all levels. However, many IMI projects already include a strong cross-sector component and their results speak to the added value of this approach.

➤ Revealing an earlier and more effective way to diagnose Alzheimer's disease 🔗

One of the clearest ways to help confirm a diagnosis of Alzheimer's disease is to check the brain for a buildup of abnormal proteins called amyloid-β. These amyloid 'plaques' can be detected even in the early stages of the disease, before symptoms start, via a brain scan using positron emission tomography (PET).

IMI project AMYPAD set out to see if PET brain scans could help to diagnose Alzheimer's disease at different stages. In their study, around 800 memory clinic patients underwent a standard baseline consultation and tests to narrow down the possible diseases they might have. They were then assigned randomly into one of three groups. The first group had a PET scan early, i.e. within one month of the baseline visit. The second had a scan 6 to 10 months after the baseline visit. For the third 'free choice' group, the scan was performed at the discretion of the physician at any time in the observation period.

The study, published in **JAMA Neurology**, shows that access to amyloid PET scans resulted in aetiological diagnoses with very high certainty in 40% of patients within the first three months of the patient's first visit compared to those where the scan was performed 6-10 months later (11%). Additionally knowing the PET scan result also led to changes in diagnosis; for example if the scan was negative, a diagnosis of Alzheimer's disease could be ruled out.

The scans were also the preferred choice of patients. Another way of detecting amyloid build-up is to extract cerebrospinal fluid from the spine for analysis. In the 'free choice' group, 11% of participants explicitly wanted to undergo an amyloid PET, while another 5% chose the scan because they refused the lumbar puncture procedure.
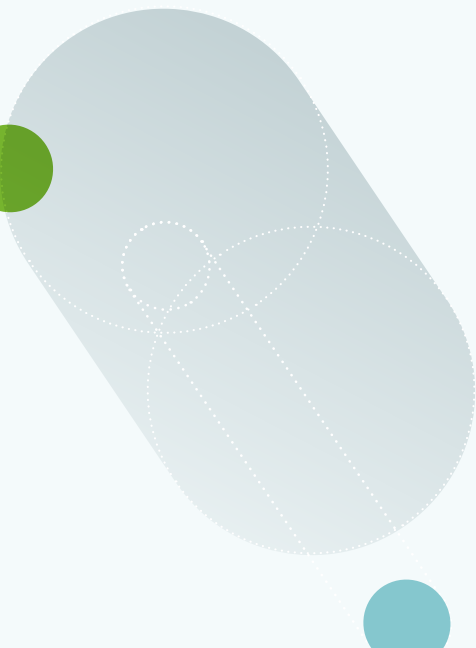
➤ **Study shows how smartphone apps can help monitor effects of depression** 🔗

For people with major depressive disorder, low moods are just one aspect of the disease. People can also feel their thinking skills such as concentration, attention and memory are also affected. Despite this, few psychiatrists regularly assess thinking skills to help treat or monitor their patients. Asking patients to self-report symptoms can be unreliable, due to inaccurate recall. Patients may be monitored in clinics or laboratories, but these are not real-life settings and so can also skew results.

Using wearable technologies and smartphone apps may overcome these problems, as a study by IMI project RADAR-CNS shows.

In a study published in **Psychological Medicine**, project researchers used an app called THINC-it® to monitor over 500 participants with depression. The study aimed to test if warning signs of a depression episode could be found, which in future could help prevent them having major effects on a person's life.

Every six weeks, the app asked participants to rate their difficulties with organisation, concentration, and forgetfulness on a scale from 0 (never) to 4 (often). The app also measured participants' cognitive performance through in-app tasks. Both measurements were taken for up to two years and then used to calculate how long difficulties in performance lasted.

The researchers found that those who reported persistent thinking difficulties (more than 75% of the time surveyed) were also reporting higher levels of depression compared to those who had less persistent thinking difficulties. Interestingly, some thinking difficulties correlated with certain effects of depressive episodes. For example, those who had difficulties with their processing speed were found to have worse symptoms of depression.

> The study confirms that using smartphones to self-report and monitor thinking difficulties could help monitor and manage depression.
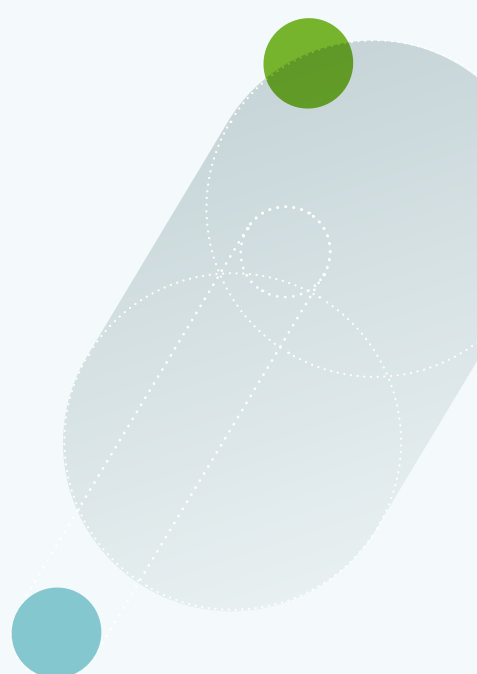
➤ **Wearable technologies can reliably measure fatigue and disturbed sleep in chronic disease** 🔗

Patients with chronic diseases like Parkinson's disease, inflammatory bowel disease and rheumatoid arthritis often rate fatigue as one of the most disabling symptoms, affecting their daily activities and quality of life. However, monitoring fatigue is rather difficult.

Wearing small devices to monitor key physiological signals throughout the day could provide more accurate and reliable results. To test this, researchers from IMI project IDEA-FAST carried out a study involving both people with chronic diseases and healthy individuals.

The 136 participants wore a small device called VitalPatch, a 12-cm long biosensor that adheres to the skin and is worn on the left side of the chest. It recorded their heart rate, the millisecond intervals between their heartbeats, and their breathing rate, among other things.

Participants were asked to carry on with their regular home life while wearing the biosensor for most of the day, including while sleeping at night. This observation period typically lasted for four weeks; five days of wearing the biosensor, followed by two days of rest. Participants were also asked their perceptions of fatigue and sleep quality four times per day over a survey app.

Writing in **Frontiers in Physiology**, the researchers note that the biosensor was able to record data that correlated well with what the patients reported in the app. The biosensor also revealed information that participants were unable to record.

> For example, after six minutes of light exercise (such as going for a walk), biosensor data showed a significant difference in heartrate recovery between healthy people and those with a chronic disease. This can be an important predictor of certain factors that can lead to fatal health events, for example a heart attack.

Meanwhile, the project approached the European Medicines Agency to get the regulatory perspective on novel digital measures of fatigue. The team subsequently shared their experiences and advice for other projects in a paper in **Digital Biomarkers**.
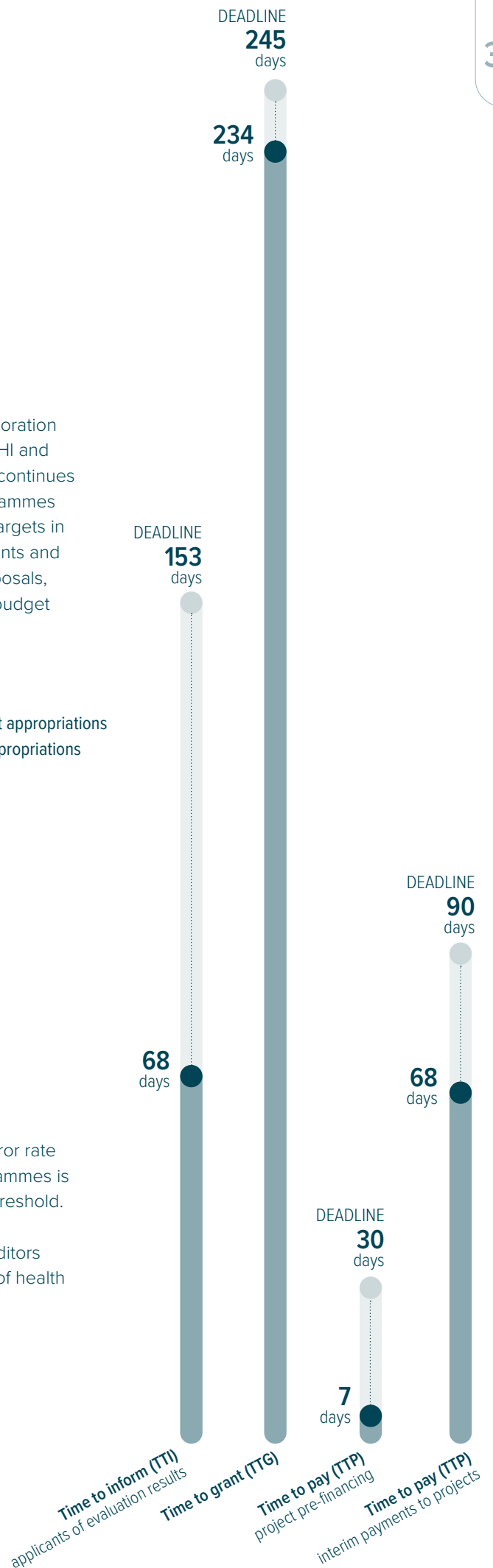
Administrative targets

The IHI Programme Office is currently managing three programmes in parallel (IMI1, IMI2 and IHI), each of which has different rules, management tools and procedures.

Thanks to strong collaboration between the teams at IHI and robust procedures, IHI continues to manage these programmes efficiently, meeting all targets in terms of making payments and managing calls for proposals, and achieving a good budget execution rate.

92.65% commitment appropriations
90.29% payment appropriations

Budget execution
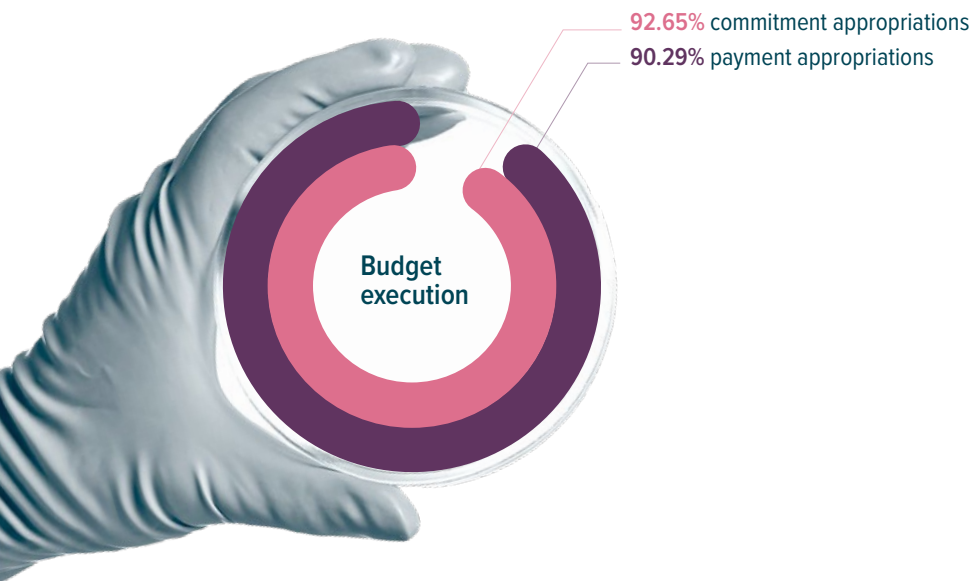
The cumulative residual error rate for the IMI1 and IMI2 programmes is under the 2% materiality threshold.

The European Court of Auditors (ECA) gave IHI a clean bill of health for the 2022 financial year!
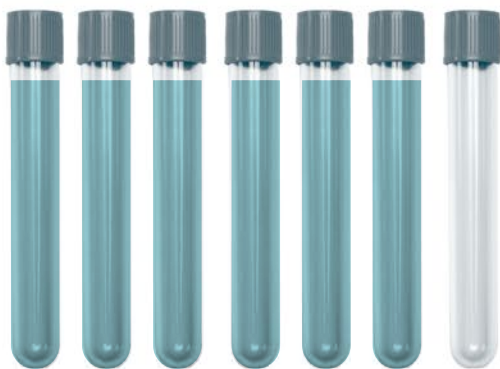
DEADLINE **245** days
234 days

DEADLINE **153** days
68 days

DEADLINE **90** days
68 days

DEADLINE **30** days
7 days

Time to inform (TTI) applicants of evaluation results

Time to grant (TTG)

Time to pay (TTP) project pre-financing

Time to pay (TTP) interim payments to projects

Gender balance at IHI

As of the end of 2023, the statistics showed that:

IHI Programme Office

70%
of staff are female

9 of 16
members are female

IHI Science and Innovation Panel

6 of the 7
named members are female

IHI Governing Board

IHI calls for proposals
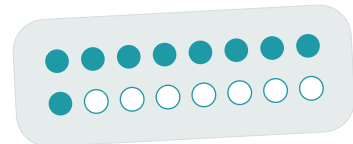
46%
of expert evaluators are female

17 out of 35
main delegates are female

IHI States Representatives Group

Women are well represented in IHI's leadership roles; at the end of the year, the chairs of the Governing Board, SRG and SIP were all female, as was the vice-chair of the Governing Board, and two of the three line managers at the Programme Office.

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health
initiative

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