innovative health initiative

# Consolidated annual activity report 2022

In accordance with Articles 20(7)(g), 21(7b) and 26 of Council Regulation (EU) 2021/2085 of 19 November 2021 and with Article 23 of the Financial Rules of IHI JU. The Consolidated Annual Activity Report (CAAR) will be made publicly available after its approval by the Governing Board.

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# Factsheet

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| **Name of the JU** | **Innovative Health Initiative (IHI)** |
| **Objectives** | IHI's general objectives are to:<br>• turn health research and innovation into real benefits for patients and society;<br>• deliver safe, effective health innovations that cover the entire spectrum of care – from prevention to diagnosis and treatment – particularly in areas where there is an unmet public health need;<br>• make Europe's health industries globally competitive. |
| **Legal Basis** | Article 187 of the Treaty on the Functioning of the European Union<br>Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe<br>Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014 |
| **Executive Director (ad interim)** | Hugh Laverty - bio |
| **Governing Board** | Chairperson: Salah-Dine Chibout - Novartis / EFPIA<br>Vice-Chairperson: Irene Norstedt, European Commission.<br>8 members in total: 4 from the European Commission, and 4 from the industry partners.<br>More information on the Governing Board can be found here. |
| **Other bodies** | Science and Innovation Panel (SIP)<br>• 18 members from the scientific community, wider healthcare community, European Commission, IHI industry partners, and the States' Representatives Group<br>• provides the Governing Board with science-based advice on a range of matters.<br>States' Representatives Group<br>• up to two representatives from each EU Member State and country associated to Horizon Europe<br>• is consulted on a range of issues, including draft call topics<br>• acts as a link between IHI and relevant national and regional research and innovation programmes. |
| **Staff number** | Number of employees in the JU Programme Office (incl. Executive Director) at the end of 2022: 49 |
| **Total budget 2022[1]** | Commitment appropriations: amount (in €)[2]: 272 383 841<br>Payment appropriations: amount (in €)[3]: 174 845 991 |
| **Budget implementation/execution** | Commitment appropriations:<br>Total consumption: (in EUR) 263 125 842. Percentage spent on total: 96.60%<br>• Title 1 (in EUR) 5 653 252. Percentage spent on total: 87.42%<br>• Title 2 (in EUR) 2 254 538. Percentage spent on total: 76.35%<br>• Title 3 (in EUR) 255 218 052. Percentage spent on total: 97.05%<br>Payment appropriations |

1 Total budget includes operational budget (used for funding selected projects) & administrative (used for funding Programme Office activities)

2 Voted commitment appropriations were EUR 9 280 000, subsequently amended to include operational commitment appropriations and unused appropriations from prior years.

3 Voted payment appropriations were EUR 176 280 000 and the amendment reduced the amount because of inferior needs and these appropriations were shifted to following years.

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| | Total consumption: (in EUR) 150 799 711. Percentage spent on total: 86.25%<br>• Title 1 (in EUR) 5 598 137. Percentage spent on total: 86.56%<br>• Title 2 (in EUR) 2 601 419. Percentage spent on total: 74.16%<br>• Title 3 (in EUR) 142 600 154. Percentage spent on total: 86.49% |
| **Grants/Tenders/Prizes** | 0 grants signed in 2022 |
| **Strategic Research & Innovation Agenda** | The Strategic Research and Innovation Agenda (SRIA) was adopted by the Governing Board on 20 January 2022. |
| **Call implementation** | Number of IHI calls launched in 2022: 3 (2 single-stage, 1 two-stage)<br>Single stage calls[4]<br>• Number of proposals submitted: 18<br>• Number of eligible proposals: 13<br>• Number of proposals granted: n/a<br>Two stage calls<br>• Number of proposals submitted: 15<br>• Number of eligible proposals: 15<br>• Number of proposals invited to stage 2: 2<br>• Number of proposals granted: n/a<br><br>Number of IHI projects as of end of 2022: 0 |
| **Participation in IHI, including SMEs** | n/a[5] |

4 Figures refer to IHI call 1 only, as IHI call 3 was still open for applications at the end of 2022.

5 Not applicable as there were no IHI projects at the end of 2022.

# Foreword

Looking back on the Innovative Health Initiative's first full year of operations, it is a good time to reflect on what a public-private partnership (PPP) is and what makes it successful.

Although I am writing this foreword as IHI interim Executive Director, I started my career at the Innovative Medicines Initiative (IMI, the forerunner to IHI) as a scientific officer, managing the first projects launched under the IMI1 programme. Since then I have been privileged to witness the PPP grow and evolve to become a model for collaborative, cross-sector partnerships on a global scale.

This experience has given me an excellent insight into the factors that make a PPP work. Funding is clearly a part of it; IMI1, IMI2 and now IHI have all leveraged immense budgets from our public and private partners that have allowed us to launch ambitious projects that are transforming health research.

However, what sets IMI and IHI apart, and is the key to our success, is our ability to mobilise the very best people and organisations in Europe and bring them together in a neutral space where they can collaborate and share their expertise, resources and ideas. Thanks to this success, our projects have attracted players from outside Europe who recognise the benefits and power of collaboration, allowing our projects to become key focal points for international collaborations.

This matters because many health challenges are global challenges, and as such need global responses, as illustrated by the COVID-19 pandemic. Our European projects have been significantly enriched by the contributions of our international partners. Furthermore, our international partners help to disseminate the results of our projects far beyond Europe's shores. This increases our impact and showcases Europe as a leader in creating innovative, ambitious partnerships.

Looking to the future, we need to continue to mobilise the research community in Europe and beyond so that we remain a world-leading health PPP. Under IHI we look to go beyond the networks established under IMI, break down the silos between the different sectors in health and support innovative research partnerships that will deliver innovation into healthcare and benefit patients. With a partnership that spans diverse sectors, including the pharmaceutical, medical technology, biotechnology, digital health and vaccines industries, I am confident that we will achieve this.

I would like to close this foreword by thanking the many people whose hard work and dedication make possible the results presented in this report.

Firstly, Dr Pierre Meulien, who served as IMI and IHI Executive Director from 2015 to 2022. He played a key role in bringing on board many of the IMI2 Associated Partners who have contributed immensely to the successes of our projects. More recently, he managed the transition to the IHI programme, overseeing the set-up of the new governance bodies and the launch of our first calls.

Setting up and implementing a new partnership is not always easy, and if we have achieved a lot in IHI's first full year, it is thanks in large part to the many people in all the IHI partner organisations, public and private, who work tirelessly behind the scenes to make the programme a success.

I would also like to thank the members of the Governing Board, States' Representatives Group and Science and Innovation Panel, whose knowledge, energy and enthusiasm have helped IHI to get off to a strong start.

Thanks are also due to our IMI project participants – year in, year out, they deliver excellent results that are making a difference in so many fields.

Finally, I would like to thank my colleagues past and present in the IHI Programme Office. They worked extremely hard to ensure we could rapidly launch IHI's first calls for proposals, all while managing our large legacy of IMI projects. On a personal note, I would also like to thank them for their support to me as I have taken on the role of interim Executive Director.

*Hugh Laverty*

*IHI Executive Director ad interim*

# Executive summary

## Laying the foundations of IHI

Following the launch of IHI at the end of 2021, the first part of 2022 was dedicated to setting up the governance structures, processes, tools and documentation that would allow the newly-created Innovative Health Initiative to launch its first calls for proposals.

### Getting going on governance

On the governance front, this entailed setting up two advisory bodies: the States' Representatives Group (SRG) and the Science and Innovation Panel (SIP). The Member States and countries associated to Horizon Europe nominated representatives to be part of the SRG, and the first meeting of the group was held on 22 February.

The SIP is new under IHI, and is designed to bring together representatives of the wider scientific and healthcare communities, as well as representatives of the IHI partners and the Member States (who are nominated by the partners / SRG respectively). On 24 January, the Programme Office launched an open call for people interested in joining the SIP as representatives of the scientific community (4 people) or wider healthcare sector, such as patients, healthcare professionals, healthcare providers, regulatory bodies, health technology assessment bodies and healthcare payers (up to six people).

The call attracted around high-calibre 100 applications, and the 10 successful candidates were announced at the end of March, when the new group met for the first time.

Meanwhile the Governing Board (which was set up at the end of 2021), formally approved the IHI Strategic Research and Innovation Agenda (SRIA), which will guide IHI's scientific priorities in the years to come.

2022 also saw changes at the IHI Programme Office, as the 7-year mandate of Executive Director Pierre Meulien ended in September. The recruitment of his replacement started in January 2022, and was still ongoing at the end of the year. Meanwhile, Dr Hugh Laverty, Head of Scientific Operations at IHI, was appointed Executive Director ad interim.

### Countdown to the first IHI calls

While the governance bodies were being set up, the IHI Programme Office worked hard to prepare all the documentation, forms and guidance needed to launch the first calls for proposals.

To give potential applicants an early glimpse of the kinds of topics they could expect from IHI, the broad themes that were initially under discussion were published online in January. Once the topics had matured and been sent for consultation to the SRG and SIP, the draft topic texts were published online in April. This allowed potential applicants additional time to start preparing a proposal and, crucially, joining or forming a consortium.

The first calls were launched on 28 June. IHI call 1 was a single-stage call with topics on neurodegenerative diseases, imaging and cancer, multi-modal cancer treatments, and the use of health data to advance care and research. IHI call 2 was a two-stage call with topics on cardiovascular disease and the development of health technologies in the EU.

To help potential applicants understand the topics and IHI's rules and procedures, and to facilitate networking and consortium-building, the Programme Office organised a series of events which attracted 1 450 participants. A hybrid event (with the on-site part taking place in Brussels) offered an overview of the

topics and the rules and procedures, and gave applicants the opportunity to deliver a pitch to showcase their value as a project partner.

In parallel, a series of webinars provided applicants with more in-depth presentations of both the topics and IHI's rules and procedures, as well as more time to ask questions. An online networking platform was set up to make it easier for applicants to find partners for their consortium.

The evaluation of the proposals submitted in response to the calls went smoothly, and by the end of 2022 the proposals selected for funding under IHI call 1 were in the Grant Agreement preparation phase. The proposals selected under IHI call 2 were working with the pre-identified industry consortia to prepare their full proposals.

IHI call 3, a single-stage call, was launched in December 2022 with topics covering rare diseases and mental health, and addressing challenges such as disease prevention, hospital care, and patient-generated evidence. Again, the call and draft topics were promoted extensively, and a web platform and series of online events allowed applicants to learn about the topics and IHI and to network with one another.

Between them, the topics address all key areas identified in the SRIA, and bring on board all the industry sectors represented in IHI.

### Putting co-creation into practice

The concept of 'co-creation' is embedded in the way IHI works. When it comes to ideas for potential new call topics, this means that we welcome suggestions from the wider health and research community. To make it easy for stakeholders to send in their ideas, the Programme Office created a structured online form which went live in July, along with advice for those submitting ideas and a description of what happens to ideas sent in. By the end of the year, 20 ideas had been submitted, covering a wide range of research and disease areas. Of these, six passed the completeness check and went to the SIP for review. The outcome of the SIP's review of the first three ideas can be found on the IHI website.

IHI's fore-runner, the Innovative Medicines Initiative (IMI) benefited immensely from contributions (both financial and in kind) from organisations around the world who joined IMI projects as IMI2 associated partners. Under IHI, the 'contributing partner' system works in a similar way, and the IHI Programme Office put in place procedures, templates and guidance to help organisations take advantage of the opportunity to become IHI contributing partners. By the end of the year, the Governing Board had accepted applications from three organisations who became the very first IHI contributing partners.

## IMI projects continue to deliver impact

Throughout 2022, IMI projects continued to deliver exciting results in a wide range of areas which highlight the value of working in an international public-private collaboration.

### IMI projects have an impact on regulatory processes

In the tightly-regulated world of medicines development, having an impact on the regulatory framework is a major achievement. Tools and resources that have been recognised by regulatory authorities are much more likely to be taken up and used more widely in drug development.

For example, IMI project PREFER developed a comprehensive framework covering when and how patient preferences on benefits and risks should be incorporated into decisions on medicinal products. In 2022, the European Medicines Agency (EMA) adopted a qualification opinion for the PREFER framework, endorsing it

as a comprehensive reference document for planning and conducting patient preference studies (PPS). The PREFER framework and associated guidance is freely available online.

IMI project NECESSITY has developed a tool to improve our ability to assess the efficacy of treatments for primary Sjögren's Syndrome (pSS), an autoimmune disease in which the immune system attacks cells in the body that secrete fluids, such as tear and salivary glands. Details of the tool, dubbed STAR ('the Sjögren's Tool for Assessing Response'), are freely available in the Annals of Rheumatic Diseases. The EMA has issued a Letter of Support for the use of STAR as a tool to assess drug efficacy, and this will facilitate its use in future clinical studies.

People with age-related macular degeneration (AMD) gradually lose their central vision in both eyes. It is a leading cause of blindness, yet treatment options are extremely limited. IMI project MACUSTAR has developed a suite of markers and measures that could be used to assess how well a potential treatment works. The project has now received a second Letter of Support from the EMA encouraging the ongoing validation of the measures.

In 2022, the EMA and the European Medicines Regulatory Network set up DARWIN EU (Data Analysis and Real World Interrogation Network), a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines, including vaccines, from real world healthcare databases across the EU. Key to the success of DARWIN EU is the availability of data partners who can generate the real world evidence needed for scientific evaluations and regulatory decision making. Many of the first data partners are already data partners in IMI project EHDEN, which is building a pan-European federated data network. EHDEN ensured the data partners' data was mapped to a common data model, and this in turn made those organisations suitable data partners for DARWIN EU.

### Exploiting synergies to ensure the further development of project results

A number of IMI projects have delivered results that were subsequently picked up by other projects, either within IMI or elsewhere, for further development.

The European Lead Factory (ELF) boasts a collection of over half a million compounds and a state-of-the-art high throughput screening centre that researchers can apply to use for their own drug discovery programmes. The Pivot Park Screening Centre (PPSC) in the Netherlands used the ELF to hunt for compounds that would stop the SARS-CoV-2 virus, which causes COVID-19, from attacking cells. The search was successful, and the compounds identified are now undergoing further development via the EU-funded ISIDORe project.

Tuberculosis (TB) kills around 1.5 million people annually, making it one of the leading causes of death worldwide. In 2022, the TRIC-TB project announced that it had successfully completed phase 1 clinical trials of BVL-GSK098, a compound designed to boost the infection-fighting ability of one of the main anti-TB drugs. The compound is now the subject of a phase 2a clinical trial being carried out via a project funded by the European & Developing Countries Clinical Trials Partnership (EDCTP2 programme).

French SME Nosopharm is developing a new class of antibiotics called odilorhabdins that show potential as a treatment for multi-drug resistant infections caused by bacteria defined as 'priority pathogens' by the World Health Organisation (WHO). The early development of odilorhabdins was supported in part by IMI project ENABLE. More recently, their development has been further advanced in another IMI project, GNA NOW. In 2022, GNA NOW announced the successful completion of toxicology studies on NOSO-502 and this, combined with other results on the compound's efficacy and other elements, has prompted Nosopharm to prepare an application to launch a phase 1 clinical trial.

Meanwhile a number of projects have set up organisations such as non-profits and SMEs to continue and build on work started with IMI funding. Examples here include diabetes project INNODIA, antimicrobial resistance project ENABLE, and data quality project EQIPD, to name a few.

### Showing the benefits of cross-sector collaboration

While the IMI programmes had a strong focus on the pharmaceutical sector, many IMI projects address wider issues in health research and include partners from fields such as digital health, big data, and imaging. These projects are now delivering exciting results that underline the added value of a cross-sector approach to health research. They could also contribute to the implementation of EU policies such as the European Health Data Space (EHDS).

For example, in a bid to address many of the quality, privacy and transparency issues surrounding health data, the BigData@Heart project worked with the European Society of Cardiology (ESC) to develop 'pragmatic advice' on the use of structured healthcare data in clinical trials and observational research. The result, dubbed the CODE-EHR framework, aims to improve the quality of studies using structured healthcare data, and provide confidence in the results of these studies for use in clinical decision-making. The framework is published via open access papers in the European Heart Journal, the British Medical Journal (BMJ) and the Lancet Digital Health.

IMI project conect4children has teamed up with CDISC (the Clinical Data Interchange Standards Consortium) to produce a Paediatrics User Guide. The guide, which is freely available online, describes how to use CDISC standards to collect and structure data used in clinical trials to facilitate the aggregation of information, take advantage of big data and support data sharing. The guide shows how IMI projects, by collaborating with global standards development organisations like CDISC, can have an impact on research worldwide, and not just in Europe.

The goal of FAIRplus is to deliver guidelines and tools to facilitate the application of 'FAIR' ('findable, accessible, interoperable, reusable') principles to data from certain IMI projects and datasets from pharmaceutical companies. One of the key outputs of the project is the FAIRplus 'cookbook' which is packed with practical guidance on how to make and keep data FAIR. ). It currently includes over 50 'recipes' contributed by over 50 professionals from 30 organisations.

The PharmaLedger project set out to deliver a blockchain-based platform for the healthcare sector. By the end of the project, the consortium had developed a number of use cases demonstrating how blockchain could be used to tackle specific challenges in three domains: supply chain, health data, and clinical trials. Although PharmaLedger has ended, the project's legacy lives on via the PharmaLedger Association, which is building on the work started in the project.

### Helping healthcare systems to breathe easier

In the winter of 2022-23, news headlines in many European countries warned of hospitals becoming overwhelmed with patients affected by respiratory diseases such as flu, respiratory syncytial virus (RSV), and COVID-19. IMI has a large portfolio of projects tackling infectious respiratory diseases, and their results could ultimately help to reduce the burden these diseases place on health systems and patients alike.

For example, RESCEU is putting figures on the scale of RSV infection. While most cases of RSV are mild, young children, the elderly and people with weakened immune systems can become seriously ill. A RESCEU paper published in the Lancet shows that in 2019, RSV was responsible for the deaths of 100 000 children under the age of 5 worldwide. A number of RSV vaccines are under development, and RESCEU's data will help to design immunisation strategies so that they offer the best protection for those vulnerable to the disease.

Another disease which impacts health systems, particularly in winter, is the flu. Every year, pharmaceutical companies develop vaccines designed specifically to combat the strains of flu that are most likely to be in circulation the following winter. The FLUCOP project has developed tools to predict the efficacy of new vaccines more reliably. Meanwhile another project, DRIVE, has developed a platform to study the effectiveness of different brands of flu vaccines in the EU.

Finally, large numbers of people continue to fall ill with COVID-19. The DRIVE project quickly took the platform it created to monitor flu vaccine effectiveness and adapted it to monitor COVID-19 vaccines. The ConcePTION project's common data model has been used in several EMA safety projects related to COVID-19 vaccines and pregnancy. And CARE, which was launched as part of IMI's special call for proposals on COVID-19, has identified a 'core gene signature' of COVID-19 convalescence (up to 6 months post-infection) associated with a history of thrombotic events (i.e. blood clots).

## Successfully managing three programmes in parallel

The launch of IHI means that the Programme Office is now managing three programmes in parallel, with different sets of rules, as a number of projects launched under IMI1 and IMI2 are still ongoing. Despite the challenges this entails, the office remained highly efficient, meeting all of its targets, making payments to projects within the official deadlines, and achieving a very good budget execution rate:

- Time to inform (TTI) applicants of evaluation results (target 153 days): 72 days
- Time to pay (TTP) projects' interim / final payments (target 90 days): 59 days (IMI1); 63 days (IMI2)
- Operational commitment and payment appropriations: 97.05% and 86.49% respectively
- Cumulative residual error rate for IMI2: 0.85 %

In addition, the European Court of Auditors (ECA) issued an unqualified ('clean') opinion on the reliability of the accounts for 2021 as well as on the legality and regularity of the revenue and payments underlying the annual accounts, while the European Parliament granted the JU discharge for the financial year 2020.

On the communication front, promoting and explaining IHI was a core goal for the Programme Office throughout the year. In January, a launch event featuring high-level representatives of the IHI partners attracted over 2 100 participants. The IHI website (which went live at the end of 2021) was enriched with additional content explaining IHI and introducing the newly-created governance groups, among other things. The communication team was also responsible for the smooth running of the events organised to promote the new IHI calls for proposals.

In parallel, the Programme Office continued to showcase IMI projects and their successes, publishing regular news stories on the website and promoting IMI projects and their activities and results via social media.

## Going green and promoting staff well-being

The COVID-19 pandemic changed our way of working, and in 2022, along with other EU bodies, the IHI Programme Office formally switched to a 'hybrid' way of working. This gives staff the option to work from home a number of days every week, if they wish. This flexibility allows staff to manage their time and tasks more effectively, improving the balance between their personal and professional lives, and so contributes to their wellbeing. The shift also meant that the Programme Office was able to significantly reduce its office space and, by extension, its carbon footprint. Furthermore, the office space IHI freed up is now subleased to fellow JU EDCTP3. This means that most JUs are now in the same building, facilitating the continued creation of synergies and implementation of back office arrangements.

## Keeping the (gender) balance

IHI has a good gender balance in a wide range of areas. At the end of 2022, the statistics showed that:

- IHI Programme Office: 65% of staff are female.
- IHI Governing Board: 5 out of 8 members (63%) are female.
- IHI Science and Innovation Panel: 10 out of 16 members (63%) are female.
- IHI States' Representatives Group: 18 out of 36 main delegates (50%) are female.
- Expert evaluators for IHI calls for proposals: 51% are female.

Women are also well represented in leadership roles; in 2022 the chairpersons of the SRG, SIP and (until 15 December) the Governing Board were all female, as were two of the three line managers at the Programme Office.

# 1 Implementation of the annual work programme for 2022

## 1.1 Key objectives for 2022, associated risks and corrective measures

The key objectives for 2022 were set out in the Work Programme for 2022. A summary of the progress made against these objectives is given below. More information on all points can be found throughout the report.

**1. Establish the IHI JU governance structure and the necessary operational and administrative processes and standards, in accordance with the Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014.**

The key focus for 2022 was to finalise the setting up of the new governance structure and initiate their operational activity, as a pre-requisite for achieving the scientific objectives set up in the IHI Strategic Research and Innovation Agenda.

This objective was fully achieved: the constitutive meetings of the States' Representatives Group (SRG) and the Science and Innovation Panel (SIP) took place (the constitutive meeting of the Governing Board had taken place at the end of 2021), and subsequently all governance bodies met regularly during the year providing the necessary framework, within the remit of their own role and tasks, for the proper functioning of IHI JU. The work of the SIP was central to the development of the scientific priorities and topics for the 2022 calls for proposals, the SRG provided its contribution as advisory body across all milestones of the IHI operations, and the Governing Board ensured a coherent strategic orientation of IHI JU by adopting key decisions and endorsing policy roadmaps.

The IHI Programme Office ensured an assertive and effective support to all governance bodies, providing all necessary information for the performance of their respective tasks, and aligning and planning activities.

**2. Execute the Strategic Research and Innovation Agenda priorities, enabling the active engagement of industry sectors covering the pharmaceutical, biopharmaceutical, biotechnology and medical technology sectors, including companies active in the digital area, and a range of other key other stakeholders involved in health care (including SMEs, academia, health care authorities, healthcare professionals and providers, and patient organisations), in particular through the launch of open and competitive calls for proposals.**

The Governing Board formally adopted the IHI Strategic Research and Innovation Agenda (SRIA) on 20 January 2022 and it was published online shortly afterwards.

In the first months of 2022 the IHI Programme Office developed all necessary templates and guidance documents for the call launch, evaluation and grant award procedures, ensuring that they reflected both the Horizon Europe rules and IHI's specificities such as the eligibility criterion that at least 45% of a project's budget must be constituted of in-kind and / or cash contributions.

In parallel, the office worked with the IHI members to draft the topics for IHI's first calls for proposals. This exercise included consultations with both the SRG and the newly-created SIP.

Consequently, IHI JU launched its first three calls for proposals implementing the scope of the scientific priorities 2022 and contributing to the achievement of the general and specific objectives of IHI JU, by tackling the challenges and progressing to achieve the expected impacts in one or more of the five SRIA scope areas/specific objectives.

IHI - call 1, a single stage call with four topics, and IHI - call 2, a two stage call with two topics, were launched on 28 June. 18 proposals were submitted to call 1 and the evaluation was completed before end of

October 2022. Grant preparation started in December and Grant Agreement signature will be completed in 2023. 15 proposals were submitted to call 2 and the first stage evaluation for this call 1 was also completed before end of October 2022. The stage 2 evaluation will take place in Q1 of 2023.

IHI call 3 (single stage, five topics) was launched on 13 December, and was still open for applications at the end of the year.

IHI continued throughout 2022 the systematic involvement of patients and carers at all levels of its activities, mainly through the IMI pool of patient experts; patients were involved both in the evaluations of proposals submitted to calls for proposals and in the monitoring of ongoing (IMI2) projects.

IHI JU developed in 2022 a process for the collection of ideas from a wide range of stakeholders, in addition to the IHI founding members SIP members, to help IHI define its annual scientific priorities and areas for future calls for proposals. The transparent and open process involves the SIP for the review of the ideas collected. Twenty ideas had been collected by the end of 2022. Out of the 20 ideas submitted, most (65%) were submitted by individuals acting in their personal capacity. The ideas came from several countries both from inside and outside the EU and covered several disease areas.

### 3. Ensure continuity with and manage the legacy from IMI2 JU.

During 2022 the Programme Office continued to follow the implementation of the portfolio of legacy projects launched under the IMI1 and IMI2 programmes. This included assessing both technical interim/final reports and costs claims as well as reported in kind contributions. In 2022, IHI conducted 10 interim reviews of ongoing IMI2 projects and five close-out meetings. During the interim reviews, external experts reviewed the performance of the projects against their original objectives and were able to provide advice and guidance to the project consortia and feedback to the IHI office.

### 4. Ensure sound budget implementation.

For the operational payment appropriations, the JU maintained a good execution rate of 86.49 %. On call and grant management, IHI achieved the regulatory targets for:

- Time to inform (TTI): 72 days out of a target of 153 days
- Time to pay (TTP) interim payments: 61 days out of a target of 90 days
- TTP final payment: 72 days out of a target of 90 days

The JU was also efficient in making administrative payments:

- TTP for titles 1 and 2: 10 days out of a target of 30 days
- TTP for evaluation expert payments: 18 days out of a target of 30 days
- TTP for review experts: 10 days out of a target of 30 days

This was achieved thanks to the continued use of the Horizon 2020 and Horizon Europe IT management tools and regular monitoring.

IHI also maintained a low error rate for ex-post audits (below the 2 % materiality threshold), demonstrating the effectiveness of IHI’s control procedures.

**5. Develop and deploy an assertive communication strategy to promote IHI JU, its objectives and new rules for participation, and to target audiences (with particular emphasis on new players and newcomers), with the aim of attracting high quality applications to IHI JU's first calls for proposals.**

The IHI Communication Policy was prepared following a collaborative process led by the Programme Office and involving all IHI partners. The policy, which will guide IHI's communication activities in the coming years, was adopted by the Governing Board.

Throughout the year, IHI organised multiple events to promote IHI calls and explain both the individual topics as well as the rules for participation. The events also included a strong networking component, to facilitate the formation of strong, cross-sector consortia.

In 2022 the Programme Office established procedures to bring on board IHI contributing partners, and published a guide and templates on the IHI website. The Governing Board accepted 3 applications from legal entities who became the first IHI contributing partners.

**6. Explore synergies with relevant programmes at Union, national, and regional level, in particular with those supporting the deployment and uptake of innovative solutions, training, education and regional development.**

During 2022, IHI JU established the foundations for exploiting the full potential of synergies with other health-related initiatives at EU and global level, complementing the areas of intervention of IHI JU.

In order to do so, a task force with representatives from the Office, industry and the EC was established, which screened the landscape of health-related initiatives and identified several areas of potential synergies within other parts of Horizon Europe (such as missions and partnerships) and international organisations. Initial contacts were established with some of them, including EDCTP3 JU, the Cancer Mission, KDT (Key Digital Technologies) JU, EIT (European Institute of Innovation and Technology) Health and HERA (Health Emergency Preparedness and Response Authority).

During this process, the Governing Board, SIP and SRG were regularly informed of the progress of the task force and their advice was sought in order to properly prioritise among the rich panorama of programmes and initiatives.

Finally, IHI JU continued engaging with its key stakeholders such as patients, regulators and SMEs, to ensure effective and continuous synergies and collaboration at this level too.

**7. Improve and broaden access to project outcomes by embedding dissemination and exploitation activities in all stages of the project lifecycle.**

During 2022, IHI took part in several working groups established to advance the Horizon Europe monitoring framework at partnership and inter-JU level. Specifically, IHI facilitated the working group formed by the industrial partners and the EC leading to the adoption of the IHI-specific key performance indicators (KPIs) in March 2022. The Programme Office also participated in the working groups with the EC's Expert Group in charge of the development of the Horizon Europe KPIs common to partnerships, and contributed to the discussions amongst the EU agencies and other JUs to summarise common understanding and requests for clarifications. In addition, IHI contributed to the Biannual Monitoring Report (BMR) which was published in 2022 and is a bi-annual survey launched by the European Commission to monitor the performance of partnerships. In terms of outreach activities, IHI gave a presentation at the European Partnerships Stakeholder Forum on 15- 6 November 2022. Additionally, IHI staff took part in several information days to

give prospective applicants and other stakeholders the opportunity to get information and ask questions about IHI funding opportunities.

While no IHI projects had started and thus produced outcomes in 2022, the office continued to improve and broaden access to the results of IMI1/IMI2 projects via constant monitoring of the dissemination and exploitation activities reported at periodic/final reporting and amplifying their access using all available communication channels. The significance of the overall body of project results disseminated to the research community during 2022 is also documented in the yearly bibliometric report.

## 1.2 Research & innovation activities and achievements

### Adoption of the IHI Strategic Research and Innovation Agenda (SRIA)

The Governing Board formally adopted the IHI Strategic Research and Innovation Agenda (SRIA) on 20 January 2022 and it was published online shortly afterwards. The SRIA was written jointly by the European Commission and the IHI industry partners, and draws heavily on a consultation on an early draft that attracted 100 responses from stakeholders including academic institutions, healthcare professionals and patients.

The SRIA focuses on the specific objectives of IHI:

a. Improve our understanding of the factors that affect our health and the development and treatment of certain diseases.

b. Integrate fragmented health research and innovation efforts by bringing together health industry sectors and other stakeholders. This will enable the development of tools, data, platforms, technologies and processes that will in turn facilitate the prevention, diagnosis, treatment and management of diseases, especially in areas where there is an unmet public health need.

c. Demonstrate the feasibility of integrated healthcare solutions that draw on various technologies from different sectors and address the needs of the people who will use them, such as patients and healthcare professionals.

d. Make better use of opportunities to gather health data and use it in research and care, all while respecting relevant privacy legislation.

e. Develop ways of assessing the value of innovative, integrated health care solutions to patients, carers, healthcare professionals and organisations, and other stakeholders.

For each specific objective, the SRIA explains in detail the current challenges; how IHI could address them; and suggests potential outputs for IHI projects and, crucially, the medium to long-term impacts.

For example, potential outputs under specific objective 1 (on improving our understanding of the factors that influence our health and diseases) include biological markers to diagnose diseases or monitor patients' response to treatment, or tools to improve the tracking of infectious disease outbreaks. Expected impacts under this objective include earlier diagnosis of diseases studied or better preparedness of EU healthcare systems in case of disease outbreaks.

#### Thematic focus

Project ideas involving a specific disease will be selected based on the burden of the disease for patients / society due to its severity or the number of people affected; and the economic impact of the disease for patients / society. This is because the IHI SRIA does not list a specific set of diseases on which IHI projects should focus. Project ideas that do not focus on a disease will be assessed based on the extent to which their results could have a transformational impact on innovation processes.

#### Activities

The SRIA emphasises that the work supported by IHI will be pre-competitive, meaning it will not deliver products or services directly into healthcare systems or the market. As such, IHI projects are expected to focus on the following kinds of activities:

- discovery of new molecules, mechanisms of action, processes, technologies;
- development and testing of these discoveries;
- development of methodologies for the assessment of safety, health outcomes, or for health-economic evaluation;
- pre-standardisation activities;
- contributions to regulatory science;
- pilots / proofs of feasibility, including in silico (i.e. virtual) trials.

Together with the Council Regulation creating IHI, the SRIA will guide IHI's decisions when choosing what topics should be included in the annual scientific priorities and, by extension, in IHI calls for proposals. The SRIA also flags up potential synergies with other initiatives.

## IMI project outputs

The IHI Programme Office continues to manage the large number of projects launched under the IMI1 and IMI2 programmes. Both programmes had ambitious goals; for example, the aims of IMI2 include improving and accelerating the drug development process; developing diagnostic and treatment biomarkers for disease; and developing new therapies for diseases where there is a high unmet need.

In order to track progress against these ambitious goals, the Programme Office classifies project outputs according to the following categories:

- new tools/resources for drug discovery & preclinical drug development;
- biomarkers and tools developed to predict clinical outcomes (efficacy and safety);
- improved protocols for clinical trial design and processes;
- biomarkers for the efficacy and safety of vaccine candidates;
- new taxonomies of diseases and new stratifications of patient sub-populations;
- development and use of cohorts, registries and clinical networks for clinical studies and trials;
- big data solutions to leverage knowledge / implementation of data standards;
- education and training for new and existing R&D scientists and stakeholders;
- impact on regulatory framework;
- implementation of project results inside industry;
- accessibility of resources/outputs beyond consortium.

These categories are aligned with the IMI2 key performance indicators (KPIs), and they allow the Programme Office to assess projects' actual impact on drug development. A detailed list of achievements for both IMI1 and IMI2 projects in these categories can be found in Annex 3 of this report.

What is notable is the number of projects whose outputs are having a real impact on drug development. In some cases, this impact comes through regulatory recognition; in others, it comes about because projects are making their results accessible to researchers outside the consortium.

Here, a selection of success stories demonstrates how IMI projects are delivering results that address a range of challenges in health research.

## Keeping the legacy alive

Maintaining resources and results once the funding period has finished is a challenge for most projects. A number of IMI projects have set up legacy organisations to ensure that the work started during the funding period can continue long into the future.

**ENABLE-ing the early stages of antibiotic development**

We urgently need new antibiotics, yet the early stages of antibiotic development are highly challenging as they require a diverse range of skills and expertise. ENABLE set up a successful drug discovery and development platform, and invited research groups to apply to use it for their antibiotic development programmes. In total, 23 programmes were accepted into the project, many of which reached key milestones in the drug development process.

The success of ENABLE prompted a group of institutes to set up the ENABLE-2 Drug Development Platform with funding from the Swedish government. Like ENABLE, ENABLE-2 aims to move potential antibiotics through the early stages of drug development, with the hope that they will successfully 'graduate' to other initiatives that focus more on the later stages of development. A number of programmes have already been accepted into ENABLE-2, including one which had reached the 'lead' stage in the initial ENABLE project.

**Non-profit set to continue IMI projects' ground-breaking diabetes work**

Over the years, the INNODIA and INNODIA HARVEST projects have delivered a wealth of new knowledge on type 1 diabetes, as evidenced by numerous papers published in scientific journals. Crucially, they have also delivered a master protocol designed to facilitate and speed up the launch of clinical trials using drugs designed to arrest type 1 diabetes in those who have been diagnosed recently. Today, they are running four clinical trials of medicines designed to prevent and cure type 1 diabetes.

To ensure their legacy, the projects have established INNODIA iVZW (internationale vereniging zonder winstoogmerk / international non-profit association) and appointed a Managing Director. At the core of INNODIA iVZW's work is the unique pan-European clinical trial infrastructure for type 1 diabetes that the projects have established. Looking to the future, the organisation hopes to expand this infrastructure, especially to southern and eastern European countries which are currently underrepresented; provide expertise on smart clinical trial design; optimise the use of data and biosamples from people with, and at risk of, type 1 diabetes for biomarker analysis; and provide access to expert research and biomarker laboratories.

**EQIPD for research quality**

Poor quality data is an issue in many research fields – all too often, results carried out in one organisation cannot be replicated elsewhere, and it is not always clear why. In medical research, consequences include poor decision-making, resulting in higher failure rates and longer drug development times.

IMI project EQIPD developed the EQIPD Quality System (EQIPD QS), which sets out a systematic approach to improving the quality of preclinical research data. EQIPD also developed a suite of tools and resources to further support researchers who want to follow best practice in this important field.

In 2022, the Guarantors of EQIPD e.V. (GoEQIPD) announced the formation of a registered association to provide the legal framework for future activities and ensure the preservation and further development of the legacy of the EQIPD project. In addition to keeping the EQIPD resources up to date, GoEQIPD aims to oversee the EQIPD certification process, and provide training to the research community on the generation of quality research.

**A collaborative partnership for the respiratory research field**

COVID-19 project DRAGON aims to use artificial intelligence (AI) and machine learning to develop a decision support system capable of delivering a more precise coronavirus diagnosis and more accurate predictions of patient outcomes. Together with the U-BIOPRED Alliance (itself a legacy of IMI1 asthma project U-BIOPRED) and the Paediatric Asthma Alliance, DRAGON established Precision Medicine BioPharmaX. This collaborative partnership brings together different disciplines, stakeholders, initiatives and disease domains such as asthma, chronic obstructive pulmonary disease (COPD), and COVID-19 to advance the concept of precision medicine. The new organisation will help to secure the sustainability of DRAGON's results.

**GetReal Institute continues to grow**

IMI projects GetReal and the GetReal Initiative developed new tools and resources to help advance the use of real-world evidence (RWE) in drug development and healthcare decision-making. The GetReal Institute was set up in 2021 as a non-profit to promote the uptake of the tools and resources developed by the IMI projects and continue to advance the adoption of RWE in decision-making in Europe and beyond.

In 2022, the institute announced its 24 founding members, which include public, private, non-governmental and academic organisations, and announced the names of its first executive board members. The new institute also continued to offer a range of courses on RWE in medicine development as well as on structured benefit-risk assessments of medicinal products.

## Showcasing synergies with other research programmes

A number of IMI projects have delivered results that were subsequently picked up by other projects, either within IMI or elsewhere, for further development.

**European Lead Factory search uncovers potential COVID-19 treatment**

The European Lead Factory boasts a collection of over half a million compounds and a state-of-the-art high throughput screening centre that researchers can apply to use for their own drug discovery programmes. In the early months of the COVID-19 pandemic, the project launched a fast-track procedure to select projects focused on the new disease. They selected a proposal from the Pivot Park Screening Centre (PPSC) based in the Netherlands. The centre wanted to find compounds that would prevent the virus's spike protein from binding with the ACE2 receptor found in human throat and lung cells – the virus's main way of attack.

The search revealed over 40 compounds that represent a good starting point for further development, as they block the interaction of the virus with the ACE2 receptor without affecting the physiological function of the receptor. The plan was to move to the next stage of drug discovery, dubbed the 'hit-to-lead' phase. This is done via the EU-funded ISIDORe project, which provides researchers with a portfolio of research services and resources to better prepare for future epidemic-prone pathogens.

**Anti-TB drug booster highlights synergies between partnerships**

Tuberculosis (TB) kills around 1.5 million people annually, making it one of the leading causes of death worldwide. The aim of the TRIC-TB project is to advance the development of two molecules that could boost the infection-fighting ability of ethionamide, one of the main frontline drugs used to treat the disease. In 2022, the project announced that it had successfully completed phase 1 clinical trials of one of the compounds, dubbed BVL-GSK098. The compound is now the subject of a phase 2a clinical trial being carried out via the

bEto-TB project, which is funded by the European & Developing Countries Clinical Trials Partnership (EDCTP2 programme).

**Studies highlight potential of IMI-funded antibiotic**

With antimicrobial resistance (AMR) on the rise, the hunt is on for a new class of antibiotics, i.e. one that works in a different way to existing antibiotics and so could prove lethal to bugs that are resistant to the antibiotics available today.

Enter Nosopharm, a French small and medium-sized enterprise (SME) which is on the verge of embarking on clinical trials of a new class of antibiotics that shows potential as a treatment for multi-drug resistant infections caused by bacteria defined as 'priority pathogens' by the World Health Organisation (WHO).

The new class of antibiotics is called odilorhabdins, and their early development was supported in part by IMI project ENABLE, which set up a collaborative platform with the expertise and resources needed to advance the development of new antibiotics. The work in ENABLE helped to refine and improve the odilorhabdins. More recently, their development has been further advanced in another IMI project, GNA NOW. GNA NOW is running three antibiotic development programmes in parallel, and two are odilorhabdins – NOSO-502 and NOSO-2G.

In 2022, GNA NOW announced the successful completion of toxicology studies on NOSO-502 and this, combined with other results on the compound's efficacy in laboratory tests and other elements, has prompted Nosopharm to prepare an application to launch a phase 1 clinical trial. In a phase 1 trial, a drug is tested for the first time in a small group of human volunteers, with the goal of assessing its safety.

## Regulatory impacts highlight PPP strength

Medicines development is necessarily a tightly-regulated world, and so having an impact on the regulatory framework is a major achievement, and project outputs with regulatory approval of some kind are more likely to be taken up and used more widely in research and drug development. The key performance indicators for the IMI2 programme show that as of the end of 2022, IMI2 projects had reported 24 completed regulatory procedures (against a target of 10).

**PREFER gets green light from EMA for patient preference work**

Patient perspective is important in all medical research and particularly in drug development. The PREFER project set out to assess when and how patient preferences on benefits and risks should be incorporated into decisions on medicinal products. One of the project's core outputs is a framework for patient preference studies that covers purpose, objectives, how to design and conduct the studies and how to interpret the results, as well as a document with points to consider when selecting the methods for carrying out a patient preference study.

In 2022, the European Medicines Agency (EMA) adopted a qualification opinion for the PREFER framework, endorsing it as a comprehensive reference document for planning and conducting patient preference studies (PPS).

The project published a report detailing its recommendations on when and how to best perform preferences studies and include patient preference in decision making during the medical product life cycle. The recommendations are accompanied by an operational guidance document that consists of 9 templates for use in the development and execution of a patient preference study. The project also released a series of 16

webinars to further assist anyone who is interested in the development and execution of patient preference studies.

Finally, Working Group XI of the Council for International Organisations of Medical Sciences (CIOMS) encourages the use of the PREFER recommendations in its 2022 report on patient involvement in the development, regulation and safe use of medicines.

**NECESSITY's STAR shines bright**

Primary Sjögren's Syndrome (pSS) is an autoimmune disease in which the immune system attacks cells in the body that secrete fluids, such as tear and salivary glands. Symptoms include itchy eyes, a dry mouth, joint and muscle pain, difficulty concentrating, and disabling fatigue. Although there are treatments to alleviate some symptoms of pSS, there is no cure. As different patients have different symptoms, and respond differently to the treatments, it is very hard to assess the effectiveness of treatments. To address this, IMI project NECESSITY developed the Sjögren's Tool for Assessing Response (STAR) to improve the assessment of drug efficacy on all aspects of pSS.

Details of the STAR are published in Annals of Rheumatic Diseases and are freely available to the scientific community for analysis of completed and future trials. Meanwhile the EMA has reviewed the STAR and issued a Letter of Support for its use as a tool to improve the assessment of drug efficacy on all aspects of Sjögren's. This recognition will facilitate the use of STAR in future academic- and industry-led clinical studies.

NECESSITY is further testing the STAR as a primary endpoint in its own trial, which will ultimately cover 300 randomised patients across 34 sites in 8 countries.

**MACUSTAR study on common cause of blindness gets regulatory nod**

People with age-related macular degeneration (AMD) gradually lose their central vision in both eyes. It is a leading cause of blindness, yet treatment options are extremely limited. Dry AMD, including the intermediate AMD (iAMD) stage, therefore represents a huge unmet need. One barrier to the development of new treatments is the lack of clinical endpoints capable of determining the effectiveness of treatments under development. Put simply, current tests do not detect all of the sight problems experienced by people with earlier stages of the disease (e.g. iAMD).

IMI project MACUSTAR was set up to develop and validate examinations that are capable of accurately detecting changes over time. They have developed a suite of markers and measures that could be used to assess how well a potential treatment works. Back in 2018, the European Medicines Agency (EMA) issued a first Letter of Support to MACUSTAR in which they endorsed the project's approach to developing and evaluating these measures. Since then, the project has completed its cross-sectional study, which assessed the ability of the measures to discriminate between patients with different stages of AMD.

The results of the cross-sectional study were promising, and EMA has now provided positive feedback on the results in a second Letter of Support. In their statement, the EMA broadly supports the project's interpretation of the results and encourages the ongoing validation of the measures.

The project is still busy with the longitudinal study part of the project involving 700 people to assess the progression of AMD to late stage AMD. Once the longitudinal data is captured, the project will again submit the results to the EMA for further scrutiny.

Regulatory feedback is important for projects like MACUSTAR, as this increases the likelihood of the project's biomarkers and endpoints being accepted for use in future interventional clinical trials for new AMD treatments. Ultimately, the project will therefore facilitate the development and testing of new treatments for AMD.

**EHDEN data partners picked up by major EMA data network**

In 2022, the EMA and the European Medicines Regulatory Network set up a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines, including vaccines, from real world healthcare databases across the EU. Dubbed DARWIN EU (Data Analysis and Real World Interrogation Network) the centre is tasked with delivering real-world evidence from across Europe on diseases, populations and the uses and performance of medicines. It is also an early flagship 'pathfinder' for the European Health Data Space.

Key to the success of DARWIN EU is the availability of data partners who can generate the real world evidence needed for scientific evaluations and regulatory decision making. The first data partners were announced in 2022, and many are already data partners in IMI project EHDEN, which is building a pan-European federated data network. EHDEN ensured the data partners' data was mapped to a common data model, and this in turn made those organisations suitable data partners for DARWIN EU.

## Helping healthcare systems to breathe easier

In the winter of 2022-23, news headlines in many European countries warned of hospitals becoming overwhelmed with patients affected by respiratory diseases such as flu, respiratory syncytial virus (RSV), and COVID-19.

IMI has a large portfolio of projects tackling infectious respiratory diseases, and their results could ultimately help to reduce the burden these diseases place on health systems and patients alike.

**RESCEU highlights scale of RSV challenge**

Respiratory syncytial virus (RSV) is a relatively common disease, and most people who have it will only experience mild symptoms. However, in some cases, it can result in pneumonia and require hospitalisation. Babies and children, as well as the elderly and people with weakened immune systems, are particularly vulnerable to the disease. IMI project RESCEU is gathering information on the scale of RSV infection in Europe and its economic impacts so that we can improve how the disease is managed, treated and (hopefully) prevented in the future.

In 2022, the project published research in The Lancet showing that in 2019, RSV was responsible for the deaths of 100 000 children under the age of 5 worldwide. This means that 2% of deaths in young children were due to RSV. Currently, there is no approved vaccine for RSV, however, a number of vaccines are under development. The data gathered by RESCEU will help in the design of immunisation strategies so that they offer the best protection for those vulnerable to the disease.

**FLUCOP: a focus on flu vaccine efficacy**

Every year, pharmaceutical companies develop vaccines designed specifically to combat the strains of flu that are most likely to be in circulation the following winter. Vaccines are also developed in response to emerging pandemics. However, accurately predicting how much protection a new vaccine would actually offer against emerging virus types is far from easy. The FLUCOP project is delivering tools and knowledge to assess the efficacy of new vaccines more reliably.

For example, the haemagglutination inhibition (HAI) assay, which measures the levels of certain antibodies, has been used for decades to assess influenza immunity (caused by either vaccination or infection). However, HAI assay results from different laboratories can differ markedly. The FLUCOP team developed a protocol to improve the consistency of these tests and explored other factors that can influence the results of

this vital assay. In an article in the journal mSPHERE, the FLUCOP team demonstrate how using a common protocol, along with standard calibrators and reference testing material, can consistently reduce variations in results from different laboratories.

While most flu vaccination strategies focus on generating an immune response to the virus's haemagglutination surface protein, there is growing interest in the immune system's response to the virus's neuraminidase protein. FLUCOP set out to develop a reliable way of testing for this, and the results are published in Frontiers in Immunology. They note that their standard operating procedure for the assay, which has been validated and is provided as an annex to the article, was 'precise, linear, robust within defined limits across multiple testing laboratories'.

**DRIVE-ing the conversation on flu vaccine effectiveness**

The DRIVE project set out to create a platform, bringing together diverse stakeholders, to study the effectiveness of different brands of flu vaccines in the EU over a five-year period. Over the 5 flu seasons from 2017 to 2022, the project gathered data from more than 35 000 patients, approximately 60 variables and 13 influenza vaccines. The DRIVE partners consider that this valuable database could be leveraged and further utilised for various reasons, such as research into the next generation of influenza vaccines, and as part of worldwide efforts to enhance global surveillance networks for respiratory viruses and associated diseases. The project therefore developed a framework for open access to research data, allowing the secondary use of the data generated since the 2018/19 season.

**Tackling infectious diseases in the elderly**

As people age, their immune systems become weaker, and they become more vulnerable to infectious diseases such as flu and COVID-19. Preventing these infections through a proper vaccination strategy is essential for promoting healthy ageing. IMI project VITAL is delivering knowledge and resources to facilitate the design of vaccination strategies tailored to older people. For example, they have developed an open access, searchable online catalogue that offers users a rapid overview of existing data sources on infectious diseases that are known to affect ageing adults. The catalogue is interesting for pre-clinical drug development, and for those interested in assessing the impact of specific infectious diseases.

**Doing better on diagnostics**

If we want to tackle antimicrobial resistance (AMR), we need to ensure that antibiotics are only used when absolutely necessary. However, data shows that in Europe, 30-50% of antibiotics are prescribed unnecessarily. Greater use of diagnostic tests could help to bring this figure down by ensuring that doctors only prescribe antibiotics when absolutely necessary. The goal of VALUE-Dx is to generate evidence on the medical, economic, and public health value of diagnostics in treating AMR. The project has produced a report entitled Recommendations for innovative fit for purpose pricing and funding models for community-acquired acute respiratory tract infections (CA-ARTI) diagnostics. VALUE-Dx proposed a total of 15 recommendations targeted at policymakers; 10 of them are clustered in the policy areas of health technology assessment (HTA), pricing and procurement, and funding. Five additional recommendations refer to overarching aspects that are conducive to the successful implementation of policies. These stress the importance of communication and stakeholder involvement, collaborative approaches (also across countries), and monitoring and evaluation as essential components of policy implementation.

**Adding to our knowledge and resources on COVID-19**

IMI projects are continuing to add to our knowledge of COVID-19 in a number of ways.

- CARE, which was launched as part of IMI's special call for proposals on the disease, has identified a 'core gene signature' of COVID-19 convalescence (up to 6 months post-infection) associated with a history of thrombotic events (i.e. blood clots).
- DRIVE quickly took the platform it created to monitor flu vaccine effectiveness and adapted it to monitor COVID-19 vaccines.
- EHDEN published research showing that COVID-19 vaccines do not raise the risk of developing four rare neurological disorders, but an increased risk was seen in unvaccinated infected people with the disease.
- A common data model from IMI project ConcePTION has been used in several European Medicines Agency safety projects related to COVID-19 vaccines and pregnancy.

## Making big data a reality in health research and drug development

The ongoing discussions on the European Health Data Space (EHDS) mean that health data, and its wider use, are regularly in Brussels bubble headlines. IMI projects are delivering results that could help to make the EHDS a reality, and also demonstrating how things like blockchain technology and machine learning can be used to advance health research.

**BigData@Heart delivers framework to boost quality of research using real world data**

In a bid to address many of the quality, privacy and transparency issues surrounding health data, the BigData@Heart project teamed up with the European Society of Cardiology (ESC) to develop 'pragmatic advice' on the use of structured healthcare data in clinical trials and observational research. The goal was to deliver something that would be applicable across different disease areas, and meet the needs and expectations of all stakeholders, including the general public.

The result, dubbed the CODE-EHR framework, aims to improve the quality of studies using structured healthcare data, and provide confidence in the results of these studies for use in clinical decision-making. The framework is published via open access papers in the European Heart Journal, the British Medical Journal (BMJ) and the Lancet Digital Health, and it was presented at the ESC Congress.

The framework focuses on five key areas: dataset construction and linkage (to provide an understanding of how the data were identified and used); data fit for purpose (to ensure transparency on the coding systems used); disease outcomes and definitions (detailing how conditions and outcome events were defined); analysis (detailing how outcome events were analysed); and ethics and governance (covering processes for consent, privacy, and patient and public involvement).

For each area, the framework sets out both minimum and preferred standards, and details the information that researchers should provide when writing up their study. The consortium contacted the top journals in the field to ask them to join the initiative; four of them already added or agreed to include this checklist as a recommendation or requirement for new publications.

**BIGPICTURE makes progress on imaging and AI plans**

Many diseases are still diagnosed, monitored and studied in part on the basis of biological samples that have been mounted on a glass slide and studied under a microscope. Today, that analysis is still carried out by a human pathologist, but what if the slides could be scanned and analysed using artificial intelligence (AI)?

And what if they could be placed in a repository and made available to the scientific community? These are the questions the BIGPICTURE project hopes to answer.

In 2022, the project uploaded the first dataset of 80 whole slide images (WSI) of 8 cases of melanoma to its platform.

The project has also developed and publicly released software tools to allow for the easy conversion of a range of existing WSI file formats to the digital imaging and communications in medicine (DICOM) standard, and published a report on the legal rules applicable to the contributors of WSI for eight countries. This report will help the project to set up local procedures for data sharing within the project, while still adhering to all applicable laws and regulations.

**conect4children and CDISC release user guide to facilitate paediatric medicines development**

IMI project conect4children has teamed up with CDISC (the Clinical Data Interchange Standards Consortium) to produce a Paediatrics User Guide. The guide, which is freely available online, describes how to use CDISC standards to collect and structure data used in clinical trials to facilitate the aggregation of information, take advantage of big data and support data sharing.

Topics covered by the user guide include participant and participants' family information (e.g., medical conditions, reproductive, diet and nutrition, body system assessments), pregnancy and birth, study conduct. The guide shows how IMI projects, by collaborating with global standards development organisations like CDISC, can have an impact on research worldwide, and not just in Europe. More importantly, it will boost the impact of data gathered during paediatric clinical trials and so help to advance research into diseases that affect children.

**EHDEN health data network keeps growing and delivering results**

The aim of EHDEN is to create a federated data network allowing access to European health data at scale, and in a GDPR (General Data Protection Regulation) compliant manner. To achieve this, the project has run regular calls for both data partners with health data, and SMEs who can transform the health data to a common data model called OMOP (Observational Medical Outcomes Partnership). The project now counts 187 data partners from 29 countries who have over 800 million patient records that are being mapped to OMOP. That mapping is taking place thanks to the SMEs the project is training to do just that; by the end of 2022, the project had a group of 64 SMEs from 22 countries.

The project has also launched its Real World Data Portal offering findable, standardised data at scale. This portal provides a one-stop-shop for study planning, data access, standardised analysis & reporting with free access to the research community. It is currently populated with 160 million patient records from 20 countries, and will grow to include the complete EHDEN network of 800 million patient records.

The usefulness of EHDEN's data network was amply demonstrated during an event run jointly with the Uppsala Monitoring Centre (UMC) to evaluate the feasibility and utility of using the EHDEN data network to support of UMC's preliminary medicine side effect assessment process. The 'evidence-a-thon' event assembled more than 30 participants who analysed data from electronic health records, hospital, and registry data from Spain, the UK, Finland, Serbia, the Netherlands, and Norway. The exercise identified 9 new drug-event combinations, and showed that an analysis in 6 countries can be run in just 15 minutes.

**Need a recipe for FAIR data? Check out the FAIRplus cookbook!**

The goal of FAIRplus is to deliver guidelines and tools to facilitate the application of 'FAIR' ('findable, accessible, interoperable, reusable') principles to data from IMI projects and datasets from pharmaceutical companies. One of the key outputs of the project is the FAIRplus 'cookbook', which is packed with practical guidance on how to make and keep data FAIR. It currently includes over 50 'recipes' contributed by over 50

professionals from 30 organisations. The cookbook, which is freely accessible, has become an official service of the ELIXIR UK and Luxembourg Nodes; and IHI is recommending other project consortia to use it in their own work.

**PharmaLedger applies blockchain technology to health challenges**

In blockchain technology, data is decentralised, meaning it is stored across multiple servers. It is also immutable; this means data records (or 'blocks') cannot be changed or tampered with. Each new 'block' of data is connected to the previous one, creating the 'blockchain'. The blocks are connected by cryptography, making the system secure. Its most famous application is the bitcoin currency, yet it could also revolutionise the way other sectors work. The goal of the PharmaLedger project was to deliver a blockchain-based platform for the healthcare sector.

By the end of the project, the consortium had created a digital trust ecosystem comprising organisations working together to implement blockchain technologies in healthcare. They had also developed a number of use cases demonstrating how blockchain could be used to tackle specific challenges in three domains: supply chain, health data, and clinical trials. The most advanced use case is on electronic patient information (ePI) and shows how a simple app with a QR code reader could provide patients with the latest, regulatory-approved information on their medicines.

Although PharmaLedger has ended, the project's legacy lives on via the PharmaLedger Association, which was set up in 2022 and is building on the work started in the project.

**MELLODDY makes mark on machine learning in medical field**

The aim of the MELLODDY project was to develop a machine learning platform that would allow pharmaceutical companies' data to be used collaboratively while respecting the highly confidential nature of the data.

The project's novel artificial intelligence (AI) framework avoids the need for this confidential data to ever leave the owner's custody, while still allowing collaborative machine learning to train and evaluate predictive drug discovery models. The system was trained on data on billions of data points, including millions of small molecules and thousands of biological assays from 10 pharmaceutical companies.

Comparisons of tests using models trained via the platform, and models trained on data from just one partner, showed that the collaborative models were better at predicting which molecules could be interesting starting points for further drug development.

MELLODDY focused on drugs based on small molecules, but its federated approach to machine learning could also be applied to other areas of drug discovery and development.

## IMI projects address diverse challenges in health research and innovation

**Diabetes project results prompt review of clinical trial outcomes**

The BEAt-DKD project previously identified a number of different subtypes of type 2 diabetes. Diabetes patients in one sub-group ('severe insulin-resistant diabetes') are particularly prone to kidney problems, a well-known complication in diabetes. The hope was that this new classification of type 2 diabetes would lead to the development of more personalised treatments for the disease.

BEAt-DKD partner Eli Lilly had a drug in development called tirzepatide, which can substantially increase insulin sensitivity. They also knew that other, related drugs had slowed the progression of kidney disease in

type 2 diabetes patients. The company therefore went back to the data gathered during the SURPASS-4 clinical trial which assessed the efficacy and safety of tirzepatide as a diabetes treatment. They found that patients in the trial who received tirzepatide did better on measures of kidney function. These new findings, which were published in The Lancet Diabetes and Endocrinology, could trigger a new clinical trial and eventually, lead to a new indication for the drug.

**Cutting animal testing in vaccine manufacture**

Every batch of human or animal vaccines that is manufactured must undergo a series of rigorous tests to ensure it meets certain standards for safety and potency. Today, many of these batch tests involve large numbers of laboratory animals. The VAC2VAC project has delivered a suite of non-animal tests that could dramatically reduce the use of animals in these tests, and so would contribute to EU's '3Rs' goal to replace, reduce and refine the use of animals in research.

Now the project has also published a roadmap for achieving meaningful change in regulatory policy through the replacement of *in vivo* (animal) methods with *in vitro* methods. The roadmap includes practical considerations and best practices for developing a strategy to encourage the adoption and implementation of non-animal methods by industry partners and regulatory agencies worldwide.

**Putting the pharmaceutical sector on the path to a GREENER future**

Active ingredients from medicines can get into the environment through a variety of routes, and once there they can prove harmful to wildlife and ecosystems. The aim of PREMIER is to deliver a framework for assessing and characterising the environmental risks of active pharmaceutical ingredients (APIs). Writing in the journal Environmental Science and Technology Letters, the PREMIER team sets out its 'GREENER' concept for the discovery and development of medicines. As a starting point, the team highlights the close links between human and environmental health, noting that decision-making in drug discovery and development can be beneficial for both human and environmental health.

Among other things, the team highlights the importance of avoiding non-target effects, reducing environmental exposure to APIs (for example by using more targeted drug delivery methods), avoiding substances that don't break down in the environment, and mitigating risks as much as possible.

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

Running clinical trials in children is challenging. There is no infrastructure across Europe capable of delivering high quality clinical trials. Furthermore, as many children's diseases are rare, finding enough patients to run a trial can prove difficult, and so major innovations are needed in the design of paediatric clinical trials. IMI project conect4children is working to address these challenges. One important project output is an advice service 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" included not only clinicians, researchers and methodology experts, but also parents and patients themselves.

The network, which is described in the journal Clinical and Translational Science, comprises over 20 expert groups involving more than 400 experts. So far, some 40 advice requests have been received. The c4c network is now working to turn the pilot into a sustainable fee-for-service endeavour, which companies throughout Europe and beyond can benefit from.

**New findings highlight value of old data**

In a demonstration of the longevity and long-term usefulness of resources generated by IMI projects, data from four IMI projects was used to shed new light on risk factors for type 2 diabetes. In the new study, scientists analysed data from 7 000 individuals in 5 countries from four IMI projects – SUMMIT, DIRECT, RHAPSODY and BEAt-DKD. Their focus was a protein called follistatin, which is produced in many tissues and has been linked to metabolic diseases. The research revealed that people with high levels of follistatin in the blood have an increased risk of developing type 2 diabetes, independent of other known risk factors. The results are published in Nature Communications. The team concludes that follistatin could be used as a target for treatments design to prevent type 2 diabetes.

Another project which has used existing data to generate new insights is BIOMAP, which is probing the underlying causes of two common skin diseases: psoriasis and atopic dermatitis. By analysing existing genetic datasets of people with psoriasis, they uncovered some previously unknown genetic factors that are associated with onset of the disease. The results are published in Human Genomics.

One thing that the data showed was that skin from a psoriatic lesion displayed genetic differences to healthy skin from the same person. Even more intriguingly, the genetic pattern looked different again when compared 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) as well as breakdowns in connections within genetic networks. The findings could be used to identify new targets for drugs to treat psoriasis.

**A vital resource for future drug discovery**

Transport proteins act as our cells' gate-keepers, controlling the flow of nutrients and other molecules (including drugs) into and out of the cell. With over 400 members, solute carriers (SLCs) represent the largest class of transport proteins. Yet although they have been implicated in diseases ranging from Alzheimer's disease and amyotrophic lateral sclerosis (ALS) to schizophrenia, solute carriers have never been studied in depth.

IMI projects RESOLUTE and RESOLUTION are studying SLCs in unprecedented detail, delivering knowledge, resources and tools to facilitate further research into, and drug discovery focusing on, these important proteins. Most importantly, the projects' outputs are freely available online, something that will boost their chances of having an impact.

For example, RESOLUTE has developed 25 assays to test the effect of different chemical compounds on individual SLC function for future use in drug discovery by the pharmaceutical industry and SMEs. These assays have been optimised and adapted to high throughput and medium throughput platforms for drug screening. The protocols and first results have been shared in the open access repository PubChem.

REsolution has compiled publicly available data on genetic variation in SLC genes and their association with diseases which can be visualised in the project's portal. An algorithm developed by the project allows the quantification and comparison of the variants across SLCs.

Other RESOLUTE public outputs can be accessed via the project website:

- tools & reagents: re-solute.eu/resources/reagents
- data generated by RESOLUTE or gathered form public repositories: resolute.eu/resources/datasets
- transcriptomics and imaging datasets in visualisation dashboards: re-solute.eu/resources/dashboards

## 1.3 Calls for proposals, grant information and other funded actions

### Launch and management of calls in 2022

Following the launch of IHI at the end of 2021, the IHI Programme Office worked hard to develop the call launch, evaluation and grant award procedures and associated templates and guidance documents, ensuring that they reflected both the Horizon Europe rules and IHI's specificities such as the 45% eligibility criterion. In parallel, the office worked with the IHI members to draft the topics for IHI's first calls for proposals. This exercise included consultations with both the States' Representatives Group (SRG) and the newly-created Science and Innovation Panel (SIP).

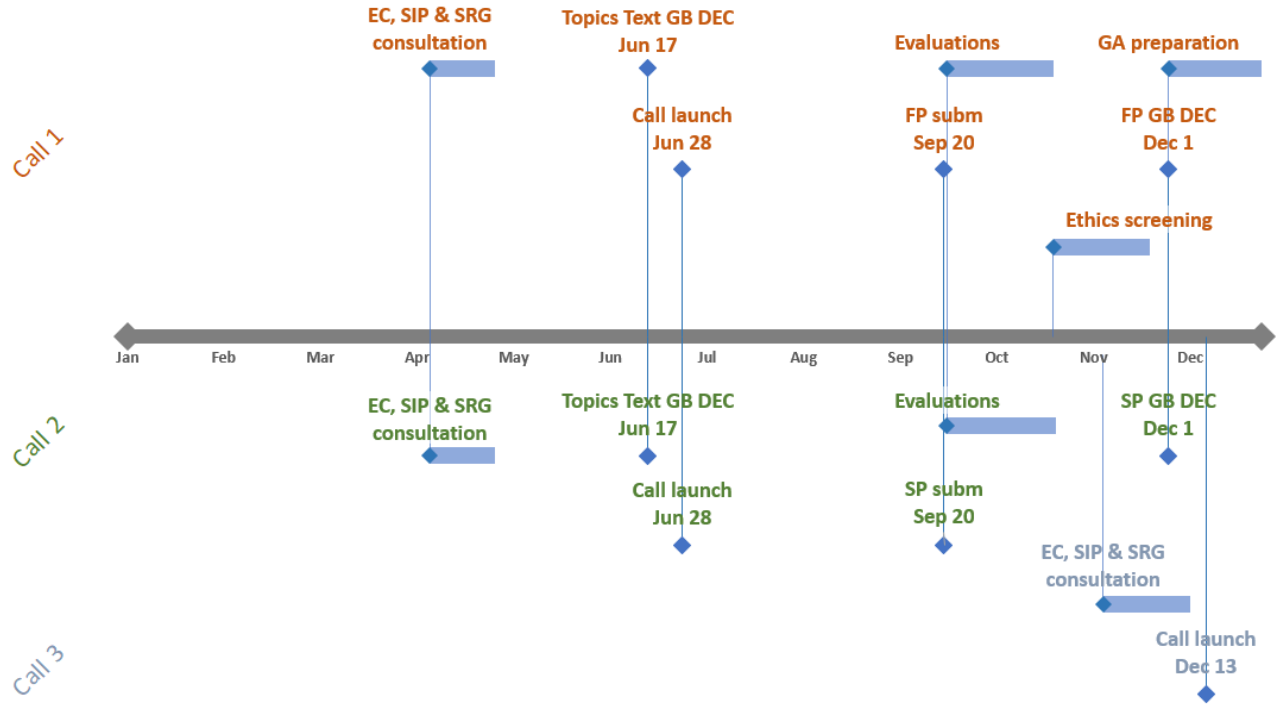
Thanks to this hard work in the first part of 2022, IHI was able to launch IHI call 1 (a single stage call with four topics) and call 2 (a two stage call with two topics) on 28 June. IHI call 3 (single stage, five topics) was launched on 13 December.

The evaluation for IHI call 1 was completed in 2022; grant preparation started in December, and Grant Agreement signature will be completed in 2023. The evaluation for IHI call 2, stage 1 was also completed in 2022 and the stage 2 evaluation will take place in Q1 of 2023. As IHI call 3 was launched in mid-December 2022, the call was still open for applications at the end of the year.

The ethics screening was carried out by a separate ethics expert panel and, in 2022, concerned only IHI call 1.

The chart below shows a timeline of the development of the calls, including the consultations with the SRG, SIP and the European Commission (EC).

*Timelines of IHI calls 1, 2 & 3* [6]




[6] SP SUBM – Short proposal submission deadline; SP GB DEC – Short proposal Governing Board decision; FP SUBM – Full proposal submission deadline; FP GB DEC – Full proposal Governing Board decision; GA – Grant Agreement; GB DEC – Governing Board decision; EC – European Commission; SRG – States' Representatives Group; SIP – Science and Innovation Panel

## Outcome of IHI's first calls – calls 1 and 2

Thanks to a strong communication campaign by IHI as well as the European Commission and COCIR, EFPIA (also representing Vaccines Europe), EuropaBio and MedTech Europe and, despite the newly introduced 45% eligibility threshold, calls 1 and 2 attracted 18 and 15 proposals respectively. IHI closely analysed the admissibility and eligibility of all proposals to move on with the scientific evaluation, which was carried out remotely and was finished before the end of October. The whole evaluation process was successful and IHI managed to inform applicants of the outcome of the evaluation just 72 days after the call launch, well ahead of the 153-day deadline for sending evaluation result letters. To be able to launch the projects as soon as possible, IHI started to work on the Grant Agreements straight after sending out the evaluation letters.

## Ethics evaluation process

In addition to the scientific evaluations, the IHI Programme Office organises ethics evaluations for single-stage proposals recommended for funding and single stage proposals placed on the main and reserve lists. As per the Horizon Europe Programme Guide[7], which outlines how the ethics appraisal framework works, the Programme Office independently operates the ethics review procedure and relies on external independent ethics experts.

In 2022, IHI ran one ethics screening session for the six above-threshold proposals of IHI call 1. Of these six proposals, three were cleared while three were conditionally cleared. Those with a conditional clearance have a set of requirements to be addressed by the consortium during the granting phase and/or as specific ethics deliverables over the project implementation phase. No proposals were sent to ethics assessment.

## Complaints

There were no admissibility/eligibility or evaluation review requests for proposals not selected for funding under IHI calls 1 and 2.

[7] https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/programme-guide_horizon_en.pdf (page 21)

## 1.4 Evaluation procedures and outcomes

Tables summarising key information related to IHI call launches, submission deadlines and Grant Agreements signed in 2022

### IHI JU single-stage calls

| Call | Topics | Launch date | Submission deadline | FPs received[8] | Applicants in eligible FPs | FPs submitted | FPs evaluated | FPs above-threshold | FPs selected for funding | GAs signed in 2022 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | An innovative decision-support system for improved care pathways for patients with neurodegenerative diseases and comorbidities<br>Next generation imaging and image-guided diagnosis and therapy for cancer<br>Personalised oncology: innovative people centred, multi-modal therapies against cancer<br>Access and integration of heterogeneous health data for improved healthcare in disease areas of high unmet public health need | 28/06/2022 | 20/09/2022 | 18 | 233<br>(197 unique participants) | 13 | 13 | 6 | 5 | open |
| 3 | Screening platform and biomarkers for prediction and prevention of diseases of unmet public health need<br>Patient-generated evidence to improve outcomes, support decision making, and accelerate innovation<br>Combining hospital interventional approaches to improve patient outcomes and increase hospital efficiency<br>Strengthening the European translational research ecosystem for advanced therapy medicinal products (ATMPs) for rare diseases | 13/12/2022 | 15/03/2023 | open | open | open | open | open | open | open |

8 'Received' proposals are the proposals sent via the Funding and Tenders (F&T) portal before the call deadline; 'Submitted' proposals are those considered admissible while the 'evaluated' proposals are those that are also eligible.

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

## IHI JU two-stage calls

| Call | Topics | Launch date | Submission deadline (Stage one) | SPs received | Applicants in eligible SPs | SPs submitted | SPs evaluated | SPs above-threshold | SPs invited to stage 2 | Submission deadline (Stage two) | Applicants in eligible FPs (stage 2) | GAs signed in 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | Cardiovascular diseases - improved prediction, prevention, diagnosis, and monitoring<br><br>Setting up a harmonised methodology to promote uptake of early feasibility studies for clinical and innovation excellence in the European Union | 28/06/2022 | 20/09/2022 | 15 | 274<br>(251 unique participants) | 15 | 15 | 11 | 2 | 28/02/2023 | open | open |

**Table summarising IHI calls for proposals launched in 2022, call launch dates and the available budget per call**

| | | | Budget | | |
|---|---|---|---|---|---|
| IHI JU Call | Evaluation mode | Launch date | EU (in EUR) | IHI private members (in EUR) | Contributing partners (in EUR) |
| Call 1 | Single stage | 28/06/2022 | 95 000 000 | See note | See note |
| Call 2 | Two-stage | 28/06/2022 | 21 929 000 | 19 729 000 | 2 200 000 |
| Call 3 | Single stage | 13/12/2022 | 138 000 000 | See note | See note |

*Note regarding IHI – calls 1 & 3: As these were single-stage calls for proposals, no IHI private member / contributing partner contributions were indicated at call launch in the call topic texts as these contributions depend on the selected proposals. Information on IHI private member / contributing partner contributions to projects funded under IHI single stage calls will be available only once the Grants are signed in 2023.*

According to the 2022 Second Amended Work Programme, the scope of the scientific priorities 2022 will contribute to the achievement of the general and specific objectives of IHI JU as defined in Council Regulation (EU) 2021/2085, by tackling the challenges and progressing to achieve the expected impacts in one or more of the five SRIA scope areas / specific objectives.

- Specific Objective 1 (SO1): addresses the challenge of unravelling causal factors of disease that are still poorly understood, such as the interplay between genetic and environmental factors.
- Specific Objective 2 (SO2): addresses one or more of the barriers for the development of new types of products or services in the health domain that integrate diverse components (such as diagnostics, medicinal products, medical devices, wearables, treatment monitoring, digital solutions).
- Specific Objective 3 (SO3): addresses patient-centricity of innovations and the challenge of effectively engaging with all relevant health care actors (patients and civil society, health care professionals, health care providers, regulators, health technology assessment bodies and payers) for the design and development of new and/or integrated health solutions.
- Specific Objective 4 (SO4): addresses the challenge that, currently, data in many countries are hard to gather and demonstrate limited interoperability.
- Specific Objective 5 (SO5): addresses the methodological challenges in assessing the added value of health interventions based on emerging and converging technologies, which can only be partially addressed with current available tools and methods.

### Table summarising the implementation of Specific Objectives per call topic

| | | SO1 | SO2 | SO3 | SO4 | SO5 |
|---|---|---|---|---|---|---|
| **Call 1** | An innovative decision-support system for improved care pathways for patients with neurodegenerative diseases and comorbidities | | x | | | |
| | Next generation imaging and image-guided diagnosis and therapy for cancer | | x | | | x |
| | Personalised oncology: innovative people centred, multi-modal therapies against cancer | | x | x | | |
| | Access and integration of heterogeneous health data for improved healthcare in disease areas of high unmet public health need | | | | x | |
| **Call 2** | Cardiovascular diseases - improved prediction, prevention, diagnosis, and monitoring | x | | | | |
| | Setting up a harmonised methodology to promote uptake of early feasibility studies for clinical and innovation excellence in the European Union | | | | | x |
| **Call 3** | Screening platform and biomarkers for prediction and prevention of diseases of unmet public health need | x | | | | |
| | Patient-generated evidence to improve outcomes, support decision making, and accelerate innovation | | | x | | |
| | Combining hospital interventional approaches to improve patient outcomes and increase hospital efficiency | | x | | | |
| | Strengthening the European translational research ecosystem for advanced therapy medicinal products (ATMPs) for rare diseases | | x | | | |
| | Digital health technologies for the prevention and personalised management of mental disorders and their long-term health consequences | x | | | | |

## Progress / activities by call in 2022

In 2022, IHI organised two evaluation sessions for the first two calls launched in 2022 (IHI call 1 (single stage, SS) and IHI call 2 (stage 1)). The two evaluation sessions were completed successfully, in line with both Horizon Europe and IHI rules and procedures. A third call was launched at the end of 2022, with a deadline for applications of 15 March 2023. The table below presents the calls in different stages of the process in 2022, from the call launch until sending the letters to start GAP.

| IHI call | Call type | N° topics | Launch date | Submission deadline (SS or S1) | Approval of evaluation results (SS or S1 | Invitation to prepare FP in S2 | Submission deadline S2 | Approval of evaluation results in S2 | Invitation to start GAP |
|---|---|---|---|---|---|---|---|---|---|
| Call 1 | Single stage | 4 | 28/06/2022 | 20/09/2022 | 30/11/2022 | N/A | N/A | N/A | 01/12/2022 |
| Call 2 | Two-stage | 2 | 28/06/2022 | 20/09/2022 | 30/11/2022 | 01/12/2022 | 28/02/2023 | open | open |
| Call 3 | Single stage | 5 | 13/12/2022 | 15/03/2023 | open | open | open | open | open |

## Applicants

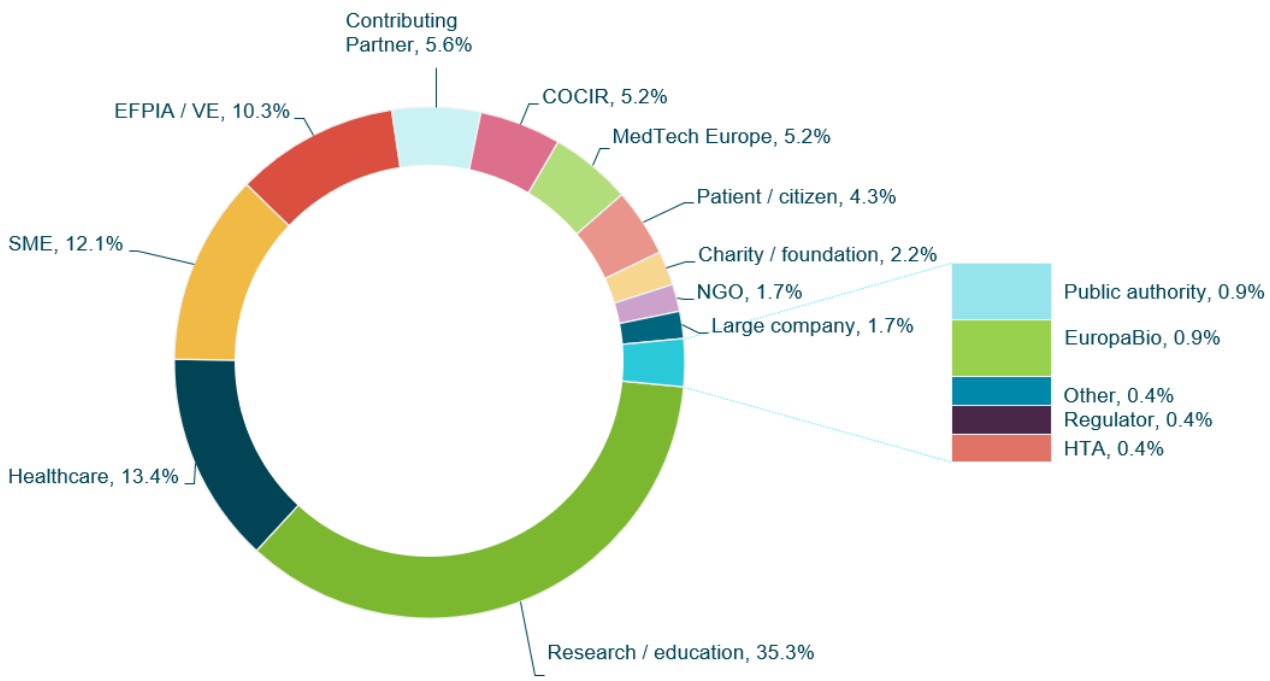
The tables and charts below show the breakdowns by country and by organisation type of applicants in eligible proposals for IHI Calls 1 and 2. Note that the organisation types given are what the applicants declared. For space reasons, the following organisation types are abbreviated in the tables and charts:

- Healthcare = Healthcare professional organisation / healthcare provider
- Large company = Large company (for-profit legal entity)
- Research / education = Research / higher or secondary education organisations (private or public)
- SME = Small & medium enterprise
- Patient / citizen = Patient / citizen organisation
- Mid-cap = Mid-cap (for-profit legal entity)
- HTA = Health technology assessment body
- Regulator = Regulator or regulatory body
- NGO = Non-governmental organisation
- EFPIA / VE = EFPIA including Vaccines Europe

## IHI call 1 (single stage): geographical distribution of applicants in eligible proposals

| | Charity / foundation | Healthcare | Large company | Public authority | Research / education | SME | Patient / citizen | N/A | Mid-cap | HTA | Regulator | NGO | Other | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Austria** | | | | | 5 | | | 1 | | | | | | **6** |
| **Belgium** | | | 3 | | 2 | 4 | 6 | | | | | 2 | | **17** |
| **Czechia** | | 1 | | | | 1 | | | | | | | | **2** |
| **Denmark** | | 1 | | | 4 | 1 | | | | | 1 | | | **7** |
| **Finland** | | | | | 5 | 2 | | | | | | | | **7** |
| **France** | 1 | 3 | 6 | | 4 | 2 | | | | | | 1 | | **17** |
| **Germany** | | 8 | 6 | | 16 | 6 | | | 1 | | | | 1 | **38** |
| **Greece** | | | | | 1 | | | | | | | | | **1** |
| **Hungary** | | | | | 2 | 1 | | | | | | | | **3** |
| **Ireland** | | | 1 | | | | | | | | | | | **1** |
| **Israel** | | | 3 | | | | | | | | | | | **3** |
| **Italy** | | 5 | 1 | | 7 | 2 | | | | | | | | **15** |
| **Lithuania** | | | | | | 1 | | | | | | | | **1** |
| **Luxembourg** | 1 | | 1 | | 1 | 1 | 1 | | | | | | | **5** |
| **Netherlands** | 1 | 1 | 6 | | 16 | 5 | 2 | | | | | 1 | | **32** |
| **Norway** | | 2 | 1 | 1 | 6 | 1 | | | | | | | | **11** |
| **Romania** | | | | | 1 | | | | | | | | | **1** |
| **Slovenia** | | 1 | | | | | | | | | | | | **1** |
| **Spain** | 2 | 4 | | | 5 | 2 | | | | | | | | **13** |
| **Sweden** | | 1 | 2 | | 5 | 5 | | | 1 | | | | | **14** |
| **Switzerland** | | 3 | 9 | | 2 | 2 | 1 | | | | | | | **17** |
| **UK** | | 2 | 4 | 1 | 2 | 3 | | | 1 | 1 | | | | **14** |
| **US** | | | 5 | | | 2 | | | | | | | | **7** |

## IHI call 1 (single stage): breakdown by organisation type of applicants in eligible proposals

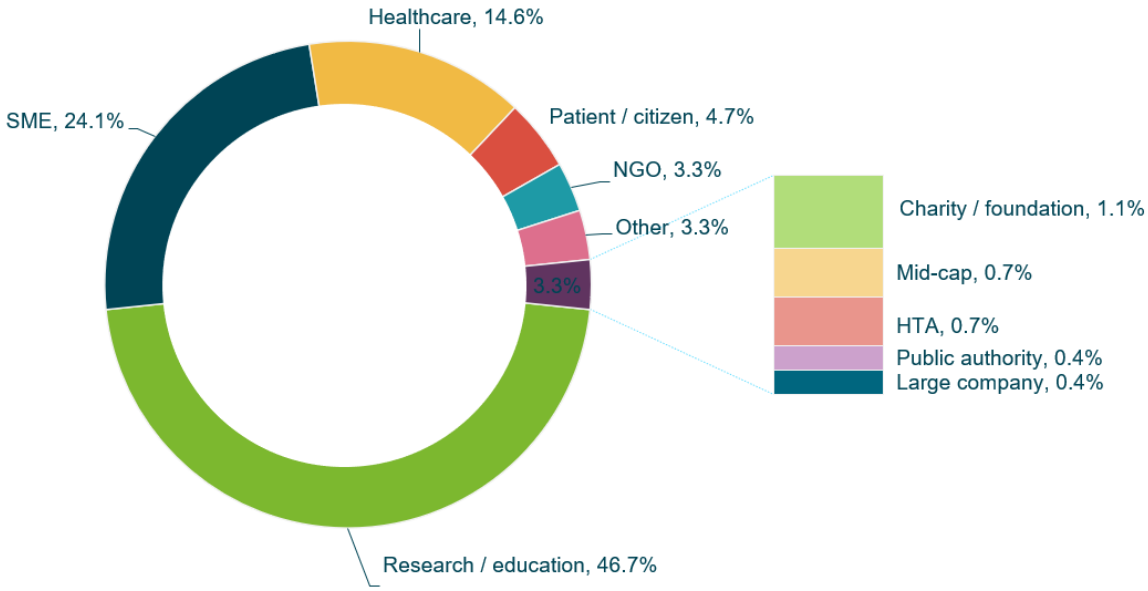



## IHI call 2 (two stage): geographical distribution of applicants in eligible short proposals

| | Charity / foundation | HTA | Healthcare | Large company | Mid-cap | NGO | Other | Patient / citizen | Public authority | Research / education | SME | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Austria** | | | | | | | | | | 5 | 2 | **7** |
| **Belgium** | | | 2 | | | 1 | | 4 | | 5 | 4 | **16** |
| **Bulgaria** | | | | | | 3 | | 1 | | | | **4** |
| **Canada** | | | | | | | | | | 1 | | **1** |
| **Cyprus** | | | | | | | | | | | 1 | **1** |
| **Czechia** | | | | | | | | | | 1 | 1 | **2** |
| **Denmark** | | | 1 | | | 1 | | | | 5 | | **7** |
| **Estonia** | | | | | | | | | | 1 | 1 | **2** |
| **Finland** | | | | | | | | | | 7 | 2 | **9** |
| **France** | | | 6 | | | | 2 | 1 | | 7 | 2 | **18** |

| | Charity / foundation | HTA | Healthcare | Large company | Mid-cap | NGO | Other | Patient / citizen | Public authority | Research / education | SME | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Germany** | | | 2 | | 1 | 2 | 2 | 1 | | 16 | 8 | **32** |
| **Greece** | | | 1 | | | | | | | 6 | 4 | **11** |
| **Hungary** | | | | | | | | | | | 1 | **1** |
| **Ireland** | | | | | | | | 2 | | 6 | 4 | **12** |
| **Israel** | | | | | | | | | | 1 | 1 | **2** |
| **Italy** | 1 | 1 | 7 | | 1 | | | | | 13 | 11 | **34** |
| **Latvia** | | | | | | | | | | 1 | | **1** |
| **Luxembourg** | | | | | | | | | | 1 | 2 | **3** |
| **Netherlands** | 1 | | 4 | | | | 1 | 1 | | 14 | 4 | **25** |
| **Norway** | | 1 | 1 | | | 2 | 1 | 1 | | 3 | | **9** |
| **Poland** | | | 1 | | | | | | | 1 | | **2** |
| **Portugal** | | | | | | | | | | 1 | | **1** |
| **Romania** | | | 2 | 1 | | | | | | | 4 | **7** |
| **Serbia** | | | 1 | | | | | | | 1 | 1 | **3** |
| **Slovenia** | | | 1 | | | | | 1 | | 3 | | **5** |
| **Spain** | | | 9 | | | | 1 | | | 11 | 5 | **26** |
| **Sweden** | | | 1 | | | | 2 | 1 | 1 | 2 | 2 | **9** |
| **Switzerland** | 1 | | 1 | | | | | | | 5 | 2 | **9** |
| **UK** | | | | | | | | | | 11 | 3 | **14** |
| **US** | | | | | | | | | | | 1 | **1** |

### IHI call 2 (two stage): breakdown by organisation type of applicants in eligible short proposals




*Note regarding the above chart. Industries appear to be under-represented because the pre-identified industry consortium members will join only in stage 2.*

## Participants

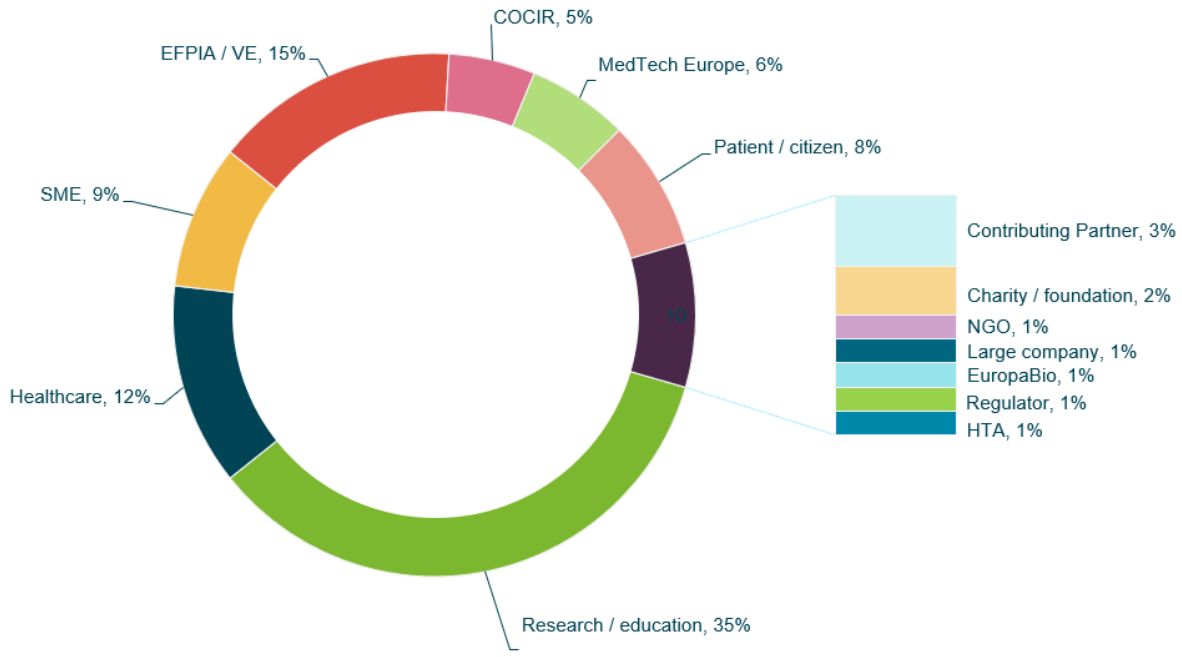
The tables and charts below show the breakdowns by country and organisation type of participants in selected proposals of IHI calls 1 and 2.

### IHI call 1 (single stage): geographical distribution of participants in selected proposals

| | Charity / foundation | Healthcare | Large company | Research / education | SME | Patient / citizen | Mid-cap | HTA | Regulator | NGO | Other | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Austria** | | | | 4 | | | | | | | | **4** |
| **Belgium** | | | 2 | 1 | 4 | 5 | | | | 1 | | **13** |
| **Czechia** | | 1 | | | | | | | | | | **1** |
| **Denmark** | | | | 4 | | | | | 1 | | | **5** |
| **Finland** | | | | 3 | 2 | | | | | | | **5** |
| **France** | | 1 | 3 | 3 | | | | | | | | **7** |
| **Germany** | | 5 | 2 | 7 | 3 | | | | | | | **17** |
| **Israel** | | | 2 | | | | | | | | | **2** |

| | Charity / foundation | Healthcare | Large company | Research / education | SME | Patient / citizen | Mid-cap | HTA | Regulator | NGO | Other | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Italy** | | 1 | | 1 | 1 | | | | | | | **3** |
| **Luxembourg** | | | 1 | 1 | 1 | 1 | | | | | | **4** |
| **Netherlands** | 1 | | 2 | 9 | 1 | 2 | | | | | | **15** |
| **Romania** | | | | 1 | | | | | | | | **1** |
| **Slovenia** | | 1 | | | | | | | | | | **1** |
| **Spain** | 1 | 2 | | 3 | 2 | | | | | | | **8** |
| **Sweden** | | 1 | | 2 | 1 | | 1 | | | | | **5** |
| **Switzerland** | | 1 | 6 | 1 | 1 | 1 | | | | | | **10** |
| **UK** | | 1 | 4 | | | | | 1 | | | | **6** |
| **US** | | | 4 | | 1 | | | | | | | **5** |

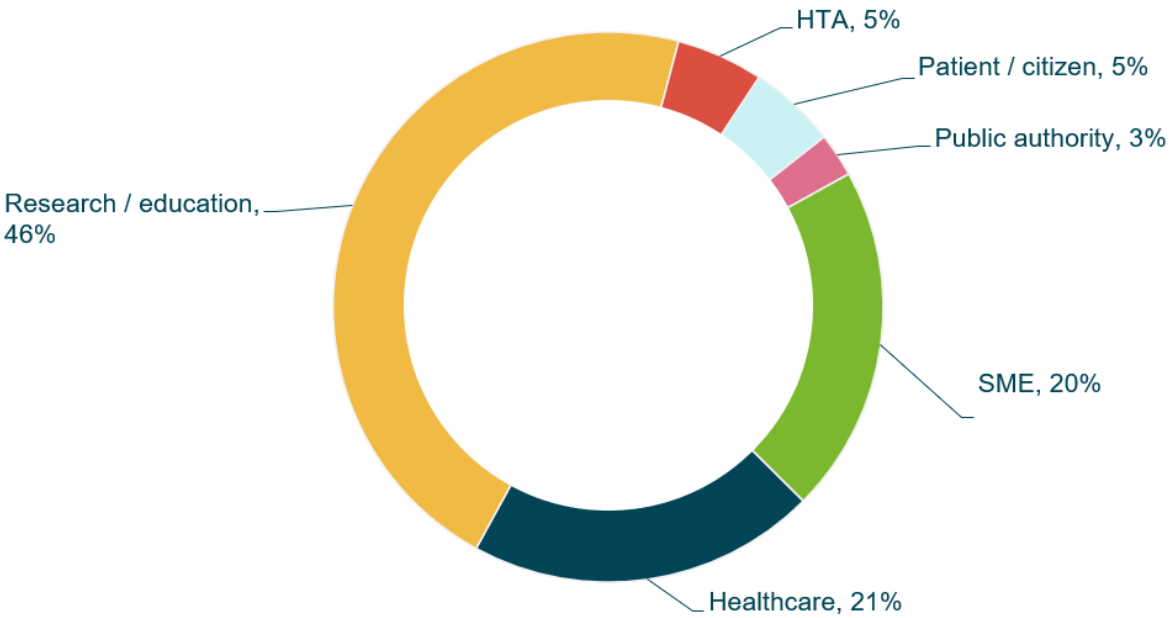
### IHI call 1 (single stage): breakdown by organisation type of participants in selected proposals



## IHI call 2 (two stage): geographical distribution of participants in selected proposals

| | Charity / foundation | HTA | Healthcare | Large company | Mid-cap | NGO | Other | Patient / citizen | Public authority | Research / education | SME | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Austria** | | | | | | | | | | 1 | | **1** |
| **Belgium** | | | | | | | | 1 | | 1 | | **2** |
| **Denmark** | | | 1 | | | | | | | | | **1** |
| **France** | | | 1 | | | | | | | | 1 | **2** |
| **Germany** | | | 1 | | | | | | | 4 | 1 | **6** |
| **Ireland** | | | | | | | | 1 | | 2 | | **3** |
| **Italy** | | 1 | 1 | | | | | | | 3 | 3 | **8** |
| **Netherlands** | | | 3 | | | | | | | 3 | 2 | **8** |
| **Norway** | | 1 | | | | | | | | | | **1** |
| **Spain** | | | 1 | | | | | | | 1 | | **2** |
| **Sweden** | | | | | | | | | 1 | | | **1** |
| **UK** | | | | | | | | | | 3 | 1 | **4** |

**IHI call 2 (two stage): breakdown by organisation type of participants in selected proposals**



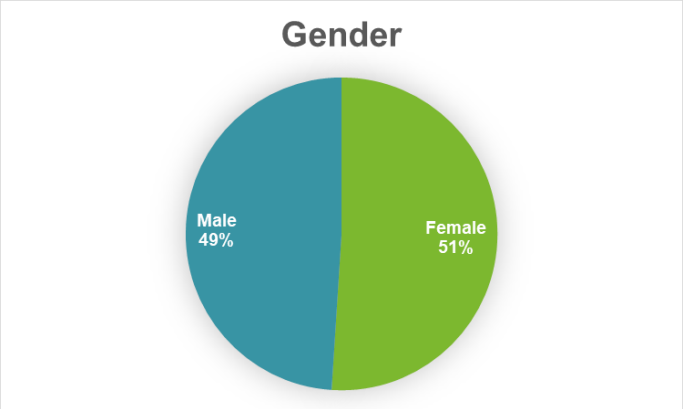
### Evaluation and ethics experts

IHI JU selected 49 experts from 26 countries in the evaluations of call 1 and call 2. Around half of the experts were female, and most (82%) came from the EU and Horizon Europe (HE) associated countries.

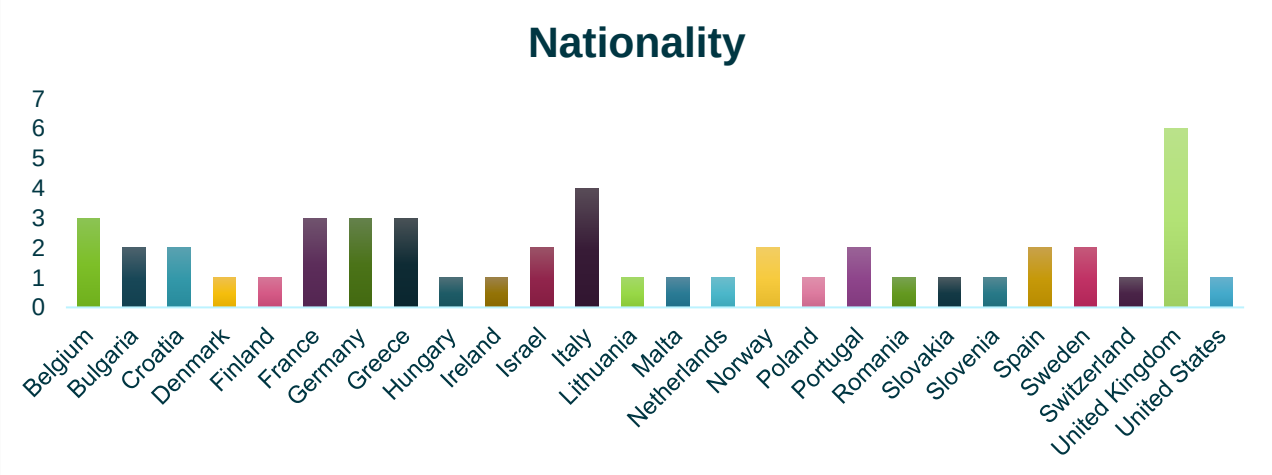
| IHI Call | Scientific evaluation experts | Rapporteurs in scientific evaluation | Ethics screening experts | Observers | Total no. experts |
|---|---|---|---|---|---|
| Call 1 – single stage | 25 | N/A | 6 | 1 | 32 |
| Call 2 – stage 1 | 16 | N/A | N/A | 1 | 17 |

Statistics on the selected experts can be found in the charts below:

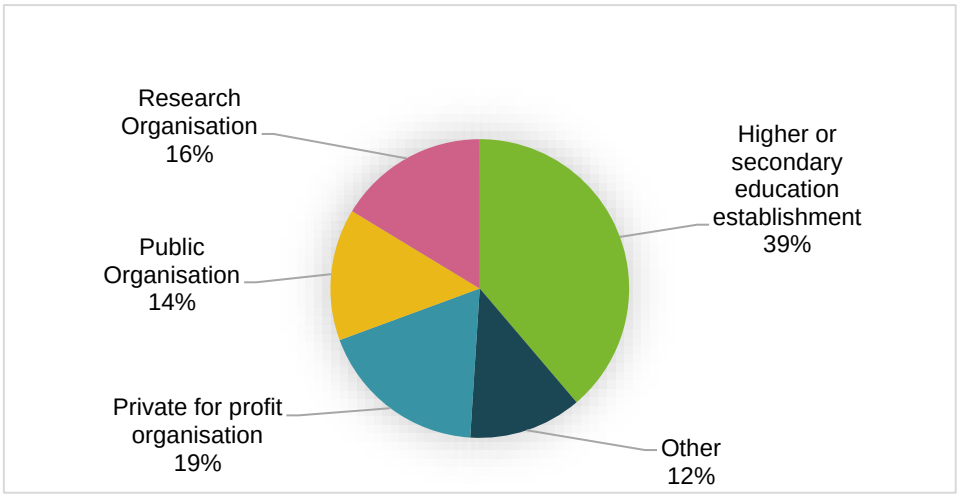
#### Call 1 & 2– Experts' gender




#### Call 1 & 2 – Experts' nationality



### Call 1 & 2 – Experts' affiliation



## 1.5 Follow-up activities linked to past calls

### Interim reviews for IMI projects

In 2022, the Programme Office conducted 10 interim reviews of ongoing IMI2 projects. Each expert reviewer panel consisted of at least three experts.

| Project acronym | IMI2 Call | Full project name | Review date |
|---|---|---|---|
| **COMBINE** | 15 | Collaboration for Prevention and Treatment of MDR Bacterial Infections | 29/03/2022 |
| **EHDEN** | 12 | European Health Data and Evidence Network | 17/02/2022 |
| **HARMONY PLUS** | 19 | Healthcare Alliance for Resourceful Medicines Offensive Against Neoplasms in Hematology – Plus | 24/06/2022 |
| **IMMUcan** | 14 | Integrated IMMUnoprofiling of large adaptive CANcer patients cohorts | 29/11/2022 |
| **Immune-Image** | 14 | Immune-Image: Specific Imaging of Immune Cell Dynamics Using Novel Tracer Strategies | 24/01/2022 |
| **ImmUniverse** | 15 | Better control and treatment of immune-mediated diseases by exploring the universe of microenvironment imposed tissue signatures and their correlates in liquid biopsies | 7-8/07/2022 |
| **INNODIA HARVEST** | 19 | Translational approaches to disease modifying therapy of type 1 diabetes - HARVESTing the fruits of INNODIA | 27/06/2022 |
| **RespiriNTM** | 16 | Progress novel assets (one FIH start) for non-tubercular mycobacteria that may act synergistically with bedaquiline and cytochrome bc drugs | 22-23/09/2022 |
| **RespiriTB** | 16 | Progress new assets (one pre-new molecular entity and one first-time-in-human start) for tuberculosis that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors | 22-23/09/2022 |
| **Trials@Home** | 13 | Trials@Home: Center of Excellence – Remote Decentralised Clinical Trials | 16/12/2022 |

### COMBINE

The COMBINE project aims to support the coordination of the IMI AMR Accelerator projects created to respond to the challenge of developing new treatment and prevention approaches to drug-resistant infections, as well as to increase the success rate of vaccine and antibiotic trials by proposing innovative study designs and novel strategies to analyse clinical trial data.

According to the reviewers, the COMBINE project has delivered on its objectives in coordinating and supporting the AMR Accelerator programme and linking with internal and external partners through workshops, meetings and online outputs. An AMR knowledge graph, AMR Accelerator external newsletter, a vaccine experts' workshop, a webinar on animal infection models, and IT tools/infrastructures to support data management across the project, have been rolled out. Some advances have been made in improving knowledge of *in vivo* model problems and standardising a murine pneumonia model, in selecting a standardised bacterial culture collection to enhance portability and utility of antibacterial study datasets, and in the identification of barriers to progress in the development of new antimicrobial vaccines.

The reviewers recommended to update the communication and dissemination strategy to be effective in reaching external stakeholders, to establish a clear action plan for the acquisition of additional data, to check the consistency of data across AMR Accelerator projects by verifying the actual data and metadata, and to

review the actual support needs of the individual projects, with a specific focus on the data management activities and the harmonisation of data structures across the AMR Accelerator.

### EHDEN

EHDEN's overall mission is to reduce the time needed to provide answers to relevant questions in health research by making standardised real world health data available at scale to researchers. The initial objective was to harmonise the data from 100 million European citizens to the OMOP common data model. To demonstrate the utility of this network, the project planned to run a small number of demonstrator projects. At the time of the review, the project had already achieved most of these goals by developing the infrastructure to host a federated data network at scale across Europe and populating this network with over 800 million quality assured patient records from 187 data partners across 29 countries. Several relevant demonstrators had also been carried out.

The review panel were highly impressed with the accelerated progress of the project and how the project managed to leverage their network to provide timely safety information on potential COVID-19 therapies and vaccines. As many of the initial project objectives had already been achieved, the panel suggested increasing the number of demonstrator projects and starting to engage the network of data partners more fully in the project.

### HARMONY PLUS

Blood cancers are a diverse and complex group of diseases that are difficult to diagnose and treat. Nowadays most treatments are extremely complex, and advances in patient diagnosis and treatment are slow due to the low number of patients per centre. IMI's HARMONY project is using big data to advance our understanding of seven blood cancers and speed up and support the decision-making process for patient access to new therapies. The aim of HARMONY PLUS is to build on HARMONY's work.

The reviewers highlighted the fact that the HARMONY PLUS project is an excellent complementary data resource to HARMONY, largely because it includes several cancer types not in HARMONY, and will include some rare malignancies. The reviewers said that the main overall concerns to be closely monitored were getting data from enough patients with rare cancer types in order to achieve the project objectives.

### IMMUcan

IMMUcan aims to study the tumour microenvironment to gain a deeper understanding of how the immune system and cancer cells interact at the molecular level. This information could be used to further improve existing treatments and to develop new ones.

The reviewers highlighted the fact that the IMMUcan consortium is very complex in nature, is clearly well managed and organised, and possesses an effective governance structure. The reviewers identified the patient recruitment rate as a key success factor that needs to be closely monitored and mitigated when necessary in order to achieve the project objectives.

### Immune-Image

The Immune-Image project aims to pioneer the use of non-invasive imaging technologies to track the activity of immune cells in the body.

According to the reviewers, the project progress is excellent, and in line with the objectives. Delays in the project were largely due to restrictions related to the COVID-19 pandemic and to insufficient access to patients and use of laboratories during the lockdowns. In addition, the results achieved by the consortium since the start of the project promise a high impact in the field of disease diagnosis, molecular characterisation of a disease, monitoring treatment response, and detection of disease recurrence.

The reviewers recommended that the project's duration be extended to compensate for the delays caused by COVID-19 and ensure the project objectives are achieved.

### ImmUniverse

ImmUniverse is investigating two immune-mediated diseases (ulcerative colitis and atopic dermatitis) using liquid biopsies to detect immune cells circulating in the blood and assessing how they interact with the tissues affected at the microenvironment scale. The work of the project will contribute to improved diagnosis, prognosis and predication of therapy responses in patients.

The expert panel reported that the project has achieved some of its objectives and milestones to date and will likely provide results with significant immediate or potential impact in the next year. The main outputs so far identified by the expert panel include the setting up of the LIPUS (low-intensity pulsed ultrasound stimulation) system which will be used for non-invasive biopsies in study participants, the establishment of a Patient Input Platform, and the creation of a virtual biobank (VBB) and electronic case report form (eCRF) platform ready for data capture.

The expert panel made a series of recommendations to improve project implementation which has been delayed by several factors including the COVID-19 pandemic and an internal reorganisation within the consortium itself. Furthermore, the panel recommended that an additional review take place in 2023 to further monitor project implementation.

### INNODIA HARVEST

The IMI2 project INNODIA added significantly to our understanding of type 1 diabetes (T1D). The aim of INNODIA HARVEST is to consolidate the INNODIA clinical network and use it to run clinical trials of drugs designed to stop T1D. Moreover, the project is continuing INNODIA's hunt for new biomarkers that could be used to track the progress of the disease, and implementing new drug discovery pipelines for novel treatments for T1D.

As per the panel of reviewers, the project is delivering on its key objectives despite unavoidable delays due to the COVID-19 pandemic. The project shows high potential impact based on their clinical results for type 1 diabetic patients and non-diagnosed diabetics in Europe. With respect to the basic science work packages, INNODIA HARVEST is demonstrating its potential impact through scientific publications and will likely be able to patent and exploit their more relevant results.

### RespiriNTM

The RespiriNTM project aims to develop novel antibiotics that target the non-tuberculous mycobacteria (NTM) respiratory pathway, the energy centre of the bacteria. RespiriNTM will also cast a wider net in its search for novel antibiotics, by targeting human factors that are needed for NTM to survive in the infected host.

Overall, the reviewers agreed that the project has so far delivered good quality results. However, the future of the project depends upon the ability of medicinal chemistry to move quickly and identify a low toxicity / high potency inhibitor compound, suitable for first in human (FIH) studies, before the project ends. To assess the progress of the project with regards to the compound, it was recommended that an additional review take place in 2023, once more results become available.

### RespiriTB

The aim of RespiriTB is to find new drug candidates as potential components of a new, more efficient combination drug regimen against tuberculosis (TB) that is less prone to resistance and allows the shortening of treatment duration for TB and multidrug-resistant TB. Such a drug combination will synergistically target the energy metabolism of *Mycobacterium tuberculosis* or complementary targets.

The reviewers recognised that several aspects of the work suggest interesting areas of additional investigation that could provide valuable background knowledge for future studies. However, they noted that the priority over the next year must be determining whether lead compounds can be identified that are viable candidates with convincing potential to enter first in human trials. To assess the progress of the project with regards to the compounds, it was recommended that an additional review take place in 2023, once more results become available.

### Trials@Home

Trials@Home aims to investigate the feasibility of running clinical trials totally decentralised and in a hybrid mode (partly decentralised, partly centralised). At the time of the review, the project had completed a feasibility study and had just received approvals for running the main RADIAL study in six European countries.

The reviewers reported that the project had achieved several important results and that the forthcoming RADIAL trial would provide important evidence on when decentralised clinical trials would be appropriate. The panel was slightly concerned that the delays due to the COVID-19 pandemic may impact on the project and suggested more time may be needed to fully analyse the results of the study.

### Workshop on BigData4BetterOutcomes (BD4BO) programme

In addition to the reviews above, a workshop was held on 8 March 2022 bringing together project leads from several IMI projects linked through the BigData4BetterOutcomes (BD4BO) programme, namely HARMONY, HARMONY PLUS, PIONEER, EHDEN and BigData@Heart, as well as external experts.

These projects all have healthcare data at the centre of their value proposition – either to integrate datasets or to develop a network of available datasets for research. Each project is focused on different diseases and has taken a different approach, but all of them come across similar challenges. This workshop aimed at facilitating the exchange of best practices between projects and sharing lessons learnt and experiences on common challenges.

## 1.6 Openness, cooperation, synergies and cross-cutting themes and activities

### Collecting ideas to support the definition of IHI's annual priorities and areas for calls for proposals

In line with the Council Regulation establishing the IHI[9], in 2022 the Programme Office developed a process for the collection of ideas from a wide range of stakeholders, in addition to the IHI founding members and Science and Innovation Panel (SIP) members, to help IHI define its annual scientific priorities and areas for future calls for proposals. The transparent and open process involves the SIP for the review of the ideas collected.

In a nutshell, any stakeholder may submit an idea for an IHI topic using an online form. Ideas that have passed the completeness and quality check performed by the IHI Programme Office are reviewed by the SIP, which agrees on which ideas merit further consideration (i.e. they are aligned with IHI's objectives and have the potential to be developed further as all or part of an IHI call topic). The SIP feedback is sent to the IHI Governing Board. For transparency, proposed ideas reviewed by the SIP are published on the IHI website along with the SIP's opinion on the idea. Ideas that receive a positive opinion from the SIP may be developed further as part of an IHI call topic. However, the topic development and approval process involves a wide range of stakeholders and all IHI governance bodies. This means that even if an idea is reviewed positively by the SIP, it may be altered significantly during the subsequent stages of topic development, or it could become a small part of a broader topic. It may also be dropped entirely.

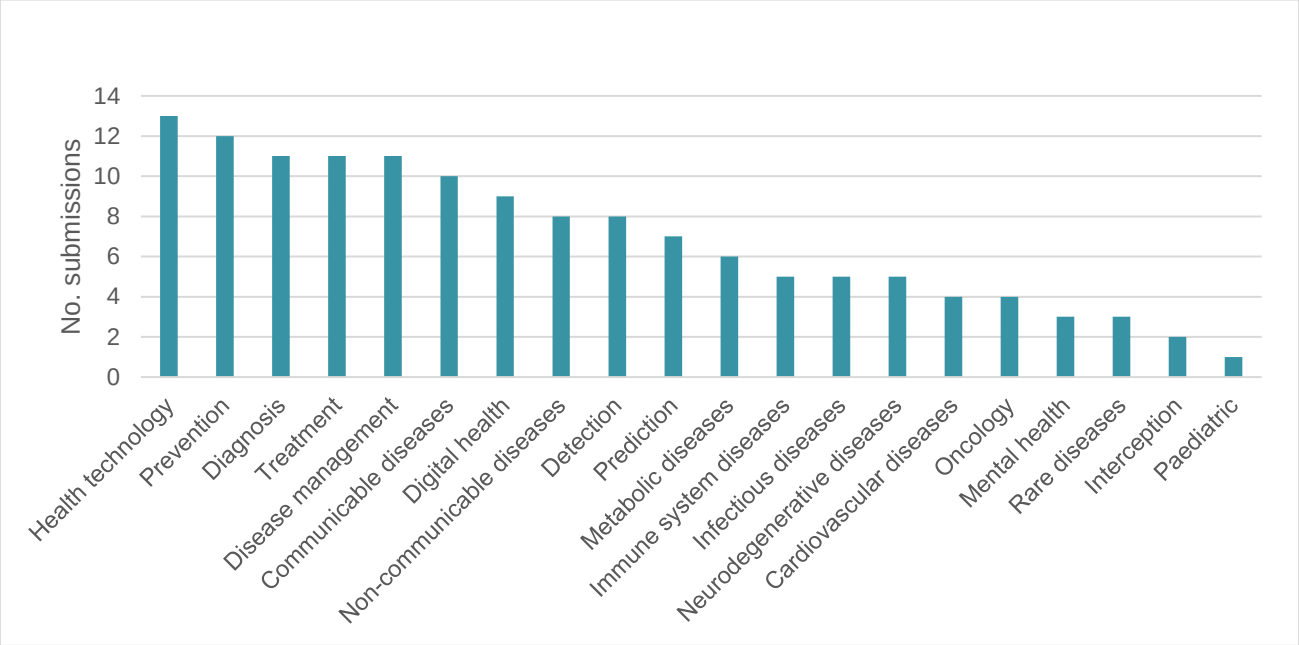
To manage efficiently the process both at the IHI Programme Office and at the SIP levels, an internal online IHI platform has been developed, which is linked to the SIP private platform. A functional mailbox has been created to support (potential) submitters (ideas@ihi.europa.eu) as well as a specific webpage with guidance on the process and how to submit an idea.

The online form and the platform for the collection of ideas were launched at the end of July 2022. Since then, the process and the online form have already been refined based on the experience gathered.

By the end of 2022, a total of 20 ideas had been collected. Most of the ideas (65%) were submitted in the personal capacity of the submitter. For those ideas submitted on behalf of an organisation, the majority (86%) came from small and medium-sized enterprises. The ideas came from the following countries: Netherlands (5); India (3); Spain (2) and the United Kingdom (2), as well as Finland, Bulgaria, Portugal, Denmark, Germany, Pakistan, Nepal and Cameroon (all one each).

As the chart below shows, the ideas submitted cover a wide range of disease and research areas:

[9] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014.




Six of the ideas submitted in 2022 have passed the IHI completeness and quality check and were transferred to the SIP. By the end of 2022, the SIP had completed the review of the three ideas. The SIP opinions along with the ideas were published on the IHI website.

### Synergies

IHI has the potential to trigger EU-wide transformations by contributing to two key European objectives: pushing the digital transformation and gaining more resilience in the health domain. Addressing these challenges demands the establishment of collaborations with other European partnerships and synergies with other relevant programmes at the international, EU, national and regional levels.

In this respect, the Programme Office set up in 2022 an internal task force with representatives from the Programme Office, the EC and industry partners. The group started by mapping the existing and planned EU strategies, programmes and initiatives of potential relevance. It went on to identify a range of mechanisms to support and implement synergies at programme and project level, complementing the EC toolbox. To complete this strategic exercise, representatives of other relevant initiatives were invited to discuss potential interconnections and synergies.

In parallel, IHI JU regularly seeks the advice of the GB, SIP and SRG regarding collaborations with other relevant initiatives and reports back to these governing bodies on the joint activities carried out.

In 2022, IHI JU interacted with the following:

- other European health-oriented initiatives such as the Cancer Mission, the Global Health EDCTP3 JU, the Rare Diseases partnership, the partnership on Transforming Health and Care Systems, and the EIT Health;
- the Member States driven initiative Important Project of Common European Interest (IPCEI) on Health;
- international organisations such as the World Health Organisation.

IHI JU also interacted with KDT JU as well as the EC team's leading key European political priorities such as the EU4Health programme (HERA, EHDS pilot action) and the Digital Europe programme.

## 1.7 Progress against key performance indicators

### 1.7.1 Progress against Horizon Europe and IHI-specific KPIs

The IHI Governing Board adopted the IHI-specific key performance indicators (KPIs) in March 2022. The Programme Office will track IHI's activities in the following strategic areas:

1. **Resources (input), processes and activities**
    1.1 Involvement of multiple health care stakeholders
    1.2 Cross-sectoriality of the partnership
    1.3. Engagement of regulators

2. **Outcomes**
    2.1. Cross-stakeholders' collaboration
    2.2. Public-private collaboration
    2.3. Project outputs for use in clinical practice and health research development and innovation (R&D&I)
    2.4. Integrated health care solutions considering end-users' needs
    2.5. Methodologies for value assessment of integrated solutions
    2.6. New or improved clinical guidelines
    2.7. Management of health data
    2.8. Demonstration of data integration
    2.9. Demonstration of AI in health care

3. **Impacts**
    3.1. Creation of sustainable resources and infrastructures that facilitate translation of the knowledge to innovations
    3.2. Development of preventive or therapeutic strategies in different therapeutic areas to address unmet public health needs
    3.3. Cross-sector activities established by the partnership that will help contribute to a globally competitive EU health care industry

IHI launched 3 calls for proposals in 2022: two single stage calls (IHI calls 1 and 3) and one two-stage call (IHI call 2). There were no Grant Agreements signed in 2022; these projects will start in 2023 and will have their first reporting period in 2024. At this stage there is therefore no progress to report against the IHI-specific KPIs. The Programme Office will report on the IHI-specific KPIs, as well as the relevant Horizon Europe KPIs and the cross-cutting KPIs for partnerships, in future reports, as soon as data will be available and will allow reporting.

### 1.7.2 Progress against IMI2 / Horizon 2020 KPIs

The Programme Office continues to monitor the performance of the IMI2 programme towards its objectives since there are many projects that are still ongoing. IMI uses several KPIs that track IMI's activities in the following strategic areas:

- the coverage of the research portfolio, showing adequate implementation of the annual scientific priorities;
- the achievements of the assets during the course of the IMI programmes;
- the impact of the IMI programmes on the regulatory framework;
- the ability of the IMI programmes to set new standards (i.e. new taxonomies, new stratifications);

- the rate of contribution of non-pharma actors to the IMI programmes (e.g. non-pharma industries, foundations, charities, professional organisations);
- the accessibility of the resources/outputs beyond the IMI consortia partners;
- the level of co-authorships and cross-sector publications between European researchers;
- the adoption of the novelty generated by the IMI programmes by the industrial partners;
- the level of involvement of patient groups or healthcare professional association;
- the level of collaboration and SME participation.

The Programme Office gathers data on these points via a dedicated web platform through which project coordinators can submit their project's results. The platform also allows IMI to aggregate and analyse data and build a picture of project achievements as they evolve over time. Although these KPIs are designed for IMI2, where relevant IMI also gathers the data for IMI1 projects, as this allows us to explore the impacts of IMI since the very beginning.

The analysis of the data collected up to 31 December 2022 shows that almost all the relevant priority areas in the IMI2 Strategic Research Agenda (SRA) are addressed by IMI2 projects (11 out of 12).

An examination of the data shows that IMI2 projects have generated 439 assets that completed a significant milestone during the project lifecycle (versus a target of 50), and if we look at both IMI1 and IMI2 programmes together, the analysis reveals that IMI projects have reached 590 assets that completed a significant milestone so far. The definitions of 'project assets and achievements' and 'significant milestone' were meticulously defined. Examples of assets are tools, methodologies, processes, services, training materials, etc.; and examples of significant milestones are key clinical trial phases, animal models, prototypes, commercialisation, patents, publications, etc.

A subset of IMI projects managed to have some impact on the regulatory framework and as reported by the project coordinators received acceptance by regulatory authorities. In IMI2 there are 24 completed procedures (versus a target of 10) and if we look at both IMI1 and IMI2 programmes together there are 44 completed procedures.

Several new tools and processes generated by IMI2 projects have been implemented by the industry participants (examples of implementations are animal models, standards, biomarkers, standard operating procedures (SOPs), use of screening platforms, clinical trial networks, etc.). The data shows 524 implementation results in IMI2 (versus a target of 50) and 838 implementation results if we consider both IMI1 and IMI2 programmes together.

Additionally, more than half of the projects (63.16%) involve patient organisations and healthcare professional associations as consortium partners, members of advisory boards, members of stakeholder groups etc., and this trend has remained stable during the course of the IMI2 programme.

This analysis reveals a dynamic in which IMI projects are getting on track and in numerous cases surpassing the established targets now that a number of IMI2 projects have finished and we are reaching the end of IMI2 programme cycle. It is clear that projects need time to generate innovation and impact that can be detected and reported, and many project outputs arise in the later phases of the project lifecycle and very often even beyond the end date (after projects have been completed). This dynamic is driven by the complex and long-term nature of IMI projects, which involve research in the healthcare space, multi-stakeholder partnerships and cross-sector collaboration.

In addition, the Programme Office also collects data to report against the relevant standard Horizon 2020 (H2020) KPIs, with the goal of tracking IMI's contribution to achieving the H2020 objectives. This allows the assessment of the results and impacts of the specific objectives of the programme, as detailed in Annex I, II, and III of the Council Decision 2013/743/EU establishing Horizon 2020. More information about the progress towards the IMI2 specific KPIs as well as towards the H2020 objectives can be found in Annex 6.

## 1.8 Dissemination and information about project results

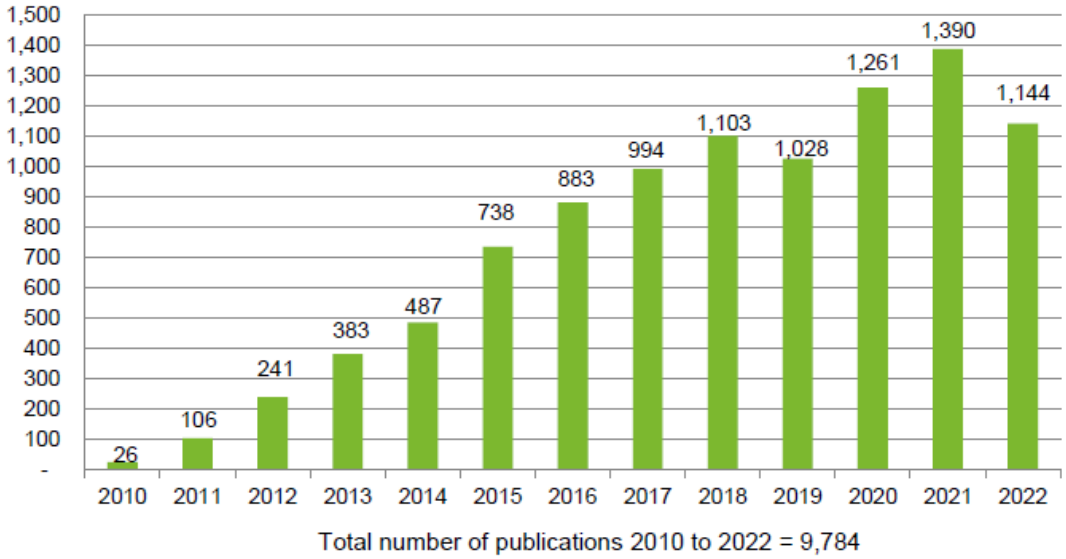
IMI projects are delivering diverse tools, resources and methodologies that are helping to change and improve the way new medicines are discovered and developed. This section describes how these resources, and information on them, are disseminated by both the project partners and the Programme Office. The Programme Office consistently reminds its projects of the importance of dissemination, and in 2016 issued a practical guide on this which remains valid to date.

### Analysis of the published output of IMI-funded research projects

Scientific publications are the key communication and dissemination channel for scientific results. IMI has been monitoring and analysing the papers coming out of its projects since 2012. The analyses, carried out by Clarivate Analytics have consistently demonstrated both the sheer volume and high quality of research taking place in IMI projects.

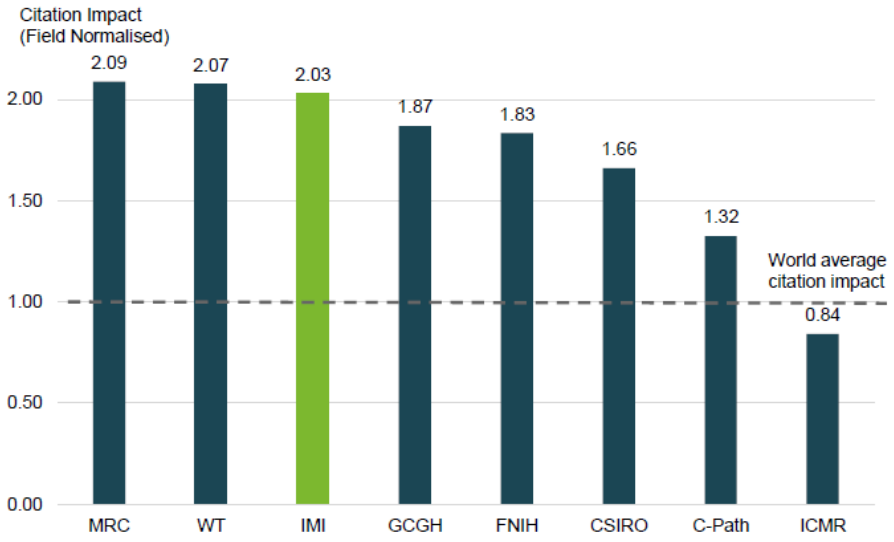
**IMI projects have produced almost 10 000 publications to date**

IMI-funded projects continue to produce a large number of publications, reaching 9 784 publications to date. In 2022 IMI projects generated 1 144 publications. In the past 5 years IMI publications have surpassed the bar of 1 000 publications registered each year with an average of 1 185 publications per year.



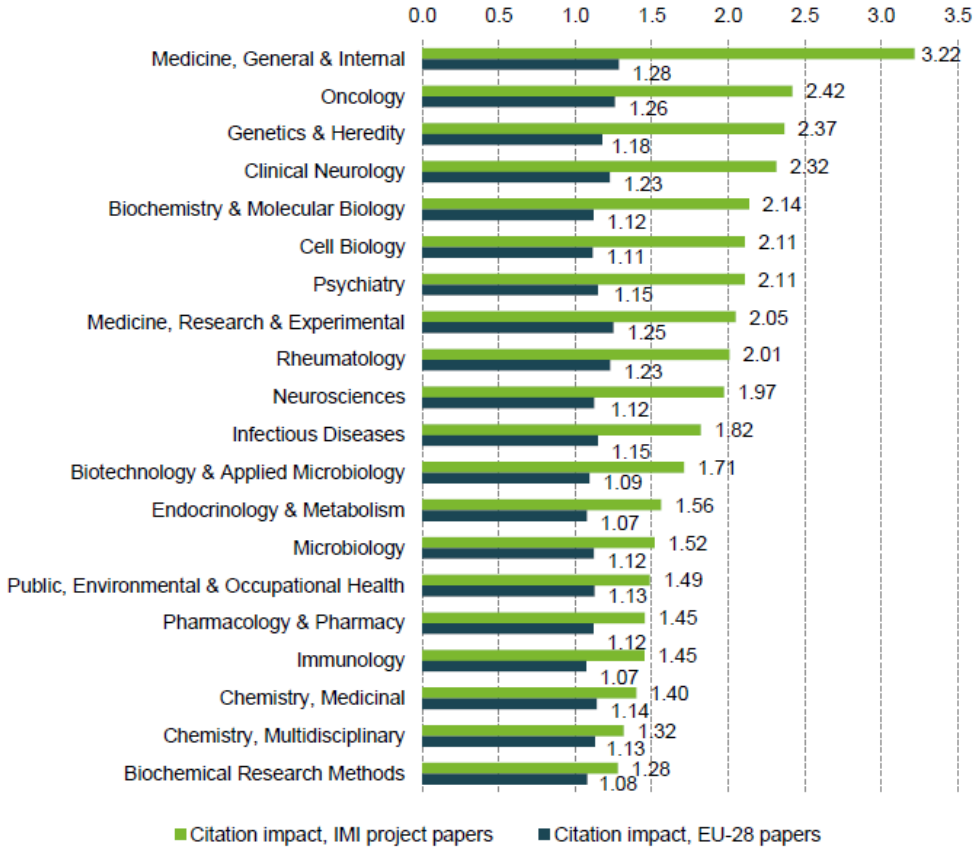

**The citation impact of IMI research is higher than EU and world averages**

The field-normalised citation impact for all IMI papers is 2.03 (compared to 1.16 for the EU and the baseline of 1 for the world). IMI also compares favourably with similar organisations such as the Medical Research Council (MRC), the Wellcome Trust and the Grand Challenges in Global Health (GCGH). This is similar to the result in previous years and shows that IMI is maintaining a high standard even as its output increases.




**In all fields, IMI research has a higher citation impact than the EU average**

As the graph below shows, IMI research is published in a range of fields within the biomedical sector. In all fields, IMI research has a higher citation impact than the EU average. This is most notable the case in the fields of medicine, general and internal, oncology, genetics and heredity and clinical neurology where the IMI citation impact is between 2.32 and 3.22.

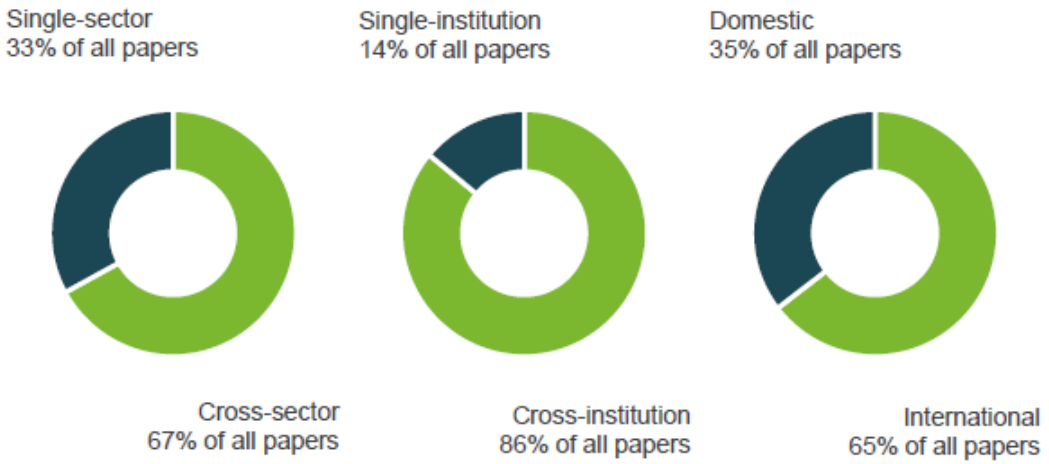



Other key facts and figures revealed by the latest analysis include the following.

- 24.6% of papers from IMI projects are ‘highly cited’, meaning they are in the top 10% of papers by journal category and year of publication.
- IMI projects have published in 1 681 journals to date, and the average journal impact factor (JIF) for IMI research is 7.53.
- Journals with a particularly high impact factor that have published IMI research include Lancet (and other Lancet Journals e.g. Lancet Respiratory Medicine and Lancet Microbe), New England Journal of Medicine, Journal of the American Medical Association (JAMA), Nature (and other Nature journals e.g. Nature Molecular Cell Biology, Nature Reviews Drug Discovery, Nature Immunology, Nature Medicine), and the British Medical Journal (BMJ).
- The internationally collaborative nature of IMI is reflected in the authorship of the papers, with over half of papers recording authors from more than one country.

**IMI research is highly collaborative**

IMI research is highly collaborative; a majority of IMI papers are collaborative.




- Two-thirds (67%) of all IMI project papers were published by co-authors working in different sectors.
- The majority (86%) of IMI project papers involved collaboration between different institutions.
- More than half (65%) of all IMI project papers involved international collaboration.

### Project snapshot

Going by the number of papers produced, the most prolific projects are unsurprisingly the older ones. The table below shows the top 10 projects, ranked by number of papers produced. As the figures show, the citation impacts range between 1.86 and 4.03.

| Project | Publications | Mean field-normalised citation impact |
|---|---|---|
| BTCure | 727 | 1.78 |
| EU-AIMS | 610 | 1.97 |
| ULTRA-DD | 452 | 1.81 |
| EMIF | 354 | 2.42 |
| AIMS-2-TRIALS | 310 | 2.92 |

| | | |
|---|---|---|
| NEWMEDS | 242 | 2.00 |
| BigData@Heart | 238 | 2.61 |
| INNODIA | 226 | 1.50 |
| CANCER-ID | 212 | 3.14 |
| EUROPAIN | 191 | 2.57 |

Between 2010 and 2022, IMI projects published papers in 1 681 different journals. The tables below show the top 10 journals by number of IMI project publications, and the top 10 journals by journal impact factor (JIF) in which IMI projects have published.

**Top 10 journals by number of IMI publications**

| Rank | Journal | JIF | IMI publications |
|---|---|---|---|
| 1 | Scientific Reports | 5.00 | 213 |
| 2 | Annals of The Rheumatic Diseases | 27.97 | 213 |
| 3 | PLoS One | 3.75 | 200 |
| 4 | Diabetologia | 10.46 | 169 |
| 5 | Nature Communications | 17.69 | 139 |
| 6 | Frontiers in Immunology | 8.79 | 117 |
| 7 | Journal of Medicinal Chemistry | 8.04 | 91 |
| 8 | Diabetes | 9.34 | 88 |
| 9 | International Journal of Molecular Sciences | 6.21 | 75 |
| 10 | Arthritis & Rheumatology | 15.48 | 74 |

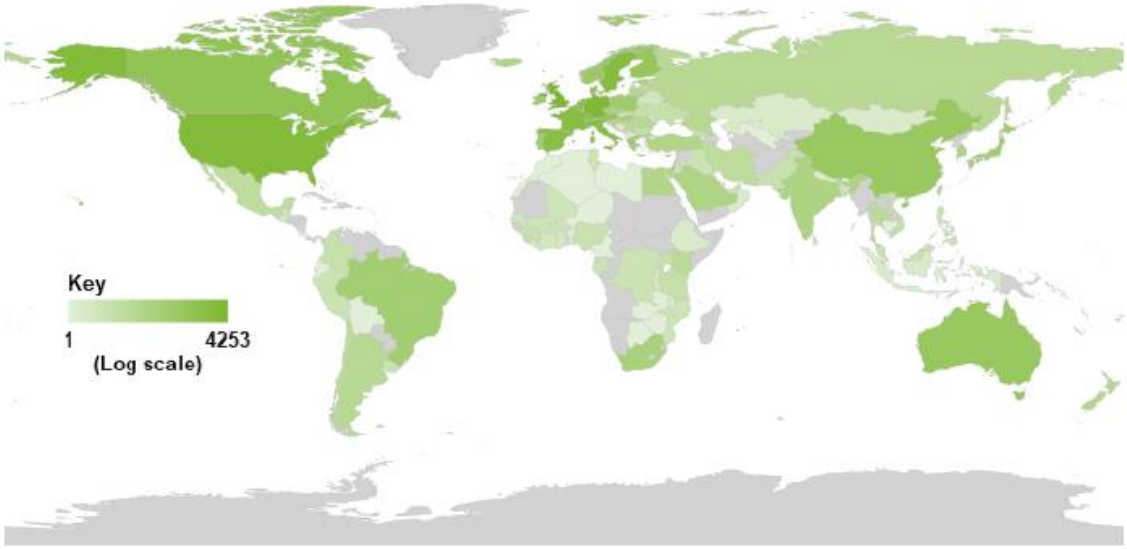
**Top 10 journals by journal impact factor (JIF) in which IMI projects have published**

| Rank | Title | JIF | IMI publications |
|---|---|---|---|
| 1 | Lancet | 202.73 | 9 |
| 2 | New England Journal of Medicine | 176.08 | 2 |
| 3 | JAMA - Journal of The American Medical Association | 157.34 | 9 |
| 4 | Nature Reviews Molecular Cell Biology | 113.92 | 2 |
| 5 | Nature Reviews Drug Discovery | 112.29 | 17 |

| | | | |
|---|---|---|---|
| 6 | Nature Reviews Immunology | 108.56 | 4 |
| 7 | Lancet Respiratory Medicine | 102.64 | 6 |
| 8 | BMJ - British Medical Journal | 93.33 | 13 |
| 9 | Nature Medicine | 87.24 | 23 |
| 10 | Lancet Microbe | 86.21 | 1 |

The analysis also reveals the global reach of IMI's research activities. In total, 126 countries have at least one paper funded by IMI.

Countries with at least one paper funded by IMI




The scale shows countries having from 1 publication to 4 253 publications (UK being the top end with 4 253 publications).

# 2 Support to operations

## 2.1 Communication activities

### Two strategic objectives and a guiding document

In 2022, IHI's communication activities supported the organisation's strategic goals by focusing on two overarching objectives: promoting IMI project results, and promoting the new partnership.

Part of the effort of setting up the new partnership went to the development of the new IHI Communication Policy, which will guide our activities in the years to come. The fact that the policy was co-created by the IHI Programme Office and IHI's founding members via a participatory process will assure the strategic alignment across the IHI office, partners and governance groups and enhance the overall coherence and consistency in IHI's communication activities. As requested by the Council Regulation establishing IHI, the IHI Communication Policy was approved by the Governing Board on 8 December.

### #WelcomeIHI

As stated above, one of the communication team's main objectives in 2022 has been to support the establishment of the new programme and to promote the IHI brand, targeting our current stakeholders and reaching out to the new sectors that have been brought on board.

#### Events

#### The launch of IHI

Over 2 100 people attended IHI's online launch event on 26 January, which combined practical information with political discussion. During the first session, IHI speakers provided an outline of the major changes in IHI vs IMI, a preview of our potential first call topics, and advice on how to get involved in our work. The second session featured a high-level discussion during which our founding members presented their vision for IHI. The information provided was well received, as shown by the responses to the post-event survey: 53.6% of participants agreed with the statement "the IHI launch has improved my understanding about what IHI is doing" and 35.2% strongly agreed.

This was confirmed by the event's high visibility on social media. It generated 43 thousand tweet impressions in one day (compared to 3.4 thousand impressions per day on average in January) and triggered more than 50 thousand impressions for the #WelcomeIHI hashtag. We gained 224 new followers in one day, confirming the event's success in reaching out to newcomers.

In addition, we reinforced the visibility of the new partnership by contracting a Politico sponsorship on the week of the launch (Morning Health Care newsletter plus website branding) which gained 288 total clicks and over 357.5 thousand impressions on POLITICO.eu.

The launch of IHI was also covered in key EU media:

- Politico Pro https://pro.politico.eu/news/145404
- EURACTIV €2.4 bn 'Innovative Health Initiative' to better address current health issues
- Science Business €2.4B Innovative Health Initiative kicks off

The launch event marked, from a communications perspective, the end of the transition period from IMI to IHI.

### First calls for proposals

The promotion of the first IHI calls for proposals started in January with the publication of a document containing the draft themes pencilled in for potential inclusion in IHI's first calls. This attracted positive press coverage in Science Business (EU Innovative Health Initiative gets innovative: publishing all its draft research plans early), and the pdf containing the themes was the document with the highest number of unique website downloads, reaching the figure of 2 467 downloads.

IHI organised a hybrid event to promote calls 1 and 2 on 14 June, which was attended by 1 450 participants (82% remote and 18% face-to-face participations). This was a great opportunity for interested applicants to learn more about the first IHI calls and meet potential partners.

Whether participants were in the room or in the virtual environment, they were able to book one-on-one meetings through an online platform with representatives who shared an interest in the same topics. The platform hosted over 600 meetings on the day of the event, 88% of them transnational. In addition, 50 live pitches were scheduled throughout the day. Over 65% of respondents found the pitching session 'extremely useful' or 'very useful'.

Following the event, a high rate of unique users kept accessing the platform to the deadline for applications. IHI created a community that facilitated 883 unique matchmaking contacts on the day of the event alone, with further contacts being made in the weeks following the event and up to the call deadline.

In addition, we held eight webinars on all the call 1 and 2 topics, plus one webinar on IHI's rules and procedures and one webinar on the financial aspects of the proposals. The overall participation reached 1 460 attendees.

For call 3, IHI decided to opt for a full online event under the branding of IHI Call Days, grouping per call topic and along several days the different building blocks that constitute our call promotion activities: dedicated webinars, matchmaking opportunities, and pitching sessions.

Over 1 600 participants (53% academia and research organisations, 22% SMEs, 10% industry) attended the different sessions, and 230 participants chose to enhance their visibility by creating a profile in the marketplace. This option was particularly used by SMEs (34% of marketplace profiles). In addition, during the Call Days, 167 meetings took place via the event tool.

### External events

IHI also participated in the following external high-profile events

| Date | Event name | Location |
|---|---|---|
| 12.01.2022 | Conference "Europe of Health: Towards an EU health union? organised by Sciences Po | Paris, FR |
| 28.01.2022 | OECD-EBRAINS-HBP Round Table | Online |
| 03.02.2022 | French Presidency of the Council of the EU - The European Meetings of the French National Cancer Institute | Paris, FR |
| 08.03.2022 | Event "Partnership research: restoring trust between the actors" organised by l'Association nationale de recherche et de technologie (ANRT) | Paris, FR |
| 09.03.2022 | Biotech Atelier - Bridging the gap between the Nordics, Bulgaria and SEE [south-east European] countries in Biotechnology, Digital Health and EU Science | Online |
| 15.03.2022 | German national launch event of the Innovative Health Initiative (IHI) - Symposium of the National Contact Point (NCP) for Health 2022 | Online |

| | | |
|---|---|---|
| 05.04.2022 | Launch of the EU-Alliance of Medical Research Infrastructures (AMRI) | Online |
| 08.04.2022 | “IHI: the new European PPP for Health”, organised by Tour4EU | online |
| 21.04.2022 | IHI infoday & expert roundtable, organised by the Technical University of Denmark | Lyngby, DK |
| 27.04.2022 | Belgium Japan Association and Chamber of Commerce event on IHI and Collaborative Innovation for the Future of Health | Online |
| 27.04.2022 | EIT Health Matchmaking event | Online |
| 03.05.2022 | OECD-EBRAINS-HBP Round Table on brain health data | Online |
| 08.05.2022 | “Building synergies with key Initiatives at EU and international level”, organised by THCS | Online |
| 10.05.2022 | Enterprise Europe Network e-kick off - Healthcare Sector Group | Online |
| 11.05.2022 | NCP training on European Partnerships | Online |
| 16.05.2022 | Novo Nordisk Public-Private Partnership (PPP) Day | Hillerød, DK |
| 19.05.2022 | ERA CoBioTech Hub Meeting on the transition process from Horizon 2020 to Horizon Europe and the new opportunities for cooperation for the different partners of ERA-Nets and other partnerships | Online |
| 19.05.2022 | European Patients’ Academy on Therapeutic Innovation (EUPATI) 10-year-anniversary | Brussels, BE |
| 20.05.2022 | IHI and Norway, organised by the Research Council of Norway | Brussels, BE |
| 24.05.2022 | Information meeting on Europe's new partnership for health, Innovative Health Initiative, organised by Vinnova | Stockholm, SE |
| 25.05.2022 | EIT Health Summit organised by Karolinska Institutet | Stockholm, SE |
| 30.05.2022 | Infoday on Horizon Europe, Cluster 1 - Poland | online |
| 01.06.2022 | Combined FIGON Dutch medicines day and EUFEPS annual meeting, organised by EATRIS | Leiden, NL |
| 06.06.2022 | “IHI Launch” organised by the Navarre Region | Online |
| 21.06.2022 | “IHI opportunities and rules” organised by CDTI | Online |
| 23.06.2022 | Science Business roundtable on the Horizon partnerships | Brussels, BE |
| 06.07.2022 | Workshop “Developing ELIXIR's Future Programme”, Brussels | Brussels, BE |
| 07.07.2022 | IHI info session- Medicen day, Paris Region | Online |
| 12.07.2022 | Portuguese Info Day Innovative Health Initiative event, organised by the Health NCP | Online |
| 21.07.2022 | Italian launch event for the IHI | Online |
| 12.08.2022 | One Year of HERA Conference | Online |
| 19.09.2022 | Austria Info Day Innovative Health Initiative event, organised by the Health NCP | Online |
| 21.09.2022 | INNOVEIT Creating resilient innovation ecosystems for better health in Europe | Online |
| 29.09.2022 | Biotech Atelier 2022 & IHI Patient Centricity | Online |
| 03.10.2022 | Patient Engagement Open Forum (PEOF) steering committee | Castelldefels, ES |
| 11.10.2022 | European Brain Research Area final conference | Brussels, BE |
| 10.11.2022 | European Partnership Stakeholder Forum - One-year review of European Partnership Initiatives in Horizon Europe | Brussels |
| 22.11.2022 | Matchmaking event Horizon4Poland'2022, organised by the Polish Industry Contact Point | Warsaw, PL |
| 01.12.2022 | Information day on calls 3 and 4 of the Innovative Health Initiative, organised by CDTI | Madrid, ES |
| 02.12.2022 | UK KTN webinar on Horizon Europe Cluster 1 (Health) | Online |

### News

We published 17 articles on key IHI milestones activities. These were primarily on the new governance structures, including interviews with the chairpersons of the IHI Governing Board, the SIP and the SRG, and on IHI research funding opportunities.

## As the IMI programme reaches maturation, so do IMI projects

IHI communication activities contribute to explaining and promoting the growing body of results yielded by our IMI projects by writing news articles, organising impact-focused events, and promoting projects via social media. The communications team also acts as sounding board for the communication activities of the projects themselves, building a continuum between IHI's communication and dissemination activities.

### News

In line with the communication policy objective of highlighting project successes, we published 45 news articles from January to December. All news articles are published in the newsroom section of the IHI website, promoted on social media, and featured in the newsletter. The three most visited articles on the website were:

New resistance-busting antibiotic combination could extend the use of 'last-resort' antibiotics, describing how researchers from the IMI projects ENABLE and ELF have discovered a treatment that could reverse antibiotic resistance in some bacteria.

HARMONY's prototype to help doctors predict in a more precise way who should undergo the invasive and risky treatment is highlighted in Machine learning tool can help identify candidates for stem cell transplant therapy for some cancers.

The article on Accounting for patient preferences: "Nothing for us, without us" discusses PREFER's framework for patient preference studies.

Many of these stories were further disseminated within the European Parliament through dedicated thematic mails to members of the Budgetary Control Committee and the Special Committee on Beating Cancer as well as the different Health Interest Groups.

In addition, a new brochure was produced to highlight recent IMI project results in fields as diverse as cancer, antimicrobial resistance or COVID-19. It also showcases how IMI projects are addressing cross-cutting challenges in health research (for example the use of big data); the impact of IMI projects on regulatory processes; and the work IMI projects have undertaken to place patients at the centre of health research.

The cover of the new brochure

We continued our media partnerships with *Science Business*. This allowed us to promote 12 articles via the *Science Business* website, newsletter, and social media accounts. Each article was promoted for a week. In total, these resulted in the following:

- Home page views while our articles were live: 46 233
- Social media impressions: 21 609
- Social media engagements: 542

- Newsletter impressions (opened): 59 704
- Clicks on article in newsletter: 967

The communications team also worked in close cooperation with its founding partners to further amplify the reach of project success stories. An article on VITAL, Next-gen vaccines set to maintain immunity as the years advance, was published in Horizon Magazine, and an article on the ADAPTED project was published by the European Commission under the title Towards a new era of tackling Alzheimer's disease as part of the Research and Innovation success stories.

### Events

We held a new #ImpactSeriesIMI event in March focusing on what SMEs contribute to IMI projects on health data management. Like the previous #ImpactSeriesIMI events, the "IMI impact on SMEs in health data management & health IT sectors" event has its own related thematic page, which can be accessed via the health spotlight section of the IHI website.


On 30 November, IHI participated in the discharge hearing organised by the European Parliament. The IHI Executive Director presented IMI's neuroscience portfolio to the members of the Committee on Budgetary Control.

## IHI communication channels and performance indicators

### Website

On 15 December 2021, the core of the IHI website went live. Throughout 2022, the website functionalities have been tested and the content enriched.

Following the IHI communication principles of transparency, clarity, visibility and trustworthiness, a number of new sections and pages on the IHI website have been either created or sharpened, such as (i) the 'apply for funding' section, (ii) the idea submission page, (iii) the section on resource for projects and (iv) the governance section.

In addition, two factsheets (ZAPI and ENABLE) have been updated with the principal findings of the projects based on the project close-out presentations and follow-up interviews with the coordinators.

### Website traffic[10]

IHI's website is the programme's main information hub, and all communication channels link back to its content. As an example, the number of referrals from LinkedIn amounted to 13,31%.

In 2022 the website received 189.7 thousand visits, with peeks of around 19 thousand unique visitors per month in February, June and November, always linked to call launch dates. Accordingly, and leaving aside the homepage, the "apply for funding" was the most visited website section, totalling last year 116.4 thousand page views.

10 Data source: Europa Analytics. For reasons external to IHI, there is no data available for the week of 7 to 15 March.

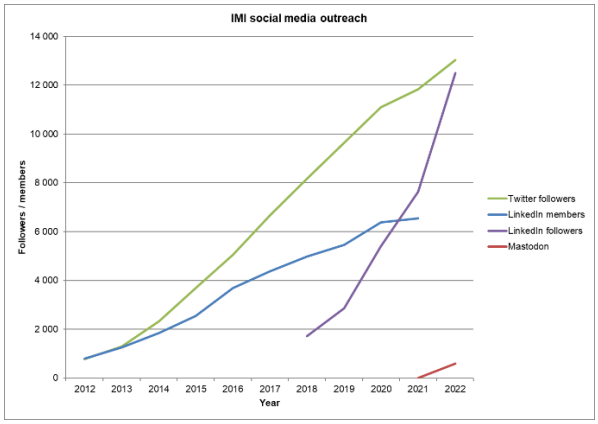
Further key indicators are:

- Number of sessions: 288.7 thousand
- Number of page views: 618.8 thousand
- Bounce rate: 66.25%
- Average session time: 2m 25s

With regards to the geographic locations of website visitors, most came from the US (17%), followed by Belgium (9%), the UK (8%), Germany (7%) and Spain (6.5%).

### Social media

We continued to primarily promote our editorial content on both Twitter and LinkedIn, with the recent addition of Mastodon. As presented in the graph, IHI's social media channels continue to grow year-on-year.




### Twitter

In 2022, @IHIEurope tweeted 417 original messages in addition to regular retweets, particularly from IMI projects, generating almost 404 thousand impressions, 1 887 link clicks, 1 906 retweets and 3 320 likes, reaching 7 172 engagements overall.

By the end of 2022, the IHI Twitter account had 13 032 followers, up from 11 827 the year before, despite experiencing a small drop in followers in November following Elon Musk's takeover of the platform. The trend was reversed again in December.

### LinkedIn

By the end of 2022, IHI had 12 487 followers on LinkedIn, up from 7 634 at the end of 2021. The followers come primarily from the pharmaceutical industry (24%), research sector (12%) and biotechnology sector (10%) as well as hospital and healthcare (8%) and higher education (7%). The account featured 300 posts, of which 118 were written by IHI, while the rest were re-posts of posts by our projects. Those 118 posts received 243 077 impressions, 7 133 clicks, 4 952 likes, 96 comments and were shared 1 257 times. The engagement rate was over 4.6%.

### Mastodon

In November, as there were a lot of uncertainties about the viability of Twitter, IHI turned to Mastodon, the open-source social media platform, and set up an account on the EU Voice server run by the European Data Protection Supervisor. IHI's first post was published on 24 November 2022. A further 52 posts followed in December.

Our experience with Mastodon was broadly positive and by the end of 2022, IHI's account had reached 595 followers.

### Newsletter

In addition to our social media channels, the IHI digital newsletter, of which we publish 11 issues throughout the year, plays a pivotal role in promoting our editorial content. By the end of 2022, there were 6 787 subscribers (compared to 4 190 in 2021).

The breakdown of subscribers' organisations is as follows: 3 229 subscribers from research organisations, universities and hospitals; 1 245 from SMEs; 816 from large industry (578 pharma industry subscribers and 238 other large industry subscribers);156 from patient organisations; and an additional 26 from non-profit organisations. It is worth noting that over 800 subscribers come from organisations that act as amplifiers of IHI such as EU, national and regional authorities (366), consultancies (396) and press/PR agencies (42) in addition to a number of organisations that simply categorise themselves as 'other'.


As in previous years, the monthly tweet highlighting the newsletter stories featured consistently among the most popular in IHI's Twitter feed, reaching an average engagement rate of 4%. Similarly, the website page hosting the newsletter appears among those with higher numbers of page views.

### Press coverage

Throughout the year, the communications team tracked the number of press articles that mentioned IMI and/or its projects. There were 4 182 articles published worldwide, of which 739 were published in the EU plus the UK. IMI reached a 6% headline / header presence, meaning IMI was mentioned in the headline or the opening part of the article. Regarding IHI, the partnership was mentioned in 222 articles, in which the percentage of headline presence was high, reaching 27%.

The communications team remained alert to issues that could damage IHI's reputation. As in previous years, we performed a content analysis to measure the tone of both the news coverage and Twitter engagement. The result was consistent with past trends. For the press, the tonality was neutral in the case of 90% of news items talking about IMI, while the content of around 9% of the pieces was positive and less than 0.5% negative. In the case of IHI, the performance was slightly better: the tone was positive in 11% of the news items and the rest was neutral. On Twitter a third of posts about IHI had a positive tonality, with the rest being largely neutral.

## 2.2 Stakeholder engagement

### 2.2.1 Patients

Patient engagement has been a priority for the organisation throughout the IMI1 and IMI2 programmes, and it remains a priority under the new IHI programme. Thanks to efforts to promote patient engagement in projects, as of the end of 2022, 59% of all IMI1 and IMI2 projects have patient organisations either as partners in the consortium or represented in advisory boards, ethics advisory boards, or being consulted for topics of relevance, while this percentage rises to 63% for IMI2 projects alone.

IHI continued throughout 2022 the systematic involvement of patients and carers at all levels of its activities, mainly through the IMI pool of patient experts, an initiative introduced in late 2019 aiming to provide in a rigorous and systematic way, patients' perspectives, needs and priorities within IMI/IHI. Specifically, in 2022 the IHI Programme Office continued to invite patients from the pool to perform a variety of roles and tasks. These include:

- Evaluation of proposals submitted for IHI calls for proposals – one patient expert participated in the expert panel that evaluated proposals submitted to IHI - call 2, stage 1: topic 2.

- Monitoring of IMI projects – two patient experts participated in expert review panels that carried out the monitoring of the IMI2 projects ImmUniverse (one expert) and INNODIA HARVEST (one expert).

To deploy the full potential of the IMI pool of patient experts, the IHI Programme Office provided tailor-made support to patient experts with one-to-one training and follow-up meetings after the conclusion of the evaluation and review process.

In an effort to promote patient participation in the whole cycle of its activities, the IHI Programme Office invited patients and carers from the IMI pool to attend project close-out meetings where they had the opportunity to get an overview of how an IMI consortium works, get valuable insights of the different tasks undertaken by an IMI project, learn first-hand about the project outcomes, identify patient relevant results, and provide input on their implementation in research. In 2022,nine patients and carers attended the following IMI close-out meetings: EQIPD (4), ZAPI (1), and APPROACH (4).

Creating and developing communication channels with patients is instrumental in keeping them engaged and informed about the latest developments in IHI. Throughout 2022, IHI provided detailed updates on its activities to patients with news of IHI activities, calls and events, and highlights from IMI projects.

In 2022, IHI also participated in external high-profile events, webinars, and meetings to raise awareness of IHI's goals and achievements while contributing to patient-centred discussions and debates.

Additionally, with the creation of IHI as a new public-private partnership and the set-up of the new objectives outlined in its Scientific and Research Innovation Agenda, in December 2022, the IHI Programme Office started to prepare a new call for expression of interest (expected to be launched in 2023). The purpose is to set up a new and wider IHI Patient Pool, confirming the interest of IMI Patient Pool members and allowing other patients/caregivers to become members of the pool and provide their perspectives within IHI activities, at both strategic and operational level.

### 2.2.2 SMEs

The involvement of small and medium-sized enterprises (SMEs) in IHI activities is crucial as SMEs can act as a key interface between the latest academic discoveries and implementation in industry, can drive projects to achieve high impact results, and can help ensure the results of IHI projects are widely available after the funding ends. Therefore, IHI aims to create a favourable ecosystem for SME innovation and growth.

At the IHI launch and brokerage event on 14 June 2022, the importance of SME participation in IHI proposals was emphasised through a dedicated SME session. This presentation showcased the benefits to SMEs of participation in IHI consortia, illustrated by some examples from IMI projects.

In March 2022 a webinar on the Impact of IMI on SMEs was broadcast. An audience of nearly 400 heard how participation in IMI projects had long-lasting impacts on three SMEs: The speaker from one SME featured, Owkin, explained how participating in the MELLODDY project had had a 'massive' impact on the company, as they had developed their technology with companies who are also their customers, and demonstrated that their technology works at scale, adds value, and meets their customers' high demands.

A number of IMI projects offer support to SMEs outside their consortia, some examples are:

The EHDEN project completed their final open call for data harmonisation SMEs, which resulted in an additional 17 trained and certified SMEs joining the EHDEN business directory. This directory now contains 64 SMEs from 22 countries which are now certified to offer a range of services which aim to make real world heath data available for research. In addition, several new training courses were added to the EHDEN academy which is a freely available educational resource that is used by the project to train SMEs and is open to other SMEs interested in this field.

In May 2022, the FAIRplus project hosted their third Innovation and SME Forum. Over 200 scientists, data managers and IT experts from academia, SMEs and industry gathered online to discuss the challenges and opportunities in implementing FAIR data principles in life science research. The forum included testimonials from SMEs who are already implementing some of the project's results, which are described in the FAIRplus cookbook.

### 2.2.3 Regulators

The regulatory environment is key to ensuring that safe and effective health innovations are developed to address public health needs. To ensure that the science generated by IMI and IHI projects is translated into people-centred healthcare solutions, the Programme Office continued to encourage and support consortia of IMI projects to interact early with regulators whenever relevant to ensure greater impact by translating research outcomes into regulatory practice. The regulators' perspective was also embedded in the IHI scientific priorities and calls for proposals through the representation of regulators in the SIP.

The IHI Programme Office met with the EMA Executive Director and key relevant senior management staff to present IHI and discuss how to further strengthen the collaboration under the new cross-sectoral partnership, building on the fruitful collaboration during the IMI2 programme. This was also an opportunity to exchange on the possible scope for IHI calls for proposals addressing EMA regulatory science research needs[11].

IHI continued to maintain in 2022 a close collaboration with the FDA (US Food and Drug Administration), with regular teleconferences throughout the year to exchange information on activities relevant for IHI, and discuss topics and projects under development.

11 www.ema.europa.eu/en/documents/other/regulatory-science-research-needs_en.pdf

The Programme Office followed the progress of the work performed by Critical Path Institute Limited through the framework contract for services to support the regulatory acceptance of IMI results. In 2022 the Critical Path Institute Limited completed the work and provided its final report that included the final analysis for the selected project results with an assessment of the probability of successful regulatory endorsement as well as specific recommendations as part of a regulatory engagement framework schema that future IMI/IHI projects could apply. Based on this final report, the relevant owners of the project results were informed of the outcome of the analysis. In addition the IHI Programme Office has developed an action plan to implement these recommendations in 2023.

## 2.3 Legal and financial framework

During 2022, IHI implemented the Council Regulation establishing IHI (Council Regulation (EU) 2021/2085), while continuing to manage projects launched under the IMI1 and IMI2 programmes (Council Regulations (EC) 73/2008 and (EU) 557/2014 respectively).

## 2.4 Budgetary and financial management

### 2.4.1 Total budget 2022

IHI JU's total budget for 2022 was **EUR 272 383 841** in commitment appropriations (CA) and **EUR 174 845 991** in payment appropriations (PA). The budget execution of the commitment appropriations and the payment appropriations reached **96.60%** and **86.25%** respectively.

The IHI JU budget is divided into three titles:

- Title 1 covers staff expenditure such as salaries, training, costs associated with recruitment procedures, missions and staff well-being.
- Title 2 covers the costs associated with functioning of IHI such as renting of premises, IT needs, meetings, expenses related to external communication and costs of ex-post audits.

Titles 1 and 2 together form the administrative expenditure.

- Title 3 covers IHI's operational activities.

The IHI JU Governing Board approved the 2022 budget on 16 December 2021. The total budget approved was EUR 9.3 million in commitment appropriations and EUR 176.3 million in payment appropriations. The budget was subsequently amended during 2022.

The first budget amendment was approved by the Governing Board on 17 June 2022. The total budget approved was EUR 264.8 million in commitment appropriations and EUR 167.7 million in payment appropriations. The first budget amendment was driven by revenue and expenditure updates as follows:

- To update the commitment appropriations related to the first three calls launched in 2022 under the Horizon Europe programme, totalling EUR 253.7 million.
- To update the contributions of the EU and the new industry members to the IHI JU budget, for both the administrative and operational budgets. In addition, the EU contribution reflected the carry-over of revenue from previous year of EUR 0.5 million.
- To enter in the budget the carry-over of the operational funds from the previous year, of EUR 1.8 million on commitment appropriations and EUR 7.9 million on payment appropriations.
- To update the operational payment appropriations by reducing them by EUR 17 million to reflect the operational needs of the IMI2 projects.

The Governing Board approved the second budget amendment on 8 December 2022, to reflect the carry-over of administrative funds from the previous year, of EUR 0.5 million on commitment appropriations and of EUR 0.1 million on payment appropriations.

The total appropriations approved with the second budget amendment for 2022 were EUR 265.3 million in commitment appropriations and EUR 167.8 million in payment appropriations. In addition, the amount of assigned revenue (amounts recovered during the year from suppliers and projects) was EUR 7.1 million in commitment appropriations and EUR 7.1 million in payment appropriations.

### 2.4.2 Operational expenditure

IHI JU's operational budget (Title 3) reflects expenses linked to the implementation of the IHI JU' research agenda. In 2022, the operational commitment and payment appropriations implementation reached a level of 97.05% and 86.49% respectively. It should be noted that, since November 2021, the IHI Programme Office has been managing three programmes in parallel.

- IMI1 (under the Seventh Framework Programme, FP7)

FP7 was the EU's research and innovation funding programme for 2007-2013. Through FP7, the EU contributed EUR 966 million to the IMI1 research programme.

In 2022, payments related to FP7 projects amounted to EUR 13.7 million. The payment appropriations related to FP7 were mainly used by payments for periodic or final reports for projects of IMI1 Calls 6, 8, 9, 10 and 11.

- IMI2 (under Horizon 2020, H2020)

As initially set out in the 2014 Council Regulation, the EU has committed to contribute EUR 1.595 billion from H2020 to the IMI2 programme, for operational activities. At the end of 2021, the total EU commitments available at programme level over the lifetime of the IMI2 programme (2014-2021) for operational activities amounted to EUR 1.4566 billion:

| | |
|---|---|
| EUR 1.595 billion | (as initially set out in Council Regulation 557/2014) |
| - EUR 139 million | (reduction in 2019) |
| - EUR 6.7 million | (redeployment to climate related activities under Horizon 2020) |
| + EUR 7.3 million | (50% of unused commitments since 2014 transferred from the administrative budget to the operational budget) |
| = EUR1.4566 billion | total EU commitments available at programme level over the lifetime of IMI2 (2014-2021) for operational activities at the end of 2021 |

In 2022, payments related to H2020 projects amounted to EUR 128.7 million. The payment appropriations related to H2020 were mainly used by interim and final payments for projects of IMI2 Calls 3-22.

- IHI JU (under Horizon Europe, HE)

Starting from 30 November 2021, the IHI JU managed a third programme, under Horizon Europe.

As set out in the 2021 Council Regulation establishing IHI, the EU has committed to contribute EUR 1.170 billion from Horizon Europe to the IHI programme, for operational activities. The IHI JU industry partners have committed up to EUR 1 billion to IHI JU, and furthermore up to EUR 200 million can be committed by other organisations that decide to support the objectives of IHI in specific areas of research, by becoming contributing partners.

Regarding the commitment appropriations, in 2022, IHI JU launched the first three calls for proposals under the Horizon Europe programme. The committed amounts were EUR 95 million for IHI call 1, EUR 22 million for IHI call 2 and EUR 138 million for IHI call 3.

### 2.4.3 Administrative expenditure

The administrative budget implementation, of the commitment and payment appropriations, reached a level of 83.9% and 82.2% respectively.

At the end of 2022, the administrative budget was EUR 9.4 million in commitment appropriations and EUR 9.9 million in payment appropriations. The implementation rates show a significant achievement for administrative expenditure (Titles 1 and 2) in 2022 compared with the previous year, as a result of continuous actions in planning and monitoring the administrative budget.

Regarding Title 1, the budget implementation of the commitment and payment appropriations reached a level of 87.4% and 86.6% respectively. Within Title 1, the payments execution rate for mission expenditures was 16%, as a result of the COVID-19 crisis and attending many meetings and events in remote mode.

Regarding Title 2, the budget implementation of the commitment and payment appropriations reached a level of 76.4% and 74.2% respectively.

A significant part of the Title 2 budget was used for expenditure linked to rent, IT, communication, ex-post audit and studies, as support provided in managing the three programmes running.

On the other hand, due to the effects of the COVID-19 crisis, formal meetings and expenditure in connection with operational activities costs were affected by meetings taking place mainly virtually.

IHI JU continued to execute its budget applying the principles of sound financial management, which resulted in several budget transfers between budget chapters, in line with operational needs. In 2022, there were no budget transfers between titles.

### 2.4.4 Overview of the total budget 2022 in EUR

#### Revenue

The table below shows the statement of revenue, per nature of revenue, indicating EFTA contribution on individual lines. The EFTA percentage was 2.47% for 2022.

**IHI JU STATEMENT OF REVENUE 2022 EUR**

| | Voted budget 2022 | | Final amended budget 2022 | |
|---|---|---|---|---|
| **Heading** | **Commitment appropriations (in EUR)** | **Payment appropriations (in EUR)** | **Commitment appropriations (in EUR)** | **Payment appropriations (in EUR)** |
| **EU contribution excl. EFTA** | **4 617 631** | **167 592 160** | **252 207 169** | **151 445 971** |
| of which Administrative | 4 617 631 | 4 617 631 | 4 617 631 | 5 061 663 |
| of which Operational | | 162 974 529 | 247 589 538 | 146 384 308 |
| **Third countries contribution including EFTA** | **22 369** | **4 047 840** | **6 137 831** | **3 649 029** |
| of which Administrative | 22 369 | 22 369 | 22 369 | 33 337 |
| of which Administrative third countries excluding EFTA | | | | |
| of which Operational | | 4 025 471 | 6 115 462 | 3 615 692 |
| **Industry financial contribution** | **4 640 000** | **4 640 000** | **4 640 000** | **4 640 000** |
| of which Administrative | 4 640 000 | 4 640 000 | 4 640 000 | 4 640 000 |
| of which Operational | | | | |

| | | | | |
|---|---|---|---|---|
| Other revenue | | | 7 060 118 | 7 060 118 |
| **SUB-TOTAL REVENUES** | **9 280 000** | **176 280 000** | **270 045 118** | **166 795 118** |
| **Reactivation of unused appropriations from administrative expenditure** | | | **537 963** | **100 000** |
| Of which from 2020 | | | | |
| Of which from 2021 | | | 537 963 | 100 000 |
| Of which from 2022 | | | | |
| Reactivation of unused appropriations from operational expenditure | | | **1 800 760** | **7 950 873** |
| Of which from 2020 | | | | |
| Of which from 2021 | | | 1 800 760 | 7 950 873 |
| Of which from 2022 | | | | |
| **TOTAL** | **9 280 000** | **176 280 000** | **272 383 841** | **174 845 991** |

For a complete overview, the table below shows the statement of revenue per Members' contributions, indicating the evolution of the budget approved, through budget amendments during 2022, per fund source (current year, carry overs and assigned revenue), balancing the expenditure per title.

CA = commitment appropriations. PA = payment appropriations

**IHI JU STATEMENT OF REVENUE 2022 EUR**

| | Revenue | Budget 2022.1 | | Budget 2022 Amendment 1 | | Budget 2022 Amendment 2 | | Assigned revenue | | Final Amended Budget 2022.2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Chapter / Line** | | CA | PA | CA | PA | CA | PA | CA | PA | CA | PA |
| **10** | **EC contribution** | | | | | | | | | | |
| **1000** | EC contribution (including EFTA contribution) for current year out of IMI2 budget | 4 640 000 | 171 640 000 | -928 000 | - 17 928 000 | | | | | 3 712 000 | 153 712 000 |
| **1002** | EC contribution (including EFTA contribution) for current year out of IHI JU budget | | | 254 633 000 | 1 383 000 | | | | | 254 633 000 | 1 383 000 |
| **1001** | EC – appropria-tions carried over from previous years | | | 1 800 760 | 7 950 873 | 537 963 | 50 000 | | | 2 338 723 | 8 000 873 |
| **10** | **EC contribution – total** | **4 640 000** | **171 640 000** | **255 505 760** | **- 8 594 127** | **537 963** | **50 000** | | | **260 683 723** | **163 095 873** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **20** | **JU members other than the Union contribution** | | | | | | | | |
| **2000** | EFPIA contribution for current year out of IMI2 budget | 4 640 000 | 4 640 000 | - 1 383 000 | - 1 383 000 | | | 3 257 000 | 3 257 000 |
| **2002** | EFPIA contribution for current year out of IHI budget | | | 661 500 | 661 500 | | | 661 500 | 661 500 |
| **2001** | EFPIA – appropria-tions carried over from previous years | | | | | | 42 175 | - | 42 175 |
| | **EFPIA contribution – total** | **4 640 000** | **4 640 000** | **- 721 500** | **- 721 500** | **-** | **42 175** | **3 918 500** | **3 960 675** |
| **2010** | EuropaBio contribution for IHI current year | | | 30 000 | 30 000 | | | 30 000 | 30 000 |
| **2011** | EuropaBio – appropria-tions carried over from previous years | | | | | | 325 | - | 325 |
| | **EuropaBio contribution – total** | **-** | **-** | **30 000** | **30 000** | **-** | **325** | **30 000** | **30 325** |
| **2020** | COCIR contribution | | | 345 750 | 345 750 | | | 345 750 | 345 750 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | for IHI current year | | | | | | | | | | |
| **2021** | COCIR – appropria-tions carried over from previous years | | | | | | 3 750 | | | - | 3 750 |
| | **COCIR contribution – total** | **-** | **-** | **345 750** | **345 750** | **-** | **3 750** | | | **345 750** | **349,500** |
| **2030** | MedTech Europe contribution for IHI current year | | | 345 750 | 345 750 | | | | | 345 750 | 345,750 |
| **2031** | MedTech Europe – appropria-tions carried over from previous years | | | | | | 3 750 | | | - | 3,750 |
| | **MedTech Europe contribution – total** | **-** | **-** | **345 750** | **345 750** | **-** | **3 750** | | | **345 750** | **349,500** |
| **20** | **JU members other than the Union contribution – total** | **4 640 000** | **4 640 000** | **-** | **-** | **-** | **50 000** | | | **4 640 000** | **4,690,000** |
| **C4** | Assigned revenue (amounts recovered during the year from suppliers and projects) | | | | | | | 7 060 118 | 7 060 118 | 7 060 118 | 7,060,118 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Total revenue** | | **9 280 000** | **176 280 000** | **255 505 760** | **- 8 594 127** | **537 963** | **100 000** | **-** | **-** | **272 383 841** | **174 845 991** |
| | **Expenditure** | | | | | | | | | | |
| **Title 1** | Staff expenditure | 6 464 000 | 6 464 000 | - | - | | | 3 043 | 3 043 | 6 467 043 | 6,467,043 |
| **Title 2** | Infrastructure expenditure | 2 816 000 | 2 816 000 | - | 455 000 | - | 100 000 | 136 734 | 136 734 | 2 952 734 | 3,507,734 |
| **Title 3** | Operational expenditure | - | 167 000 000 | 255 505 760 | - 9 049 127 | 537 963 | - | 6 920 341 | 6 920 341 | 262 964 064 | 164,871,214 |
| **Total expenditure** | | **9 280 000** | **176 280 000** | **255 505 760** | **- 8 594 127** | **537 963** | **100 000** | **7 060 118** | **7 060 118** | **272 383 841** | **174 845 991** |

## Expenditure

The table below shows the **commitment appropriations (CA) implementation** for financial year 2022, reflecting the following fund sources: current year credits, recoveries from beneficiaries and re-activation of appropriations from preceding financial years.

In line with article 174.14 from the Council Regulation establishing IHI and article 6 of the Commission Delegated Regulation (EU) 2019/887, the unused appropriations may be carried over up to following three financial years. The unused appropriations shown in the table below, to be carried over, are estimated, being subject to Governing Board approval.

In line with article 26 of the Council Regulation establishing IHI, any unused part of the contribution for administrative costs may be made available to cover the operational costs of the Joint Undertaking. As such, 50% of the 2022 unused administrative appropriations (EC part) is available to be carried over to operational expenditure in 2023. Such appropriations are foreseen to be used for new calls under the Horizon Europe programme.

### IHI JU statement of expenditure 2022 (commitment appropriations) in EUR

| | Chapter | Amended budget 2022 | Amended budget 2022 after transfers | Executed budget 2022 | % | Unused commitment appropriations 2022 | Estimated to be carried over to 2023 | Estimated Available for future use (N+3 rule) |
|---|---|---|---|---|---|---|---|---|
| **1** | **Title 1 - Staff expenditure** | **6 464 000** | **6 467 043** | **5 653 252** | **87%** | **813 791** | **406 896** | **-** |
| 11 | Staff in active employment | 6 032 000 | 5 956 100 | 5 249 928 | 88% | 706 172 | 353 086 | |
| 12 | Miscellaneous expenditure on staff recruitment | 5 000 | 12 861 | 11 581 | 90% | 1 280 | 640 | |
| 13 | Missions | 80 000 | 78 414 | 15 543 | 20% | 62 871 | 31 435 | |
| 14 | Socio-medical structure | 212 000 | 244 731 | 204 876 | 84% | 39 855 | 19 927 | |
| 15 | External staff | 125 000 | 161 437 | 160 000 | 99% | 1 437 | 719 | |
| 17 | Representation expenses | 10 000 | 13 500 | 11 324 | 84% | 2 176 | 1 088 | |
| **2** | **Title 2 - Infrastructure expenditure** | **2 816 000** | **2 952 734** | **2 254 538** | **76%** | **698 196** | **349 098** | **-** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 20 | Rent and related expenditures | 660 000 | 867 259 | 705 726 | 81% | 161 533 | 80 767 | |
| 21 | IT (hardware and software) | 1 009 000 | 884 000 | 748 578 | 85% | 135 422 | 67 711 | |
| 22 | Office equipment | 5 000 | 5 000 | - | 0% | 5 000 | 2 500 | |
| 23 | Current administrative expenditure | 124 000 | 124 046 | 72 386 | 58% | 51 660 | 25 830 | |
| 24 | Postage and telecommunications | 38 000 | 38 067 | 23 241 | 61% | 14 827 | 7 413 | |
| 25 | Meetings | 70 000 | 73 000 | 33 715 | 46% | 39 285 | 19 642 | |
| 26 | Expenditure in connection with operational activities | 200 000 | 197 000 | 80 075 | 41% | 116 925 | 58 463 | |
| 27 | External communication information and publicity | 300 000 | 304 361 | 178 045 | 58% | 126 316 | 63 158 | |
| 28 | Service contracts | 410 000 | 460 000 | 412 772 | 90% | 47 228 | 23 614 | |
| | **Administrative expenditure Total Title 1+ Title 2** | **9 280 000** | **9 419 777** | **7 907 790** | **84%** | **1 511 987** | **755 994** | **-** |
| **3** | **Title 3 - Operational expenditure** | **256 043 723** | **262 964 064** | **255 218 052** | **97%** | **7 746 012** | **1 034 723** | **-** |
| | Previous years' calls | 2 338 723 | 2 338 723 | 1 824 000 | 78% | 514 723 | 514 723 | - |
| | Current year's calls | 253 705 000 | 260 625 341 | 253 394 052 | 97% | 7 231 289 | 520 000 | - |
| | **GRAND TOTAL (Title 1 + Title 2 + Title3)** | **265 323 723** | **272 383 841** | **263 125 842** | **97%** | **9 257 999** | **1 790 717** | **-** |

For a complete overview of the unused appropriations, the table below shows the implementation of fund source that reflects the commitments carried forward from 2021.

| Chapter | Statement of Expenditure Commitment appropriations | Commitment appropriations 2022 carried forward | Commitment appropriations Consumed | Unused commitment appropriations 2022 | Estimated to be carried over to 2023 | Estimated Available for future use (N+3 rule) |
|---|---|---|---|---|---|---|
| Title 1+ Title 2 | Administrative expenditure Total Title 1+ Title 2 | 1 531 105 | 1 392 628 | 138 477 | 69 239 | - |
| Title 3 | Title 3 - Operational expenditure | 703 636 122 | 674 502 735 | 29 133 387 | - | - |
| **GRAND TOTAL (Title 1 + Title 2 + Title3)** | | **705 167 227** | **675 895 363** | **29 271 864** | **69 239** | **-** |

In terms of total commitment appropriations, the first estimate of the 2022 surplus that remains within the Joint Undertaking is EUR 38 529 863 with the following breakdown:

EUR 36 879 399 unused commitment appropriations of operational activities. Out of it, estimated available appropriations to be carried over are EUR 1 034 723. The difference of EUR 35 844 676 is estimated not to be available to be carried over as it is stemming from closed programmes FP7 and H2020 (de-commitments, recoveries from beneficiaries).

EUR 1 650 464 unused commitment appropriations of administrative activities. Out of it, estimated available to be carried over is the amount of EUR 825 232, representing 50%, EC part, that can be carried over to operational activities in 2023.

## IHI JU statement of expenditure 2022 (payment appropriations) in EUR

The table below shows the **payment appropriations (PA) implementation** for financial year 2022, reflecting the following fund sources: current year credits, recoveries from beneficiaries and re-activation of appropriations from preceding financial years.

| | Chapter | Amended budget 2022 | Amended budget 2022 after transfers | Executed Budget 2022 | % | Unused commitment appropriations 2022 | Estimated to be carried over to 2023 | Estimated Available for future use (N+3 rule) |
|---|---|---|---|---|---|---|---|---|
| **1** | **Title 1 - Staff expenditure** | **6 464 000** | **6 467 043** | **5 598 137** | **87%** | **868 906** | **115 773** | **-** |
| 11 | Staff in active employment | 6 032 000 | 5 952 356 | 5 249 928 | 88% | 702 428 | | |
| 12 | Miscellaneous expenditure on staff recruitment | 5 000 | 16 605 | 13 638 | 82% | 2 967 | | |
| 13 | Missions | 80 000 | 78 414 | 12 243 | 16% | 66 171 | 3 300 | |
| 14 | Socio-medical structure | 212 000 | 244 731 | 179 623 | 73% | 65 108 | 34 313 | |
| 15 | External staff | 125 000 | 161 437 | 131 381 | 81% | 30 056 | 78 161 | |
| 17 | Representation expenses | 10 000 | 13 500 | 11 324 | 84% | 2 176 | | |
| **2** | **Title 2 - Infrastructure expenditure** | **3 371 000** | **3 507 734** | **2 601 419** | **74%** | **906 315** | **985 088** | **-** |
| 20 | Rent and related expenditures | 702 000 | 909 259 | 705 813 | 78% | 203 446 | 3 745 | |
| 21 | IT (hardware and software) | 1 089 000 | 964 000 | 872 331 | 90% | 91 669 | 592 446 | |
| 22 | Office equipment | 5 000 | 5 000 | - | 0% | 5 000 | | |
| 23 | Current administrative expenditure | 149 000 | 149 046 | 81 458 | 55% | 67 588 | 16 003.4 | |
| 24 | Postage and telecommunications | 38 000 | 38 067 | 29 259 | 77% | 8 809 | 9 219 | |
| 25 | Meetings | 87 000 | 90 000 | 33 655 | 37% | 56 345 | 60 | |
| 26 | Expenditure in connection with operational activities | 225 000 | 222 000 | 85 050 | 38% | 136 950 | 30 800 | |
| 27 | External communication information and publicity | 300 000 | 304 361 | 251 982 | 83% | 52 380 | 5 846 | |
| 28 | Service contracts | 776 000 | 826 000 | 541 872 | 66% | 284 128 | 326 968 | |
| 29 | Expert contracts and cost of evaluations | - | - | | | | | |
| | **Administrative expenditure Total Title 1+ Title 2** | **9 835 000** | **9 974 777** | **8 199 557** | **82%** | **1 775 220** | **1 100 861** | **-** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **3** | **Title 3 - Operational expenditure** | **157 950 873** | **164 871 214** | **142 600 154** | **86%** | **22 271 060** | **22 271 060** | **-** |
| | Previous years' calls | 7 950 873 | 7 950 873 | 7 950 873 | 100% | - | | - |
| | Current year's calls | 150 000 000 | 156 920 341 | 134 649 281 | 86% | 22 271 060 | 22 271 060 | - |
| | **TOTAL** | **167 785 873** | **174 845 991** | **150 799 711** | **86%** | **24 046 280** | **23 371 921** | **-** |

In terms of total payment appropriations, the first estimate of the 2022 surplus that remains within the Joint Undertaking is EUR 24 046 280, with the following breakdown:

- EUR 22 271 060 unused payment appropriations of operational activities to be carried over to financial year 2024.
- EUR 1 775 220 payment appropriations of administrative activities are available to be carried over to 2023. Out of it, the amount of EUR 1 100 861 is estimated to be carried over to 2023, as it is related to administrative commitments carried forward to 2023.

### 2.4.5 Budget transfers

In 2022, there were no budget transfers between titles. Budget transfers between chapters were authorised in 2022, which led to the following changes in commitment appropriations.

| Chapter | | Budget approved and assigned revenue (EUR) | Budget transfers (EUR) | Budget after transfers (EUR) |
|---|---|---|---|---|
| | | Commitment Appropriations | Commitment Appropriations | Commitment Appropriations |
| 11 | Staff in active employment | 6 032 000 | -75 900 | 5 956 100 |
| 12 | Staff recruitments - miscellaneous expenditure | 5 000 | 7 861 | 12 861 |
| 13 | Mission expenses | 80 000 | -1 586 | 78 414 |
| 14 | Socio-medical structure | 212 000 | 32 731 | 244 731 |
| 15 | External staff services | 125 000 | 36 437 | 161 437 |
| 17 | Representation | 10 000 | 3 500 | 13 500 |
| 20 | Office building and associated costs | 660 000 | 207 259 | 867 259 |
| 21 | Information technology (hardware and software) | 1 009 000 | -125 000 | 884 000 |
| 22 | Office equipment | 5 000 | 0 | 5 000 |
| 23 | Current administrative expenditure | 124 000 | 46 | 124 046 |
| 24 | Telecommunication and postal expenses | 38 000 | 67 | 38 067 |
| 25 | Formal meetings | 70 000 | 3 000 | 73 000 |
| 26 | Administrative expenditure in connection with operational activities | 200 000 | -3 000 | 197 000 |
| 27 | External communication, information and publicity | 300 000 | 4 361 | 304 361 |
| 28 | Service contracts | 410 000 | 50 000 | 460 000 |
| | **Total** | **9 280 000** | **139 777** | **9 419 777** |

### 2.4.6 Overview of total commitments outstanding

The summary of commitments outstanding at the end of 2022, for administrative and operational expenditure, was as follows:

| | EUR |
|---|---|
| Commitments carried from previous year | 705 167 227 |
| De-commitments (-) | -29 527 180 |
| Payments made during 2022 related to commitments carried forward (-) | -143 746 911 |
| Commitments made during 2022 | 263 125 842 |
| Payments made during 2022 related to commitments made during 2022 (-) | -7 052 800 |
| **Total commitments outstanding at the end of 2022** | **787 966 178** |

De-commitments made during 2022 were mainly related to FP7 and H2020, programmes closed.

Commitments made during 2022 were EUR 263.1 million, of which operational commitments EUR 255.2 million and administrative commitments EUR 7.9 million. The operational commitments were related to the first three calls for proposals under IHI. The committed amounts were EUR 95 million for IHI call 1, EUR 22 million for IHI call 2, EUR 138 million for IHI call 3 and EUR 0.2 million for evaluation experts.

The payments made during 2022, related to commitments carried forward and commitments made during 2022, were operational of EUR 142.6 million and administrative of EUR 8.2 million. The operational payments were related to interim and final payments of projects under the FP7 and H2020 programmes. The pre-financing payments related to Horizon Europe will be done in 2023, following conclusion of the Grant Agreements.

### 2.4.7 Operational budget per programme

IHI JU's operational budget (Title 3) reflects expenses linked to the implementation of the IHI JU SRIA. It should be noted that since November 2021, IHI JU has been managing three programmes in parallel:

- IMI1 (under FP7)
- IMI2 (under H2020)
- IHI (under Horizon Europe)

## IMI1 (under FP7)

The table below outlines the breakdown per call of EU committed funds for IMI1 (FP7) as well as open amounts, remaining to be paid, at the end of 2022.

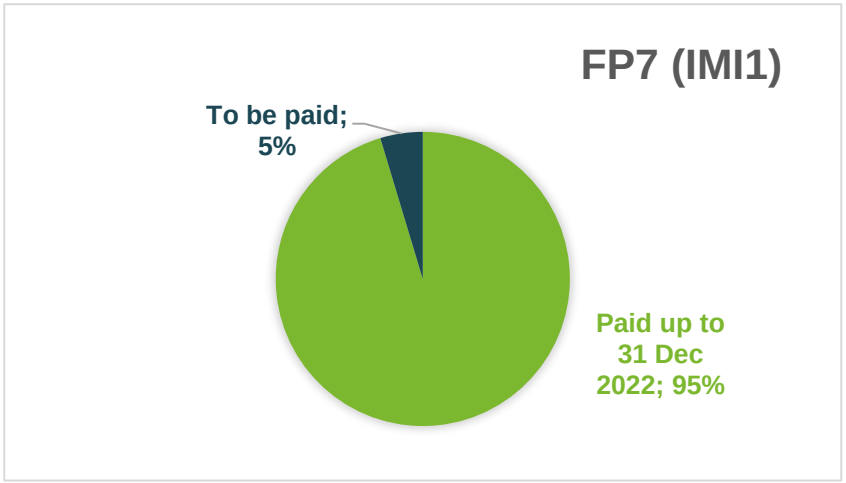
*EUR'000*

| FP7 (IMI1) | Committed 1 | De-committed 2022 2 | Paid up to 31/12/2022 * 3 | To be paid 4 = 1 –2 -3 |
|---|---|---|---|---|
| **Call 1** | 116 082 | 1 475 | 114 607 | - |
| **Call 2** | 85 765 | 549 | 85 216 | - |
| **Call 3** | 112 854 | 306 | 112 548 | - |
| **Call 4** | 97 944 | 776 | 97 168 | - |
| **Call 5** | 80 021 | 644 | 79 377 | - |
| **Call 6** | 125 417 | | 112 039 | 13 378 |
| **Call 7** | 13 000 | 936 | 12 064 | - |
| **Call 8** | 98 742 | | 85 032 | 13 710 |
| **Call 9** | 56 441 | | 50 571 | 5 870 |
| **Call 10** | 6 100 | | 5 599 | 501 |
| **Call 11** | 173 410 | 21 000 | 140 932 | 11 478 |
| **Total FP7 (IMI1)** | **965 776** | **25 686** | **895 152** | **44 938** |

**Including pre-financing*

At the end of 2022, 95% of the commitment appropriations had been paid out.

The graph below shows the percentage of what has been paid and what remains to be paid out of committed funds for IMI1 (FP7).



## IMI2 (under Horizon 2020)

The table below outlines the breakdown per call of EU committed funds for IMI2 (H2020) as well as open amounts, remaining to be paid, at the end of 2022.

*EUR'000*

| H2020 (IMI2) | Committed EU (level 1) (1) 1 | Committed Associated Partners and other members 2 | De-committed (level 1) 3 | Paid up to 31/12/2022 (2) 4 | To be paid 5 =1+2 –3 -4 |
|---|---|---|---|---|---|
| **Call 1** | 17 630 | | | 15 867 | 1 763 |
| **Call 2** | 114 090 | | 136 | 104 040 | 9 915 |
| **Call 3** | 49 060 | 7 000 | | 54 176 | 1 884 |
| **Call 4** | 1 130 | | 52 | 1 078 | (0) |
| **Call 5** | 47 477 | | | 43 752 | 3 725 |
| **Call 6** | 46 496 | 200 | 153 | 42 273 | 4 269 |
| **Call 7** | 46 795 | | 366 | 42 722 | 3 706 |
| **Call 8** | 47 462 | | 3 045 | 38 827 | 5 590 |
| **Call 9** | 53 606 | 4 000 | | 52 157 | 5 449 |
| **Call 10** | 173 874 | | 262 | 136 238 | 37 374 |
| **Call 11** | 3 284 | | 18 | 3 092 | 175 |
| **Call 12** | 64 052 | | 25 | 53 226 | 10 800 |
| **Call 13** | 114 152 | | 255 | 81 467 | 32 430 |
| **Call 14** | 82 310 | | | 37 123 | 45 187 |
| **Call 15** | 165 608 | | | 79 379 | 86 229 |
| **Call 16** | 35 184 | | | 26 892 | 8 292 |
| **Call 17** | 40 786 | | | 22 467 | 18 319 |
| **Call 18** | 74 866 | | 6 | 32 054 | 42 806 |
| **Call 19** | 12 715 | | | 8 934 | 3 781 |
| **Call 20** | 133 009 | | | 33 286 | 99 723 |
| **Call 21** | 72 000 | | 2 | 45 911 | 26 087 |
| **Call 22** | 11 427 | | 2 702 | 5 980 | 2 745 |
| **Call 23** | 47 790 | | 3 | 13 280 | 34 508 |

| | | | | | |
|---|---|---|---|---|---|
| **Total H2020 (IMI2)** | **1 454 803** | **11 200** | **7 025** | **974 222** | **484 756** |

*(1) The committed amount of EUR 1,454.8 million is at Call launch (level 1 commitments), which resulted in 123 projects for a granted amount of EUR 1,452.1 million.*

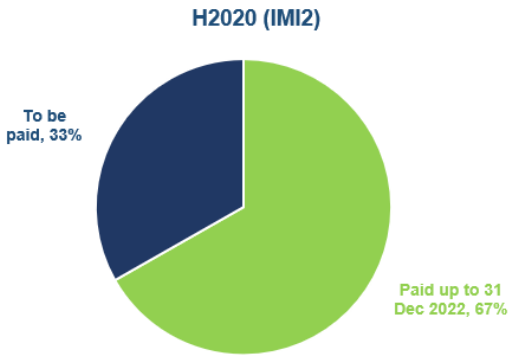
*(2) Including pre-financing*

The Associated Partners' commitment includes a financial contribution from Bill and Melinda Gates Foundation (BMGF), an IMI2 Associated Partner, for Call 3. The commitments for Calls 6 and 9 include a financial contribution from EFPIA companies.

In addition to the total amount to be paid, at the end of 2022, in ABAC there is the amount of EUR 2.1 million representing the open amount of the Periscope project.

At the end of 2022, the total EU commitments available at programme level over the lifetime of the IMI2 programme (2014-2021) for operational activities amounted to EUR 1.4566 billion. Compared with the total EU commitment at the end of 2022, the difference was EUR 8.8 million. This difference comes from the total de-committed amount of EUR 7.1 million, administrative carry overs to operational expenditure of EUR 1.6 million, and unused commitment appropriations of EUR 0.1 million, which could not be carried over as the programme was closed.

At the end of 2022, 66% of the commitment appropriations had been paid out. The graph below shows the percentage of what has been paid and what remains to be paid out of committed funds for IMI2 (H2020).




## IHI (under Horizon Europe)

The table below outlines the breakdown per call of EU committed funds for IHI JU (HE) as well as open amounts, remaining to be paid, at the end of 2022.

*EUR '000*

| IHI JU (HE) | Committed EU | Paid up to 31/12/2022 | To be paid |
|---|---|---|---|
| **Call 1** | 95 000 | | 95 000 |
| **Call 2** | 21 929 | | 21 929 |
| **Call 3** | 138 000 | | 138 000 |
| **Total HE (IHI JU)** | **254 929** | **-** | **254 929** |

## 2.5 Financial and in-kind contributions from Members other than the Union

This chapter presents the contributions of members other than the Union for the three different programmes IHI JU is managing in parallel (IMI1, IMI2, IHI).

IHI JU is a public-private partnership between the EU (represented by the European Commission) and life science industries represented by COCIR, EFPIA (also representing Vaccines Europe), EuropaBio and MedTech Europe (hereafter the members other than the Union). IHI JU's prior initiatives, the IMI1 and IMI2 programmes, were public-private partnerships between the EU and the European pharmaceutical industry represented by EFPIA.

All IMI and IHI projects are based on the same co-funding principle between public and private funds:

- On the one hand, in each IMI/IHI project, legal entities eligible for JU funding receive financial support from IMI/IHI to fund their project activities.
- On the other hand, members other than the Union contribute their own resources to the projects. Some projects also include the own resources of contributing partners (for IHI projects) or Associated Partners (for IMI2 projects). These contributions consist of in-kind and financial contributions as explained below in the respective sections of each programme.

This chapter presents the commitments made by members other than the Union as well as Associated Partners / contributing partners (when applicable) at call and project launch, and actual contributions made during the lifetime of the projects. The equivalent EU commitments / actual contributions are also provided throughout this chapter to facilitate the comparison between public and private contributions, which should match by the end of each respective programme.

Members other than the Union and Associated Partners / contributing partners are contractually obliged to report to the Programme Office all costs that they incur in IMI and IHI projects. The Programme Office controls the eligibility and regularity of the contributions and carefully monitors the development of the total contributions to the three programmes.

For each programme, Council Regulations clearly define the matching requirements.

### 2.5.1 IMI1 programme

#### IMI1 EU and EFPIA commitments

This section highlights the commitments pledged by EFPIA companies to the 59 projects in the IMI1 portfolio. These commitments are made up of:

- in-kind contributions[12], i.e. costs incurred by EFPIA companies in the implementation of the IMI1 projects for researchers, research equipment, and materials;
- financial contributions at project level to beneficiaries receiving JU funding.

EFPIA's commitment to the IMI1 programme totalled EUR 914.2 million as of 31 December 2022, representing an increase of EUR 1.2 million from the previous year following the amendment of an ongoing IMI1 grant in 2022 (iABC). The EU commitment remained unchanged at EUR 937.1 million.

| IMI1 | EU commitment | EFPIA commitment |
|---|---|---|
| Number of projects | 59 | |
| TOTAL (in EUR million) on 31/12/2022 | 937.1 | 914.2 |

#### IMI1 EU and EFPIA validated contributions - comparison by year

As of 31 December 2022, EFPIA contributions of EUR 808.8 million had been formally validated (checked by IHI staff and / or audited by external auditors). The table below gives an overview of validated IMI1 contributions, in EUR millions, for every year since the start of the programme.

| Year | Validated cost claims from beneficiaries (*) | EFPIA in-kind validated contributions |
|---|---|---|
| **2010** | 0.5 | |
| **2011** | 15.2 | |
| **2012** | 33.5 | 52 |
| **2013** | 59.4 | 58 |
| **2014** | 80.5 | 132.2 |
| **2015** | 80.4 | 65.4 |
| **2016** | 141.9 | 80.9 |
| **2017** | 129.2 | 141.3 |
| **2018** | 112.5 | 103.5 |
| **2019** | 62.5 | 55.2 |
| **2020** | 63.1 | 49.0 |
| **2021** | 23.4 | 29.1 |
| **2022** | 43.6 | 42.2 |
| **TOTAL** | **845.7** | **808.8** |

12 In-kind contribution is defined as follows: Article 11(4)(a) of the IMI JU Statutes annexed to the Council Regulation No 73/2008 – 'non-monetary contributions (hereinafter referred to as contributions in kind) by the research based pharmaceutical companies that are members of EFPIA, with resources (such as personnel, equipment, consumables, etc.) at least equal to the financial contribution of the Community'.

*(*) excluding pre-financing*

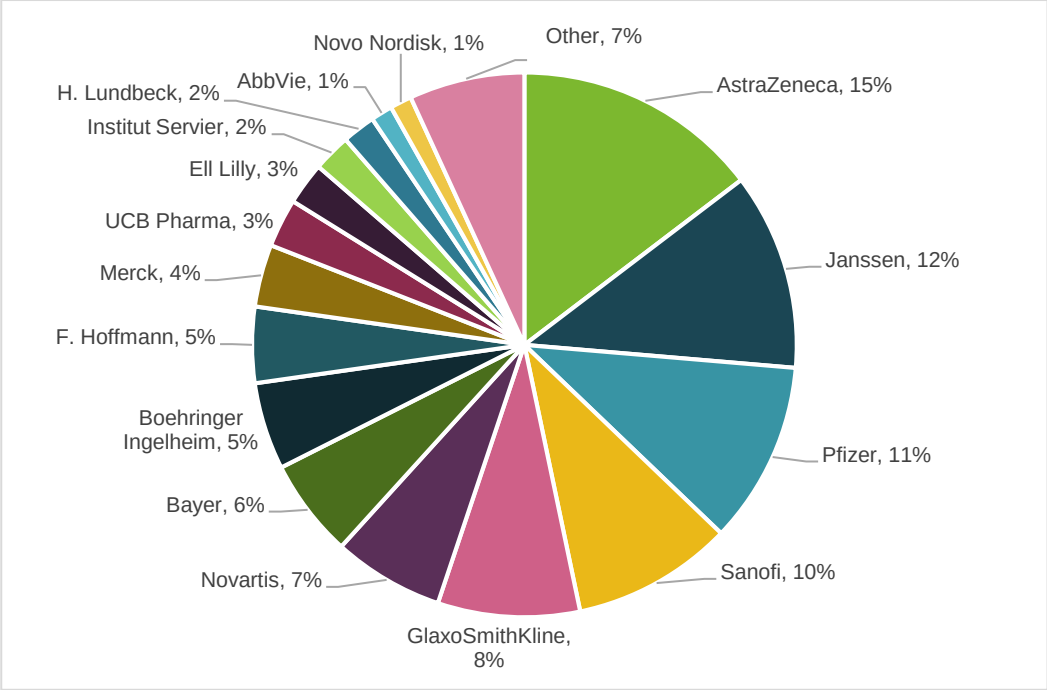
The difference between validated EU cost claims and EFPIA contributions results from the fact that, in some projects, tasks for the different consortium partners do not run in parallel but are often sequential.

Since 2016-2017, the number of IMI1 projects has started to decrease as the IMI1 programme winds down. Accordingly, the value of EU cost claims validated as well as EFPIA in kind reported per year has been decreasing steadily since 2018. At the end of 2022, there were three projects still running out of the initial 59 IMI1 projects.

The outstanding contributions should be reported by 2024 as the last IMI1 (FP7) projects will end in 2023.

### IMI1 EFPIA contributions - by company

The pie chart below sets out the breakdown of validated EFPIA companies' contributions to IMI1 projects since the start of the programme.




*Companies listed under 'Other' are: Abbott, AC Immune, Aicuris, Amgen, Astellas, Almirall, Basilea Pharmaceutica, Biogen, Bristol-Myers, Chiesi Farmaceutici, Da Volterra, Eisai, Employers' Union, Evotec, Farmaindustria, Genzyme, Grünenthal, Ipsen, Islensk, Laboratorios del Dr. Esteve, The Medicines Company, Merck Sharp & Dohme, Orion, Polyphor, Seqirus, Sigma-Tau, Silicon Biosystems, Takeda, Teva Pharmaceuticals Europe, Verband forschender Arzneimittelhersteller, Vifor.*

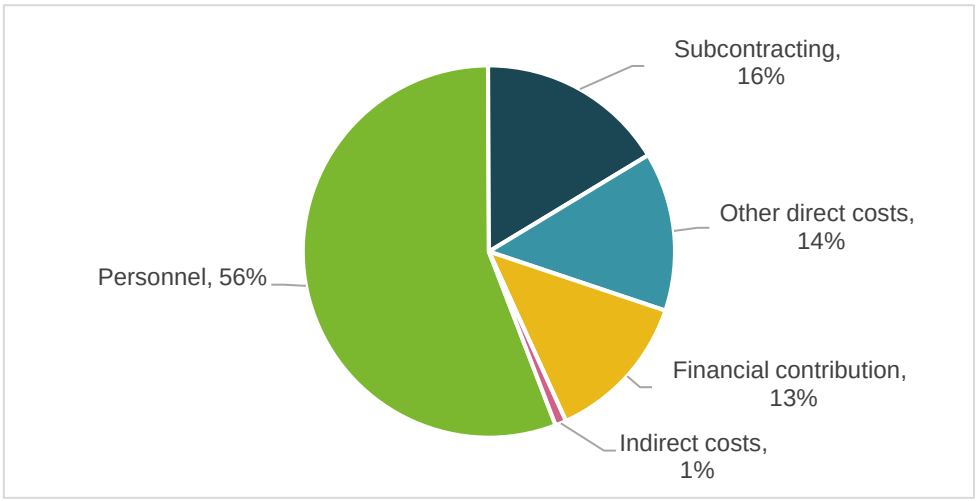
### IMI1 EFPIA contributions - by cost category

The EFPIA contributions at project level can be broken down into the following cost categories:

- Personnel: staff employed by EFPIA companies directly working on IMI projects.
- Other direct costs: consumables, equipment depreciation, samples, compounds.
- Subcontracting: clinical trials, subcontracting to clinical research organisations, subcontracting to data management companies, lab services, communication, project management support, etc.

- Financial contribution: in addition, EFPIA contributions can also be provided through financial contributions (FC), i.e. a transfer of funds from an EFPIA company to an academic institution within the same project/consortium. This financial contribution can be used by the academics to hire researchers during the lifetime of the IMI project or to cover project costs, such as the purchase of consumables or equipment.
- Indirect costs: overheads.

The share of each cost category is shown in the chart below.



## 2.5.2 IMI2 programme

### IMI2 EU, EFPIA and Associated Partner commitments

This section highlights the commitments pledged by EFPIA companies and Associated Partners (APs) in IMI2 projects. Both EFPIA and Associated Partner commitments include in-kind contributions, as well as financial contributions directly to the IMI2 programme's operational costs, or at project level to beneficiaries receiving JU funding.

The last IMI2 Grant Agreements were signed in 2021, bringing the total number of IMI2 projects to 123. No IMI2 grants were signed during 2022. At the end of 2022, the total commitments to the IMI2 programme were:

- EUR 1 452.1 million in EU funding.
- EUR 1 499.4 million commitments from EFPIA companies (EUR 1 296.7 million) and APs (EUR 202.7 million).

The following table provides an overview of EU, EFPIA and AP commitments to IMI2 projects:

| IMI2<br>In million EUR | EFPIA commitment | AP commitment | Total EFPIA + AP commitment | EU commitment |
|---|---|---|---|---|
| **Number of projects** | | 123 | | |
| **Up to 31/12/2021** | 1 315.2 | 203.0 | 1 518.2 | 1 452.1 |
| **2022** | -18.5 | -0.3 | -18.8 | 0 |
| **TOTAL on 31/12/2022** | 1 296.7 | 202.7 | 1 499.4 | 1 452.1 |

Compared to 2021, the EU commitment remained at EUR 1 452.1 million while the commitment from EFPIA and APs decreased from EUR 1 518.2 million to EUR 1 499.4 million. The reduction of EUR 18.5 million in EFPIA commitments and EUR 0.3 million in AP commitments can be mainly attributed to the amendment of an ongoing IMI2 project following the discontinuation of one clinical study. This discontinuation, which was due to multifactorial reasons including difficulties in recruiting patients into the study, does not however impact the project's ability to achieve its objectives.

Out of the overall commitment of EUR 1 452.1 million from the EU over the programme lifetime, at least 70% - which is EUR 1 016.4 million - should be matched by industry contributions incurred in the EU and H2020 Associated Countries, by the end of the IMI2 programme. At the end of 2022, from the total committed by EFPIA and Associated Partners, EUR 1 042.8 million was from the EU and H2020 Associated Countries, thus fulfilling the minimum requirement of 70%.

### IMI2 EU, EFPIA and Associated Partner validated contributions - comparison by year

In 2022, EFPIA companies and APs had contributed EUR 247.7 million to the IMI2 programme (amount certified by external auditors and validated by the JU). For comparison, accepted cost claims for JU funding from beneficiaries stood at EUR 180.6 million. The following table shows the validated EFPIA and Associated Partner contributions, in EUR millions, as well as validated cost claims from beneficiaries receiving EU funding.

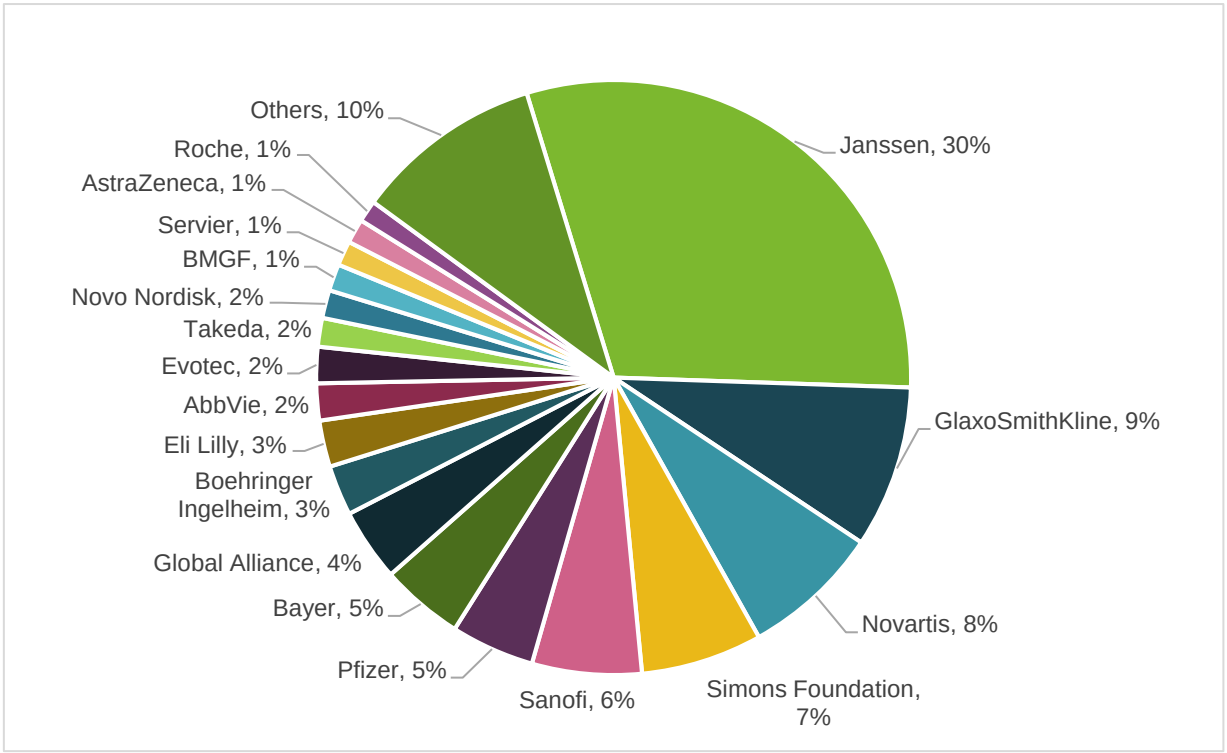
| | EFPIA contributions | AP contributions | Total validated EFPIA and AP contributions (1) | Validated cost claims from beneficiaries receiving EU funding (2) |
|---|---|---|---|---|
| **2016** | 47.3 | 2.9 | 50.2 | 13.0 |
| **2017** | 35.3 | 1.0 | 36.3 | 26.3 |
| **2018** | 47.7 | 1.3 | 49.0 | 50.4 |
| **2019** | 75.5 | 8.7 | 84.2 | 80.7 |
| **2020** | 115.6 | 28.2 | 143.8 | 128.4 |
| **2021** | 201.6 | 52.4 | 254.0 | 161.8 |
| **2022** | 223.2 | 24.5 | 247.7 | 180.6 |
| **TOTAL** | **746.2** | **119** | **865.2** | **641.3** |

*(1) Includes EUR 11.2 million paid directly by EFPIA and APs to IMI for the projects PERISCOPE, DRIVE and HARMONY*

*(2) excluding pre-financing*

### IMI2 EFPIA and Associated Partner contributions - by organisation

Up to the end of 2022, there were more than 70 EFPIA companies and Associated Partners contributing to IMI2 projects. As the organisational breakdown below shows, 30% of the IMI2 contribution is provided by Janssen. This is because Janssen has a high level of involvement in IMI2 projects (more than 50 projects). The remaining 70% comes from other EFPIA companies and Associated Partners. The chart below includes both in-kind contributions and financial contributions at the level of the project to beneficiaries receiving IMI funding; this totals EUR 865.2 million certified by external auditors and validated by the JU.



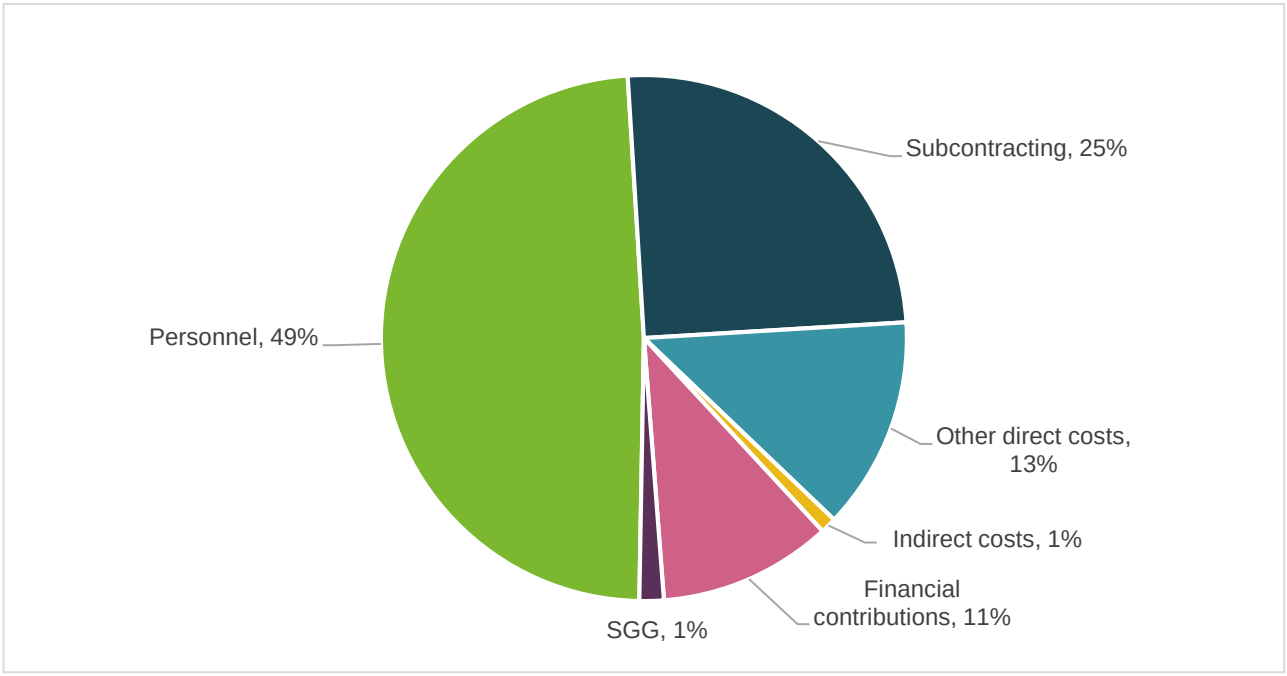
*Organisations under 'other' include Abbott, ABPI, Actelion, Amgen, Biogen, bioMérieux, Bristol-Myers, Celgene, Cepheid, Charles River, Children's Tumor Foundation, Coalition for Epidemic Preparedness Innovation, Covance Laboratories Ltd, CSL Behring GmbH, Curevac, Da Volterra, Deutsches Zentrum fur Infektionsforschung, Diamond Light Source, EFPIA, Ellegaard Gottingen, Esteve Pharmaceuticals, Farmaindustria, GE Healthcare, Grünenthal, H. Lundbeck, Helmsley Charitable Trust, Icon Clinical Research, Illumina Cambridge, Imcyse, Institut Pierre Fabresas, Intercept Pharma Europe, Intervet, Ipsen, JDRF, JLP Health, Kungliga, Labcorp, Leo Pharma, Life Molecular Imaging, Link2Trials, Lonza, Ludwig-Maximilians-Universitaet Muenchen, Lundbeck, Menarini, Merck, MSD, Ontario Institute for Cancer Research, Orion, Otsuka Novel Products, Pharmamar, Psychogenics, Rentschler, Seqirus, Spark Therapeutics, Teva, Transgene, UCB, VFA, Vifor, Viscofan, Zoetis.*

### IMI2 EFPIA and Associated Partner contributions - by cost category

EFPIA companies' and Associated Partners' contributions can be broken down into in-kind and financial contributions.

- Personnel costs: staff employed by EFPIA companies directly working on IMI projects.
- Subcontracting: clinical trials, subcontracting to clinical research organisations, subcontracting to data management companies, lab services, communication, project management support, etc.
- Other direct costs: consumables, equipment depreciation, samples, compounds.
- Indirect costs: overheads
- Financial contribution: EFPIA companies can also make a financial contribution (FC), i.e. a transfer of funds from an EFPIA company to beneficiaries receiving IMI2 JU funding within the same project/consortium. This financial contribution is used by the beneficiaries receiving funding to cover project costs, such as hiring researchers during the lifetime of the IMI project or buying consumables or equipment.
- SGG/Certification: In addition to costs incurred on projects, in-kind contributions also include costs (contributions) related to Strategic Governing Group (SGGs) and the costs of having their in-kind contribution certified by external auditors.

The graph below shows the breakdown of the reported EFPIA / Associated Partner contributions.




The higher percentage of subcontracting costs in IMI2 projects compared to IMI1 projects is due to the particularities of the IMI2 projects with significant clinical trials (among others ERA4TB, AIMS-2-Trials, and Ebola projects).

### 2.5.3 IHI programme

#### Contributions from JU Members other than the Union in 2022

This section highlights the commitments pledged by COCIR, EFPIA (also representing Vaccines Europe), EuropaBio and MedTech Europe (hereafter the IHI private members) as well as contributing partners in IHI projects. These commitments are made up of:

- in-kind contributions to operational activities (IKOP)[13], i.e. costs incurred by IHI private members and contributing partners in the implementation of IHI projects for researchers, research equipment, and materials;
- financial contributions (FC) made by IHI private members and contributing partners to IHI project beneficiaries eligible to receive funding;
- in-kind contributions to additional activities (IKAA)[14] , i.e. costs incurred by IHI private members in the implementation of additional activities (not applicable for contributing partners).

While IHI private members can contribute all types of contributions (IKOP, IKAA, FC), contributing partners can only contribute IKOP and FC, not IKAA.

During 2022, IHI JU launched the first three calls of the IHI programme (Horizon Europe).

In order to be eligible, applicant consortia must ensure that at least 45% of their proposal's eligible costs and costs for additional activities are provided by contributions from IHI private members and/or contributing partners. If that threshold of 45% contributions is not reached collectively by IHI private members and/or contributing partners, the proposal is considered ineligible and is therefore not evaluated. This threshold should also be maintained during the project implementation.

#### Values of IKOP - evolution

There was no IKOP to report by IHI private members and contributing Partners in 2022 as no IHI project had started yet. The first IHI Grant Agreements will be signed in 2023 and as a result, the first contributions in term of IKOP and FC will be reported in 2024 together with the first project periodic reports.

#### Values of certified IKAA – evolution

Additional activities can be of two types:

- Project-specific additional activities contribute towards the achievement of the objectives of the IHI-funded projects, or the dissemination, sustainability, or exploitation of IHI project results.
- Programme-specific additional activities contribute to the uptake of results from projects funded by IHI or its preceding initiatives (i.e. IMI1 or IMI2), or have a significant added value for the Union.

There was no IKAA to report by IHI private members in 2022 as no IHI project had started yet and because there were no programme-specific additional activities planned at the start of the IHI JU programme for the year 2021.

[13] In-kind contributions to operational activities ('IKOP') is defined in Article 2.8 of the Council Regulation (EU) 2021/2085 as follows: 'contributions made by private members and contributing partners, their constituent or affiliated entities consisting of the eligible costs incurred by them in implementing indirect actions less the contribution of the IHI JU and of the participating states of that JU to those costs'.

[14] In-kind contributions to additional activities ('IKAA') is defined in Article 2.10 of the Council Regulation (EU) 2021/2085 as follows: 'contributions made by the private members, their constituent or affiliated entities consisting of the costs incurred by them in implementing additional activities less any contribution to those costs from the Union and from the participating states of the IHI JU'. More information on IKAA can be found in the IHI JU Guidelines for in-kind contribution to additional activities (IKAA).

The additional activities undertaken during the year 2022 (i.e. from 1 January until 31 December 2022) and reported by IHI private members to the Programme Office by 31 May 2023 are under assessment by the Programme Office. The value of these additional activities will be validated in 2023 and included in the CAAR 2023.

## 2.6 Administrative procurement and contracts

The majority of IHI's contractual commitments in 2022 were concluded on the basis of existing multiannual framework contracts (FWCs). In terms of volume, the FWCs used most were in the field of IT, human resources, and audit services. Several of the framework contracts in question are interinstitutional, thus minimising the administrative burden and ensuring economies of scale.

The table below shows tender procedures in 2022 outside existing FWCs with a value exceeding EUR 15 000.

| Subject of the contract | Type of contract | Contractor | Tender procedure | Signature date | Amount in EUR |
|---|---|---|---|---|---|
| Office furniture | Low value supply contract | Beddeleem | Negotiated Procedure | 16/06/2022 | 24 453.65 |
| Communication strategy | Low value service contract | FASTLANE | Negotiated Procedure | 31/03/2022 | 15 950.00 |

All procedures were administered in compliance with the IHI JU Financial Rules and the European Union Financial Regulations to ensure fair competition amongst economic operators, and the most sound and efficient use of IHI JU funds.

In 2022, IHI concluded the following service level agreements (SLA):

| Subject of the contract | Type of contract | Parties | Signature date |
|---|---|---|---|
| Back Office Arrangement for Accounting Services | SLA | EU-Rail, CBE JU, CAJU, Clean Hydrogen JU, KDT JU, SESAR 3 JU, EuroHPC JU, IHI JU | 01/12/2022 |
| Office arrangements | SLA | EDCTP3, IHI JU | 16/06/2022 |
| Work to support the delivery of IHI JU Work Programme and the objective of sound budget implementation | SLA | EU-Rail, IHI JU | 19/04/2022 |
| Survey to examine the areas identified in the SBA for the possible Back Office Arrangements | SLA | EU-Rail, CBE JU, CAJU, Clean Hydrogen JU, EDCTP3 JU, KDT JU, SESAR 3 JU, EuroHPC JU, SNS JU, IHI JU | 28/03/2022 |

### Back-office arrangements (BOA)

In order to prepare for the BOA under the procurement, IHI JU participated actively in the inter-JU study and workshops to explore the enhanced collaboration and synergies cross the JUs. As a result, the final concept on the design and implementation of the procurement BOA was prepared and endorsed by all JUs' Executive Directors.

## 2.7 IT and logistics

IT activities in 2022 were mainly focused on design and support of the new post-COVID hybrid working pattern, and the further development of appropriate and secure IT infrastructure and business support tools, including their evolution towards IHI.

### Common IT infrastructure and Microsoft 365 (M365) online services

IHI JU shares a common IT infrastructure and facilities with five other joint undertakings co-located in the White Atrium building and participates in the formally established IT governance structure. Following the common IT annual work plan, the most notable achievements in 2022 are:

- Successful common call for tenders for IT managed services. The awarded contractor will be onboarded in 2023.
- Microsoft Identity Manager (MIM) implementation as prerequisite for migration of our e-mail service to Exchange online (EXO)

The Joint Undertakings are migrating from a single, shared on-premises environment towards separate Microsoft 365 (M365) tenants. In order to support and streamline the collaboration between them the identity information needs to be shared and synchronised. This is also mandatory to maintain the exchange of address books and certificates with the European Commission. The migration to MS Exchange online (EXO), part of M365, went smoothly without any e-mail service interruption or negative user impact.

- Intune onboarding

Onboarding on Intune is the last part of our M365 journey. Microsoft Intune is a cloud-based endpoint management solution. It manages user access and simplifies app and device management across many devices, including mobile devices, desktop computers, and virtual endpoints. It helps to protect access and data on organisation-owned and users' personal devices and provides compliance and reporting features that support a zero-trust security model.

- Back-office arrangements (BOA)

IHI JU participated actively in the study on the BOA and in the inter-JUs working group dedicated to ICT. The group defined the ICT service catalogue, including a common part and JU-specific services, and identified potential areas for enhanced collaboration and synergies. The final concept note capturing these elements was endorsed by all JU Executive Directors. Clean Hydrogen 2 (CH2) JU will lead the BOA ICT, with the co-lead of IHI JU.

- Upgrade of audio-video equipment in common meeting room 1

The final implemented solution is based on the standard "package A", defined in the DG Interpretation (SCIC) AV&C-2 FWC, complemented by some technical improvements identified in the preceding study. It ensures the best end-user experience and enables vendor-neutral hybrid meetings (supports all video conference platforms – MS Teams, Webex, Zoom, GoToMeeting etc.).

### Data Warehouse and Qlik sense reporting

Our data warehouse aims to combine all available data in a central repository, serving the organisation as single point of truth. Currently our main data sources are SOFIA, SEP datastore, CORDA, website content management system (CMS), publications data from Clarivate, project results from all previous Annual Activity Reports (AARs) and reference files with data not available in our operational applications. In 2022 it was further extended with some additional data, namely:

- IHI applicants' affiliation (Excel file filled in by the proposal coordinator and uploaded in SEP as PART B, section 4);
- topic ideas from the new idea submission tool.

All existing Qlik sense reports were redesigned to accommodate data from IHI proposals. This work will continue in 2023 with data from signed IHI Grant Agreements.

### Business support tools

Following the delivery of the new Science and Innovation Panel (SIP) platform, all new IHI governance and advisory bodies have in place modern, collaborative platforms to facilitate their work and activities.

The IT team created several complementary tools, supporting call coordination and proposal submission:

- The Topic Ideas tool, published on the IHI website, is designed to support the concept of 'co-creation' of ideas for potential new call topics by collecting suggestions from the wider health and research community. Based on M365 technology, the tool provides input to the SIP platform where the proposed ideas are further evaluated.
- A template for the annual in-kind contributions to additional activities (IKAA) plan at programme level.
- A tool for building IHI project budget tables (separate versions for one and two stage calls).
- A template on IHI-specific participant and stakeholder types, completed by coordinators and submitted as an annex in SEP.

### SOFIA (Submission of Information Application)

SOFIA was upgraded with the following main enhancements:

- Single sign on (SSO): Single sign-on (SSO) is an authentication method that enables users to securely authenticate with multiple applications and websites by using just one set of credentials. In 2022 we enabled in SOFIA "Sign in with Microsoft" (including M365 and personal accounts) which brought certain benefits such as reducing password fatigue, time spent re-entering passwords for the same identity, and IT efforts due to the lower number of IT help desk calls about passwords.

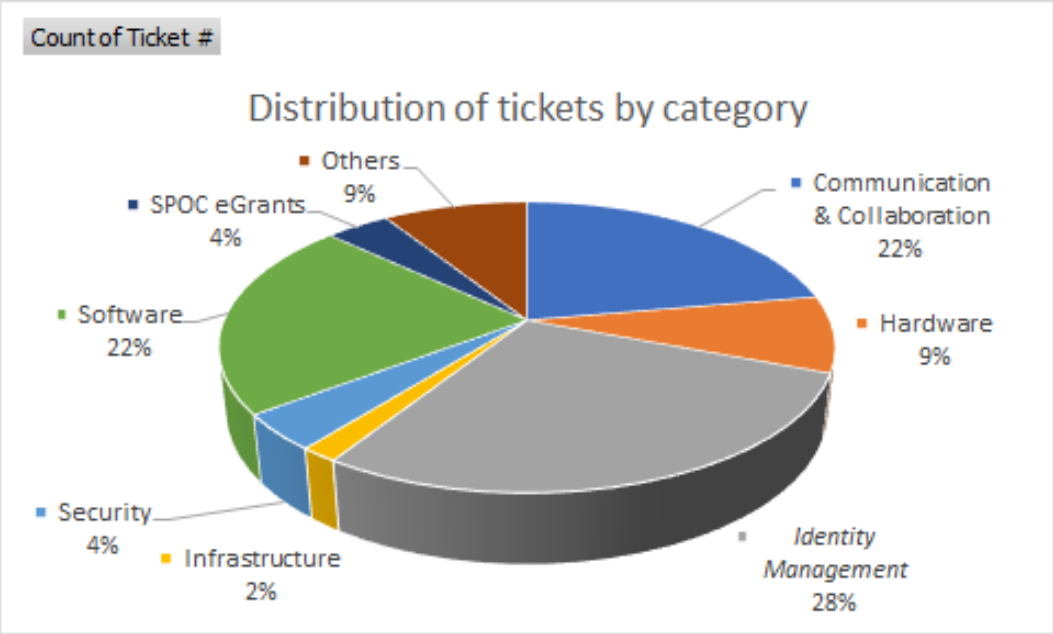
- Advanced search functionality on merged projects results collected in the data warehouse (DWH) from several different sources – AAR results, catalogues of project tools, innovation radar, website news, project monitoring assessment, success stories from projects, periodic reports' publishable results, publishable summaries, publications etc.

### Cybersecurity and collaboration with Computer Emergency Response Team for the Institutions, Bodies and Agencies of the European Union (CERT-EU)

As coordinator for collaboration with CERT-EU (the Computer Emergency Response Team for EU institutions, bodies and agencies) on behalf of the six JUs, in 2022 IHI JU organised M365 security assessment, red team and phishing awareness exercises. The reported outcomes provided valuable input on our cybersecurity maturity level and recommendations for further improvements. CERT-EU gave a general cybersecurity awareness refresher session with high participation of IHI staff.

### Helpdesk support

In 2022, a total of 894 requests for support were handled by the IHI IT Helpdesk. The following graph depicts the various categories assigned to the tickets.




### New hybrid working environment

Following the new guidelines from the EC with flexible working conditions, and the Executive Director's decision to free up office space for a new JU, EDCTP3, the Programme Office switched in 2022 to a hybrid working environment with shared desking. The flexible working conditions have helped the staff to maintain a better work life balance. Specific attention was paid to the work desks and equipment to ensure the ergonomic setting for the staff. The change has also benefited the Programme Office economically and environmentally by reducing both costs and carbon footprint.

Enabling EDCTP3 to enter into a ready-made office space by IHI JU saved them from the efforts and time spent in preparing the office space for their staff. IHI JU has continuously provided support to EDCTP3 by providing advice e.g. on IT-related matters. EDCTP3 has also benefited from utilising the existing IT infrastructure and meeting rooms without costs related to their set-up.

## 2.8 Human resources

### Staff selection and recruitment

The staff establishment plan (SEP) allows for 39 temporary agents, 15 contract agents and 1 Seconded National Expert (SNE), in total 55 staff members. On 31/12/2022 there were 49 positions occupied: 36 out of 39 temporary agents (92.30%), 11 out of 15 contract agents (73.30%) and 0 out of 1 seconded national experts (0%)[15]. The table below provides a summary of the staff planning:

| | Positions planned in SEP | Positions filled on 01/01/2022 | Resignations / end of service in 2022 | Recruitment / appointment in 2022 | Positions filled on 31/12/2022 |
|---|---|---|---|---|---|
| Temporary agents | 39 | 36 | 7 | 6 | 36 |
| Contract agents | 15 | 11 | 2 | 3 | 13 |
| SNEs | 1 | 1 | 1 | 0 | 0 |
| **Total** | 55 | 48 | 10 | 9 | 49 |

Staff turnover in 2022 was 20.6% (10 staff members).

- 50% of the staff turnover was due to the staff retiring (four staff members) and post suppression (one SNE contract ended in June and the post was cut at the end of the year).
- 50% was due to IHI staff moving to the Executive Agencies or the European Commission as officials (five staff members).

Nine new staff members joined IHI in 2022, and they were recruited either via the existing reserve lists or via new selection procedures. In detail, in 2022 IHI JU launched and organised three selection procedures which were conducted remotely:

- One AD 5 temporary agent external selection procedure;
- Two FGIV contract agent external selection procedures, one of these selection procedures was a joint selection procedure organised together with KDT JU.

### Learning and professional development

Organisational efficiency is dependent upon learning and professional training in order to keep staff members up to date. The main areas covered were:

- Operational and legal framework: staff followed general training on various aspects of the Horizon 2020 framework and Horizon Europe such as IHI eligibility criteria and funding schemes, IHI industry contributions; IMI amendment specificities – highlights, and IMI2 in-kind contribution (IKC) assessment and validation.
- Data protection: two training sessions were organised to raise awareness on the importance of the protection of data. One session focused on an introduction to the subject and key data protection concepts, and a second one focused on staff duties - processing, breaches and requests.
- In-house soft skills and specific training courses were organised by IHI on subjects such as such as the appraisal exercise for all staff, performance management for managers, specific well-being sessions for

[15] Temporary agents (TAs): the empty posts will be filled in 2023, as one selection procedure is expected to be closed in February 2023 and the ED selection procedure is ongoing; Contract agents (CAs): one post will be filled in February 2023 and a selection procedure will be launched for the vacant post during 2023; Seconded National Experts (SNEs) as in 2023 the remaining SNE post will be suppressed and no SNE positions are foreseen in the IHI SEP as of 2023, no new SNE was recruited when the contract of the previous IHI SNE ended in June 2022.

IHI staff and managers on how to support a colleague or a team member to reintegrate to work after a long sick leave. In addition, some in-house training courses were organised and delivered in cooperation with the other Joint Undertakings, for example a global cybersecurity awareness session with CERT-EU to raise awareness among JUs staff, a CAS (Common Audit Service) workshop on the HE guidance on ex-ante checks to detect potential fraud, an anti-fraud training course, a JSIS info session, and a refresher training course on mediation skills for HR officers and confidential counsellors.

- Online 'soft' and 'hard' skills courses, language training and well-being lunchtime conferences and courses were followed using the 'EU Learn' catalogue which helped IHI staff in the selection of their training according to their learning need.
- Five HR info sessions for staff and managers were organised in order to provide IHI staff with a wider understanding of HR procedures and processes and to increase transparency for example on teleworking and the appraisal and reclassification exercises, as well as an induction training for newcomers.
- An IHI Away Day was also organised in order to help staff to reconnect and to uphold IHI's organisational culture.

### Staff well-being and new ways of working

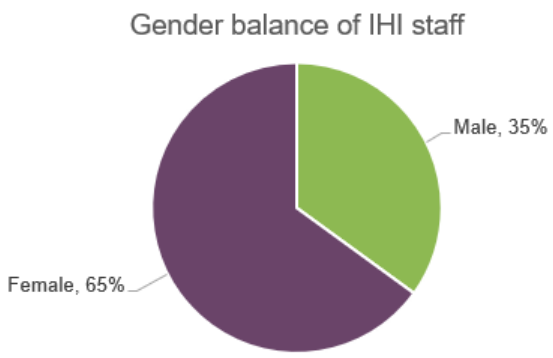
To promote and guarantee staff well-being, IHI organised specific training sessions to support its staff in coping with stress and dealing with difficult situations, and promoted a healthy working environment by redefining its working space and by adopting by analogy the European Commission's decision on working time and hybrid working. The overall IHI staff satisfaction regarding the new ways of working and well-being was quite high as demonstrated by the internal staff survey (overall satisfaction rate 4.15 out of 5). Moreover, the survey results showed that IHI staff feel that (i) IHI cares about their physical well-being; (ii) IHI cares about their mental well-being; and (iii) they are satisfied with their work-life balance. The staff also welcomed the flexibility provided by the teleworking policy which improved significantly their work-life balance and well-being.

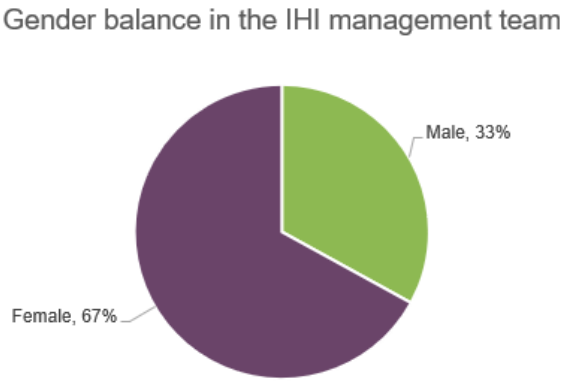
### Reclassification exercise

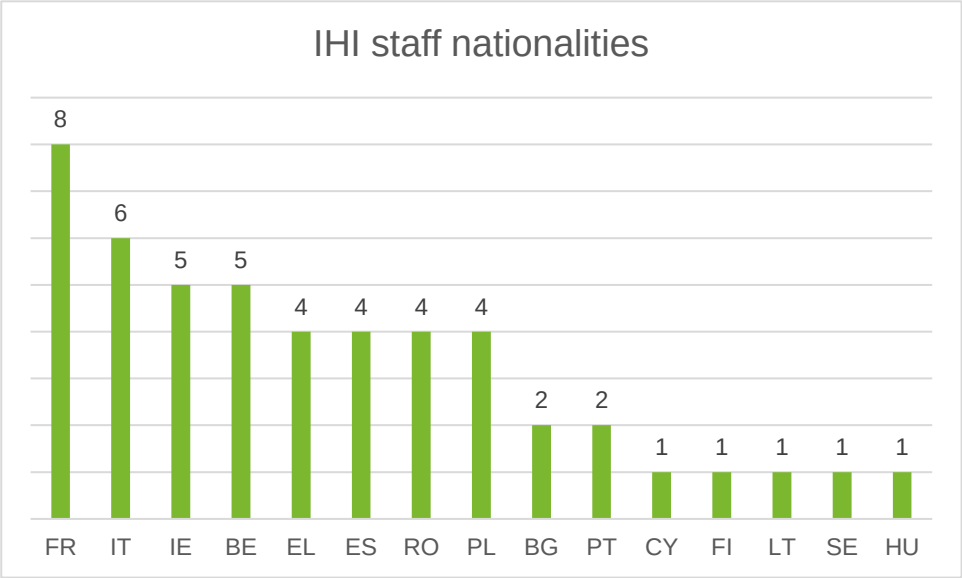
The reclassification exercise is a valuable tool to recognise and promote the performance of highly qualified staff members. The reclassification exercise for both temporary and contract staff took place successfully in 2022, in accordance with the Staff Regulations. As a result, three staff members (one temporary agent and two contract agents) were reclassified to the immediate higher grade.

### Staff statistics

The graphs below show the gender and geographical balance (15 EU nationalities were represented in IHI) within IHI on 31 December 2022.






### Synergies

In 2022 the Programme Office paid particular attention to the efficiency and cost-effective management of its resources as the year was characterised by a reduction in the number of human resources allocated to IHI JU, combined with the increased complexity of IHI projects and the necessity to manage the large and complex legacy from IMI1 and IMI2 projects.

To this end, during the year 2022, IHI proceeded with the reshuffling of its internal resources in order to fully complete the transition from IMI2 to IHI and to face the new challenges raised by the new partnership, while strengthening the collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks.

In 2022 IHI optimised efficiency gains and synergies with the other JUs by (i) organising a joint selection procedure with KDT JU to recruit two accounting and finance correspondents, one for each JU; (ii) sharing its reserve lists with the other JUs and agencies to shorten their time to recruit (three candidates from IHI JU's reserve lists were hired by other organisations); (iii) participating in the new call and appointment of additional confidential counsellors in order to strengthen the inter-JU network of confidential counsellors (CCs); ( iv) organising training courses of general interest for the other JUs (e.g. a refresher mediation training course for the HR officers and CCs of the different JUs, and the anti-fraud training course for 8 JUs with 120 participants); and (v) supporting new Joint Undertakings during their on-boarding / start-up phases. In detail, IHI closely worked with EDCTP3 providing guidance and templates for the launch of EDCTP3's selection procedures and recruitments, providing guidance and assistance on the relevant implementing rules (IRs) to be adopted, involving EDCTP3 in the weekly meetings with the JUs' HR officers and providing advice and information, when requested by ECDPT3. Moreover IHI JU actively participated in the inter-JU study and workshops to explore the enhanced collaboration and synergies cross the JUs. As a result, the final concept was prepared and endorsed by all JUs' Executive Directors. IHI JU took the back-up role for the HR back-office arrangements and supports the lead JU, CBE (Circular Bio-based Europe).

In addition, in 2022 the JUs continued sharing the human-resource IT tools (e.g. the e-recruitment tool SYSTAL, SYSPER, etc), sharing information and best practices with the different JUs through meetings and working groups e.g. the Executive Directors, Heads of Administration, HR officers, legal officers, and adopted a common approach to implementing rules of the EU staff regulations.

### 2.8.1 HR management

**Staff implementing rules (SIR) implemented in 2022**

| Title of the SIR | Reference and date of the GB decision |
|---|---|
| GB Decision laying down implementing rules as regards temporary occupation of management posts. | IHI-GB-DEC-2022-11 on 13/07/2022 |
| GB Decision on the application by analogy of the EC Decision C(2020) 4818 of 20 July 2020 amending the Commission Decision C(2011)1278 of 3 March 2011 on the general implementing provisions of Articles 11 and 12 of Annex VIII to the Staff Regulations on the transfer of pension rights. | IHI-GB-DEC-2022-18 on 01/12/2022 |
| GB Decision on the application by analogy of the EC Decision C(2021) 8179 of 16 November 2021 laying down general implementing provisions regarding the payment of the education allowance provided for in Article 15 of Annex X to the Staff Regulations to staff members for the duration of temporary assignments to the seat of the institution of any other place of employment in the Union. | IHI-GB-DEC-2022-18 on 01/12/2022 |
| GB Decision on the application by analogy of the EC Decision C(2022) 1713 of 24 March 2022 on home leave for officials, temporary staff and contract staff serving in a third country and repealing Commission Decision c (2013) 9035 final of 16 December 2013. | IHI-GB-DEC-2022-18 on 01/12/2022 |
| GB Decision on the application by analogy of the rules on the reimbursement of expenses incurred by people from outside the Commission invited to attend meetings in expert capacity. | IHI-GB-DEC-2022-21 on 07/12/2022 |
| GB decision on the application by analogy of the EC Decision on working time and hybrid working | IHI-GB-DEC-2022-26 on 12/12/2022 |

### 2.8.2 Efficiency gains and synergies

The Council Regulation establishing IHI and the other Joint Undertakings (SBA) states that the JUs shall achieve synergies via the establishment of back-office arrangements (BOA), operating in some identified areas. The Regulation also underlines that these synergies should be implemented where screening of resources has proved to be efficient and cost effective, while respecting the autonomy and the responsibility of each Authorising Officer.

In order to obtain an independent view on the possible synergies among the JUs and the impact in terms of efficiencies, the JUs contracted an external consultant to perform a study on the common back-office arrangements. The study was finalised in July 2022 and its specific objectives were to:

- identify areas, or sub-functions of areas, for operation under back-office arrangements (BOA), including necessary elements of cost efficiency, risks and opportunities;
- support the JUs to assess the viability (including the screening of resources) of these areas.

The study concluded that the estimated efficiency gains in terms of full time equivalent (FTE) savings were modest for most synergies, but there were potential benefits in terms of harmonisation of current practices, standardisation of procedures, establishment of critical mass for effective negotiation, coordination and cost savings. The largely preferred model for the BOA among JUs is a setup with one JU taking the lead in coordinating tasks with one backup JU, organising the work among staff of several JUs and having a clear scope and decision-making power. For example: BOA for the provision of accounting services (following the decision by DG BUDG to terminate the services for the JUs). For some synergies a more flexible option was chosen, with collaboration involving only some JUs, while remaining open for the others to join at a later stage.

The preparation work led to the establishment of coordinated plans, prioritising those aspects of the BOA that had the objective to bring most value in the short term. These included, as top priorities, (in) the accounting function; (ii) IT deployment; (iii) common synergies regarding the White Atrium office building housing JUs; (iv) joint procurement opportunities; and (v) HR support. These topics encompass five of the seven synergies as per Article 13 of the Council Regulation. This approach was endorsed by the JUs' Governing Boards.

When these arrangements were presented, the respective Governing Boards stressed the need to have a balanced approach to the BOA implementation, ensuring, as a priority, the execution of JUs' core business (ensuring budget execution and call implementation) which is very challenging in the context of a new programme with new legislation, new actors and ambitious timelines due to the delayed launch of the Horizon Europe programme.

The following arrangements were put in place in 2022:

### BOA Accounting

Following the termination of the accounting services by DG BUDG, the JUs took over the accounting from 1 December 2022. Accounting officer services are provided by three JUs: Clean Aviation (CA) JU, SESAR JU, and EU-Rail JU. The three accounting officers deliver the services to one or more JUs and are responsible for the accounts they sign off, while counting on the support and coordination by EU-Rail JU who is the lead JU for the accounting services. The new accounting officer for IHI JU is from SESAR JU and was appointed by the IHI JU GB in November 2022.

### BOA HR

Concerning HR, the study recommended to explore synergies by coordinating the management of SYSPER, possibly obtaining a single contract for all JUs, performing joint recruitments, harmonising job profiles and procedures. These synergies will allow a better harmonisation among the JUs, exploiting best practices, achieving efficiency gains and economy of scale. In particular the areas where this BOA will act are recruitment, legal framework and IT landscape in the HR domain.

### BOA ICT

Following the completion of the study, a number of inter-JU workshops were organised to develop a catalogue of services. The services were structured in six groups:

- Inter-JU IT governance
- Management of shared ICT infrastructure
- Management of ICT tools, services and contracts
- Workplace services provision
- Security and compliance management
- Specific ICT activities per JU.

The underlying concept is that, out of the ICT service catalogue, everything that is non-specific to a JU should be managed through the ICT BOA.

### BOA Procurement

This BOA has been established with the objective of centralising administrative procurement capability and processes to maximise open tenders for award of inter-JUs FWCs and middle value negotiated procedures. The focus is on the critical joint administrative procurement such as ICT, building management/corporate

services and common support services that will be identified and agreed via joint public procurement planning (PPP).

## 2.9 Data protection

In 2022, the JU pursued its efforts to render its processes and working methods fully compliant with Regulation (EU) 2018/1725. Foremost among these efforts were the updating and improvement of the JU's online register of processing operations, data protection documentation for use by the Programme Office, and updating/implementing data protection measures for IHI's new electronic platforms and tools.

The JU participated in various interinstitutional data protection activities, including events held by the European Data Protection Supervisor (EDPS).

In September 2022, a series of staff trainings on the general principles of data protection Regulation (EU) 2018/1725 were held to acquaint staff with data protection principles and terminology, and obligations arising under the data protection rules.

# 3 Governance

## 3.1 Major developments

IHI JU established its governance structure and the necessary processes and standards, in accordance with the Council Regulation.

The 2022 activities were focused on:

- the smooth functioning of the Governing Board (GB) for its first year of full operation activity;
- the setting-up and proper operation of the two other governance bodies of the IHI JU, the States' Representatives Group (SRG) and the new scientific advisory body, the Science and Innovation Panel (SIP);
- interactions between IHI JU and the different governing bodies, and also between the bodies themselves.

## 3.2 Governing Board

The Governing Board (GB) is the main decision-making body of IHI. Its main tasks include adopting key documents such as the Strategic Research and Innovation Agenda (SRIA) and financial rules as well as the annual budgets, work programmes and staffing plans, appointing and monitoring the performance of the Executive Director, assessing applications from potential associated members and contributing partners.

The GB is composed of eight members (four from the EC and four from industry). Until 15 December 2022, the Chairperson was Irene Norstedt (EC), and the Vice-Chairperson was Salah-Dine Chibout (EFPIA-Novartis). During the meeting in December 2022, a new Chairperson (Salah-Dine Chibout) and Vice-Chairperson (Irene Norstedt) were appointed for a period of one year. Information on GB membership, including CVs and declarations of interest, can be found on the GB page of the IHI website.

The GB was set up in December 2021; 2022 was therefore its first year of full operational activity.

In 2022 the GB met four times:

- 20/01/2022, when the SRIA, the selection criteria and the call for expressions of interest to select the SIP panellists representing the scientific community and the wider healthcare community were adopted;
- 25/03/2022, when the SIP panellists were selected and the key performance indicators endorsed;
- 17/06/2022, when the amended work programme 2022 and the Consolidated Annual Activity Report (CAAR) 2021 were adopted, the notes concerning implementation of Article 125(3) of the Council Regulation establishing IHI, and of Article 40(4) were endorsed and the opinion on the Annual Accounts 2021 was issued;
- 08/12/2022, when the second amended Work Programme 2022 and the IHI Communication Policy were adopted, and the status of the back-office arrangements were presented by the EC and IHI Office.

To ensure smooth and effective communication with the GB, in 2022 the Programme Office established a GB platform which constitutes the focal point of communication between the Programme Office and the GB. For instance, here all GB meetings documents and draft decisions that that undergo written procedure are posted.

Several decisions were adopted by the GB, either during the meetings mentioned above, or by means of a written procedure. Among such decisions, to be highlighted are those adopting the Work Programmes for 2022 (and the related amendments) and 2023, the SRIA, the list of proposals selected under calls 1 and 2, the Accounting Officer for IHI JU, the contributing partners and several decisions on HR matters. The full list of decisions adopted is available on the IHI JU website.

## 3.3 Executive Director

Dr Pierre Meulien was Executive Director until 15 September 2022. When his mandate ended, the Governing Board appointed Dr Hugh Laverty as Executive Director *ad interim*. He will lead the organisation until the new Executive Director takes up their duties. The recruitment of a new Executive Director for IHI JU was initiated in January 2022 is currently ongoing, and is being handled by the European Commission. The CV and declaration of interest of the Executive Director *ad interim* are available on the IHI website.

## 3.4 States' Representatives Group

The States' Representatives Group (SRG) is composed of up to 2 representatives and up to 2 alternates from EU Member States and countries associated to the EU's research programme Horizon Europe. It is an advisory body tasked with the role of supporting IHI JU in achieving its targets and expected impacts. In particular, it is consulted about the SRIA, the Work Programmes, the CAAR, and the involvement of SMEs and academia in IHI calls for proposals. The SRG acts as an interface between IHI and relevant stakeholders within their respective countries.

In 2022, the Chairperson was Martha Cahill (Ireland), and the Vice-Chairperson was Jan Skriwanek (Germany). Information on SRG membership, including CVs and links to national websites can be found on the SRG page of the IHI website.

In 2022 the SRG met three times:

- 22/02/2022 (web meeting), when the SRG was officially established and its draft rules for procedure discussed, and the Programme Office introduced the specifics of the new programme;
- 11/03/2022 (web meeting), when its rules of procedure were adopted, and the Chairperson and Vice-chairperson were appointed;
- 13/10/2022 (hybrid meeting), when the Programme Office presented the specifics of the new programme and provided detailed updates on its activities, including on IMI2 closed and ongoing projects, budget execution and forecasts, etc. Furthermore, work programme and calls were discussed.

Several actions were implemented by the Programme Office to ensure smooth and effective communication with the SRG, as presented below.

In 2022, the Programme Office established an SRG private site, where all main news linked to the IHI JU activities are posted regularly and which constitutes the focal point of communication between the Programme Office and the States' Representatives. For instance, the States' Representatives posted their opinions on this private site during consultation on IHI corporate documents such as the amendments to the Work Programme 2022, the Work Programme 2023 and CAAR 2021, and were invited to support candidates submitting an application in response to the call for expressions of interest for the selection of SIP panellists.

Regular interaction between the Programme Office and the SRG was ensured throughout the year on several relevant issues, by means of notifications and publications on the private site, emails, and meetings with the Chairperson and Vice-Chairperson. Additionally, the Qlik Sense business intelligence platform is available for the SRG members where all information and aggregated data concerning IHI JU calls and ongoing projects is regularly updated.

Considering that several States' Representatives were new to the IHI JU / Horizon Europe framework, the Programme Office organised a workshop specifically focusing on the main legal and financial aspects of IHI JU and Horizon Europe, in order to ensure that all States' Representatives have the necessary information concerning the IHI activities and operations.

With the aim of enhancing transparency, the Programme Office prepared two notes:

- a note providing details on the nature and timing of the information to be shared with the SRG;
- a note describing the principles and measures applied by the IHI Office to ensure maximum transparency and openness on governance activities (see sub-section below).

Finally, regular interactions between the SRG and the SIP were enabled by the fact that the SRG Chairperson and Vice-Chairperson are panellists of the SIP, while the Chairperson of the SIP was invited to the SRG meetings. Additionally, preliminary information on topic generation was shared with the SRG and agendas and minutes of the meetings of each governance body was shared with the other body in a timely manner.

During 2022, the SRG was formally consulted on the CAAR 2021, and on the amendments to the Work Programme 2022 as well as on the Work Programme 2023. In compliance with the requirements of the Council Regulation, the SRG provided its annual report to the Governing Board. The report is available on the SRG page of the IHI website.

## 3.5 Science and Innovation Panel

The Science and Innovation Panel (SIP) is an advisory body to the Governing Board which has been set up to gain input from a wider range of health and research stakeholders much earlier in the call topic design process.

The SIP may advise, either at the Governing Board's request or on its own initiative, on a range of matters relevant to the research and innovation activities of IHI JU. The full description of the SIP role and tasks is provided in article 21(7) and 124 of the Council Regulation.

The SIP is composed of 18 permanent panellists (the full list is available on the Science and Innovation Panel page of the IHI website). They include two representatives of the European Commission, four representatives of the industry founding members, two representatives of the SRG, four representatives of the scientific community and six representatives of the wider healthcare community. The representatives of the European Commission and the industry founding members were appointed by their respective organisations. The SRG agreed to appoint its Chairperson and Vice-Chairperson as SIP panellists. In accordance with Article 21(4) of the Council Regulation, an open selection process was launched on 21 January 2022 to select the representatives of the scientific community, and of stakeholders involved in health care (covering in particular the public sector, including regulatory bodies, patients and end-users in general), as permanent panellists of the SIP. IHI JU proceeded with the assessment of the 98 admissible applications. Following the completion of the selection process described in the call for expressions of interest, the Governing Board appointed 10 representatives of the scientific community and stakeholders involved in health care. The GB focused on applicants' expertise and experience, while also ensuring the panel is balanced in terms of subject areas and stakeholder groups, geographical coverage, and gender. The GB also took into consideration the potential candidates supported by the SRG.

The mandate of the SIP permanent panellists runs for three years, and this may be renewed by the Governing Board.

In 2022, the permanent SIP panellists elected Anna Chioti as Chairperson and Ralf Herold as Vice Chairperson for a period of three years. The SIP panellists adopted their rules of procedure during the constitutive meeting; these are available on the Science and Innovation Panel page of the IHI website, along with the CVs of the members.

In 2022, the SIP met four times. The agendas of the meeting are available on the SIP page of the IHI website. During the year, the work of the SIP focused mainly on discussing and providing opinions on the annual scientific priorities and the first ideas submitted by the wider health and research community and draft topic texts proposed by the IHI JU founding members (the SIP outcomes on the ideas that passed the completeness check is available on the IHI website). The SIP was also consulted on the process for collecting ideas, the amendments to the Work Programme 2022 and the Work Programme 2023. Discussions were also already initiated on how to best create synergies with other Horizon Europe activities, including other European partnerships, as well as other EU and national programmes.

After each meeting, the SIP issued a report to the Governing Board that includes its opinion and recommendations on the matters discussed. The reports are available on the Science and Innovation Panel page of the IHI website.

Finally, the Programme Office developed a secured IT environment to ensure adequate sharing of data and information between IHI JU and the SIP panellists.

## 3.6 Transparency and collaboration between IHI governance bodies

Operating openly and transparently, sharing information with the appropriate bodies, and promoting activities to the wider public is a prerequisite of good governance and indispensable for ensuring citizens' understanding of EU decision-making processes and confidence in the EU institutions.

Within this context, IHI JU published in a timely manner a wide range of information and documents on its governance bodies, including all information required in the Council Regulation as well as information requested by the European Parliament. Information published includes a description of the IHI JU governance structure, role, tasks, and decision-making process, the list of decisions adopted by the Governing Board, a short biography of the members of each governing body, and (where relevant) the declarations of confidentiality and annual declaration of interests, approved agendas of the meetings, and the declaration of interests of the Executive Director *ad interim*, all this while ensuring the protection of personal data and sensitive information.

To ensure proper coordination and collaboration between governance bodies under the new legal framework, the SRG Chairperson and Vice-Chairperson are members of the SIP as well as observers to the GB meetings. Furthermore the GB Chairperson and the SIP Chairperson were invited to the SRG meetings as observers. They all participated in the discussions and exchanged feedback on the new way of working under IHI JU.

In addition, with the agreement of the SIP and the SRG, the Programme Office shared via the respective private site the minutes of their respective meetings, to enhance collaboration and alignment between these two advisory bodies.

## 3.7 Contributing partners

The 'contributing partner' category was created with the goal of opening up IHI to a wide range of stakeholders who may want to invest in IHI without becoming full members. Contributing partners invest their own resources (which can be researchers' time, laboratories, data) or cash in a specific IHI project or projects. Any country, international organisation or legal entity that wants to contribute to the IHI objectives

can apply to become an IHI contributing partner, provided they are not a member of IHI or an affiliate of an IHI member.

In 2022 IHI put in place procedures related to receiving and reviewing applications from legal entities interested in becoming IHI contributing partners. The IHI published on its website a guide for contributing partners, a comprehensive source of information for entities interested in applying to become a contributing partner.

In 2022 the Governing Board of IHI accepted three applications of legal entities who became IHI's first contributing partners.

# 4 Financial management and internal control

## 4.1 Control results

IHI JU implements an internal control framework applicable at all levels of management which is designed to provide reasonable assurance that operations are effective and efficient, but also that the financial reporting is reliable, and that the JU complies with applicable laws and regulations.

This section explains how the results described in the previous sections have been achieved by the JU[16]. It focuses on the results generated by the whole internal control system and presents other relevant information that supports management assurance on the achievement of the financial management and internal control objectives[17].

Moreover, following the transition from the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) to Innovative Health Initiative (IHI JU), a revised guidance[18] for the implementation and measurement of the IHI JU internal control framework defining new internal control indicators and targets was adopted and is used as a basis of internal control self assessment 2022.

### 4.1.1 Effectiveness of controls (ex-ante and ex-post)

To assure the effective and efficient implementation of the expenditure, IHI JU has set out an internal control framework[19] embedded across its organisational structure, which relies on a combination of ex-ante and ex-post controls as summarised in the following table.

| | Ex-ante controls | Ex-post controls |
|---|---|---|
| Timing | Before the transaction is authorised. | After execution of the authorised transaction. |
| Frequency | Mandatory for all transactions. | Made on a sample basis. |
| Methodology | At least a desk review of documents (e.g. proposal received, reports, etc.) and available results of controls already carried out on the operational and financial operation. | On-the-spot checks at the beneficiary's premises. |
| Impact | Errors detected are rectified before the transaction is approved. | Errors detected are corrected. Where the error gives rise to an ineligible expenditure, a recovery order is issued, or offsetting is made with future payments. |
| Level of assurance | Primary means of ensuring sound financial management and legality and regularity of transactions, based on desk review of available documentation. | Secondary means of ensuring sound financial management and legality and regularity of transactions, but more robust as normally carried out on the spot. |

In order to prevent errors and irregularities before the authorisation of operations and to mitigate risks of non-achievement of objectives, each operation shall be subject, at least, to an ex-ante control. This type of

[16] Including both IMI2 JU up to 29.11.2021 and then the IHI JU as explained above.

[17] According to Art 36.2 FR those objectives are: a) effectiveness, efficiency and economy of operations; b) reliability of reporting; c) safeguarding of assets and information; d) prevention, detection, correction and follow-up of fraud and irregularities; and e) adequate management of risks relating to the legality and regularity of underlying transactions.

[18] IHI JU ED decision No 43 of 22.12.2022

[19] The Internal Control Framework of IHI JU adopted by the Governing Board on the 16 December 2021 (IHI-GB-DEC-2021-03).

control relates to the operational and financial aspects of the operation, on the basis of a multiannual control strategy which takes risk into account. The purpose of the ex-ante controls shall be to ascertain that:

- the expenditure is correct and complies with the applicable provisions;
- the principle of sound financial management set out in Article 13 of the IHI Financial Rules[20] has been properly applied.

Ex-ante controls provide the Authorising Officer with the assurance that costs claimed are accurate and in compliance with the applicable legal and contractual provisions. A complementary level of assurance on the costs paid is provided by the ex-post audits carried out at the beneficiaries' premises, after the costs have been incurred and declared.

Ex-post audits can be carried out up to 2 years after the payment of the balance for the HE and H2020 programmes. For the FP7 programme, an audit can be carried out up to 5 years after the project is closed. In case of findings, they can also be implemented as part of the project management cycle.

## Ex-ante controls on operational and administrative expenditure

In order to support the statement of assurance on the achievement of the internal control objectives, this section covers reporting on and assessing various kinds of expenditure, i.e. operational and administrative, with references to the budget coverage and the indicators set out.

The JU's annual budget is implemented through the administrative expenditure (i.e. related to staff and day-to-day activities – Titles 1 and 2 of the budget) and the operational expenditure (i.e. related to the research programme and payments of beneficiaries - Title 3 of the budget)[21].

IHI JU has developed and continues to apply comprehensive procedures defining the controls to be performed by scientific project and financial officers for every commitment, payment of financial claim, payment of invoice, and recovery order, taking into account risk-based and cost-effectiveness considerations.

For operational expenditure, the processing and recording of transactions in the IT accounting system (ABAC) are performed via the corporate Horizon 2020 IT tools (SyGMa/COMPASS) for H2020 grants and evaluation experts, which ensures a high degree of automation as the controls are embedded in each workflow.

A pivotal element of this control system is the implementation of the horizontal guidance on H2020 and HE ex-ante controls for interim and final payments. This allows a consistent, simplified and trust-based approach to beneficiary controls with risk-based considerations.

**Overview and ex-ante control results on operational expenditure**

The tables below show the balance between the actions implemented under the IMI1/FP7, IMI2/H2020 and IHI/HE programmes in terms of project portfolio and the value of operational expenditure at the cut-off date of 31 December 2022.

[20] Decision of the Governing Board of the Innovative Medicines Initiative 2 Joint Undertaking Adopting the Financial Rules of the Innovative Medicines initiative 2 Joint Undertaking on 27.05.2020 (IMI2-GB-DEC-2020-16) and readopted by IHI JU GB decision on 16.12.2021 (IHI-GB-DEC-2021-03).

[21] See Section 2.4 'Budget and financial management'.

There were no IHI projects started in 2022.The first IHI JU calls for proposals were launched in June 2022.

As shown in the table below, a total of 123 projects were funded under the IMI2 programme at the end of 2022. 78 projects continue to run on 31.12.2022. In 2022, a total of EUR 128 744 813 was paid to the beneficiaries.

| IMI2 (H2020) project portfolio | | | Pre-financing payments | Interim & final payments[22] |
|---|---|---|---|---|
| **123** | Running on 01/01/2022 | 100 | 0 | 128 744 813 |
| | Ended during 2022 (-) | -22 | | |
| | Signed during 2022 | 0 | | |
| **Total IMI2 projects still running on 31/12/2022** | | **78** | | |

Note that the last IMI2 projects were signed in 2021, with an expected end date in 2028.

As shown in the table below, a total of 59 projects have been funded under IMI1 programme. At the end of 2022, there were still 3 on-going projects expected to finish in 2023.

In the course of 2022, EUR 13,717,776 of interim and final payments were made to the beneficiaries.

| IMI1 (FP7) project portfolio | | | Pre-financing payments | Interim & final payments[23] |
|---|---|---|---|---|
| **59** | Running on 01/01/2022 | 5 | 0 | 13 717 776 |
| | Ended[24] during 2022 (-) | -2 | | |
| **Total IMI1 projects still running on 31/12/2022** | | **3** | | |

| IMI1 and IMI2 total project portfolio | | Pre-financing payments | Interim & final payments[25] |
|---|---|---|---|
| **Running on 01/01/2022** | 105 | | |
| **Ended during 2022 (-)** | -24 | 0 | 142 462 589 |
| **Signed during 2022** | 0 | | |
| **Total IMI1 + IMI2 projects still running on 31/12/2022** | **81** | | |

[22] These amounts represent only direct payments to beneficiaries. Clearing of pre-financing is not considered in this table as it is accounted as part of the volume of operational transactions (see below).

[23] These amounts represent only direct payments to beneficiaries. Clearing of pre-financing is not considered in this table as it is accounted as part of the volume of operational transactions (see below).

[24] IMI1 projects which have ended their activities and submitted, or are due to submit the final report

[25] These amounts represent only direct payments to beneficiaries. Clearing of pre-financing is not considered in this table as it is accounted as part of the volume of operational transactions (see below).

### Volume of operational transactions

The total number of operational transactions performed during the year is one of the main indicators used by IHI to assess the efficiency of the Programme Office and the use of human resources to handle the workload related to project management.

The table below provides a multiannual overview of operational transactions[26], including pre-financing payments (new projects), interim and final payments made to ongoing projects funded under FP7, H2020 and HE programmes and shows the evolution of the programme implementation.

| Number of operational transactions (project payments) | 2022 | 2021 | 2020 |
|---|---|---|---|
| Pre-financing payments | 0[27] | 16 | 25 |
| Interim and final payments | 94[28] | 83 | 76 |
| **Total** | **94** | **99** | **101** |

The tables below give a picture of the modalities of the reporting process, where the number of cost claims processed (94, line 4) during the year may not match with the number of reports received (97, line 2). This is because reports received during the last quarter - and to be handled within the legal deadline of 90 days – are carried over to the following year.

The total number of claims reached a number of 94 for the year 2022 which is in line with the trend of the previous two years.

| | Cost claims | 2022 | 2021 | 2020 |
|---|---|---|---|---|
| **1** | Cost claims received before 01.01.2022 | *22* | 16 | 14 |
| **2** | Cost claims received during 2022 | *97* | 89 | 77 |
| **3** | Cost claims not validated at the end of year 2022 >to be paid the following year | *25* | 22 | 16 |
| **4** | Cost claims processed during the year (1+ 2 - 3) | 94 | 83 | 75 |

### Value of operational transactions

The breakdown of the costs accepted and paid in 2022 is presented in the table below. In 2022, the value of payments reached the value of EUR 224 211 251 of which EUR 180 624 235 were actually paid to beneficiaries as interim/final payments, while EUR 43 587 016 are the result of full and partial clearing made

[26] The wording “transaction” is used here to indicate both direct payments, and “clearings”. In some cases, payments for the interim or final periods are fully or partially compensated (“cleared”) against the ‘pre-financing’ paid as an advance by IHI. In technical terms, the clearing is the recognition of costs incurred against the pre-financing paid to projects.

[27] Pre-financing payments = no Pre-financing were paid in 2022.

[28] 94 = 9 IMI1 + 80 IMI 2 + 5 RO( Final cost claim)

against pre-financing paid at the beginning of the project. The interim and final payments are related to IMI2 projects whereas the clearing payments of EUR 43 587 016 relate to IMI1 projects.

| IMI1 (FP7) | | No of transactions | Value of payments in EUR | Value of clearings in EUR | Value of all transactions in EUR |
|---|---|---|---|---|---|
| | Interim payments (1) | 3 | 13 717 776 | 29 869 240 | **43 587 016** |
| | Final payments (2) | 5 | | | |
| | Full Clearing (3) | 1 | | | |
| | **Total (1) + (2) + (3)** | **9** | **13 717 776** | **29 869 240** | **43 587 016** |

| IMI2 (H2020) | | No of transactions | Value of payments in EUR | Value of clearings in EUR | Value of all transactions in EUR |
|---|---|---|---|---|---|
| | Interim payments (1) | 67 | 128 744 813 | 51 879 422 | **180 624 235** |
| | Final payments (2) | 10 | | | |
| | Full Clearing (3) | 8 | | | |
| | **Total (1) + (2) + (3)** | **85** | **128 744 813** | **51 879 422** | **180 624 235** |

| | | | | |
|---|---|---|---|---|
| **TOTAL** | **94** | **142 462 589** | **81 748 662** | **224 211 251** |
| **Annual approved budget 2022 - TITLE 3** | | **157 950 873** | | |
| **Annual budget after recoveries** | | **164 871 214** | | |
| **Budget execution % - TITLE 3** | | **86%** | | |

The budget execution rate for project payments has reduced from 96% in 2021 to 86% in 2022. This can be explained by two factors. On the one hand, the duration of several projects was formally extended in 2022 by a few months and hence payments scheduled in 2022 were postponed to 2023. On the other hand, the initial budget of EUR 150 million increased to EUR 164.9 million due to recoveries and carry-overs from 2021. It has to be noted that the 2022 budget is prepared in January 2021 and there is little, if any, flexibility to update the budget afterwards. Hence the budget execution rate is calculated on the increased budget of EUR 164.9 million (86%) instead of the initially forecasted budget 150 million (95%).

### Costs rejected following ex-ante controls

In order to monitor and measure the efficiency of the ex-ante controls, another key indicator is the percentage of declared costs considered ineligible (i.e. rejected) by IHI.

| | Reported costs in EUR | Accepted costs in EUR | Rejected costs in EUR | Accepted costs in % | Rejection rate in % |
|---|---|---|---|---|---|
| **IMI1** | 39 757 972 | 37 068 938 | 2 689 034 | 93.2% | 6.8% |
| **IMI2** | 183 733 949 | 180 903 197 | 2 830 753 | 98.5% | 1.5% |
| **TOTAL** | **223 491 921** | **217 972 135** | | | |

The rejection rate of 6.8% for IMI1 project costs compared to 2.9% in 2021 is mainly due to projects that came to an end and reported more costs in the final report than the maximum grant amount. Hence, the eligible costs were capped to the IMI1 grant amount.

**Overview and ex-ante control results on administrative transactions**

The following table shows the number and amount of all administrative transactions in 2022, including experts for project monitoring under Title 2. Regarding administrative expenditure, the time to pay (TTP) indicators presented further refer to all transactions (excluding budget Title 1 salary related costs).

| Administrative transactions made in 2022 - Title I and Title II | No | % | TTP average in days |
|---|---|---|---|
| Total # payments (including experts) | 402 | 100% | 10 |
| # payments on time (within 30 days) | 399 | 99% | |
| No. late payments | 3 | 1% | |

| Administrative transactions made in 2022 - Title I Title II | Amount paid in EUR | % |
|---|---|---|
| Total # payments (including experts under Title 2) | 4 199 400 | 100% |
| # payments on time (within 30 days) | 4 190 108 | 99.8% |
| Late payments | 9 292 | 0.2% |

The rate of payments on time reached 99.8% in 2022 which is an excellent rate and has further improved in comparison to the 2021 rate which amounted to 99%. This demonstrates efficient implementation of the workflows and monitoring in place.

## Ex-post controls of operational expenditure and error rates identified

Ex-post controls are the final stage of IHI's control strategy in the project lifecycle. This stage includes the ex-post audits as well as the recovery / correction of any unduly paid amounts. Ex-post audits are carried out on the cost claims accepted and paid following the ex-ante controls

Since the legal basis and the budgetary frameworks are different, the Programme Office reports separately on the IM1 programme under FP7 and the IMI2 programme under H2020.

**Ex-post control: audit and corrective actions**

Ex-post audits have three main objectives:

1. to assess the legality and regularity of expenditure on a multi-annual basis;
2. to provide an indication of the effectiveness of the ex-ante controls;
3. to provide the basis for corrective and recovery mechanisms.

IHI mainly uses two types of audits in order to arrive at a substantial representative coverage across beneficiaries as well as to identify and correct irregularities by providing coverage of certain participants' risk profiles.

- **Representative audits** contribute to an error rate representative of the whole population. This kind of audit is conducted by IHI on the basis of representative samples in accordance with the sampling methodology identified in the ex-post audit strategy. Each sample includes a combination of the largest cost claims by beneficiaries and randomly selected entities.

- **Corrective audits** aim to identify and correct irregularities and allow the coverage of certain risk profiles through **risk-based audits**. There may be populations which are not sufficiently covered by representative audits and which may present specific risks. This kind of audit provides IHI with flexibility, ensuring particular risks are adequately addressed.

The main legality and regularity indicators for payments made to beneficiaries, as defined in the ex-post audit strategy, are the **representative** and **residual error rates** detected through financial ex-post audits.

- The ***representative error rate*** **(RepER)** is the detected error rate resulting from the representative audits. It provides a reasonable estimate of the level of error in the population relating to the accepted JU contributions on completion of the audits, but does not take into account the corrections and follow-up undertaken by IHI. The formula for the calculation of the representative error rate is presented in Annex 12 – Materiality Criteria.

- The ***residual error rate*** (**ResER**) is the level of error remaining in the population after deducting corrections and recoveries made by IHI. This includes the extension of audit results to non-audited financial statements of the audited beneficiaries to correct systematic errors. The formula for the calculation of the residual error rate is presented in Annex 12 – Materiality Criteria.

Given the multi-annual nature of both programmes and individual research projects, the **residual error rate** calculated on the duration of the programme provides the most meaningful indication of the financial impact of errors. It takes into account the corrections made by IHI and the fact that IHI extrapolates the systematic findings of the audits, significantly increasing the cleaning effect of audits. Moreover, as the programmes advance, beneficiaries learn from their errors. Drawing from the lessons learned from the audit findings, IHI also works continuously to better inform beneficiaries of any pitfalls to help them report their costs correctly.

## Ex-post control of operational expenditure under IMI1 (FP7)

### Resources

Since the lean structure of IHI does not allow for the setting up of an internal team of auditors for regular audit fieldwork, ex-post audits are outsourced to external audit firms. Nevertheless, the IHI Programme Office remains responsible for the management of ex-post audits under FP7 operational expenditure, namely:

- selection of audits;
- coordination with the EC;
- preparation of the audit input files;
- contract management;
- monitoring of the external audit firms' progress and deliverables, in particular, regular follow up of the audit status and quality checks of audit reports;
- endorsement of the audit firm opinion and recommendations;

- analysis of errors detected and implementation of audit results.

**Indicators of coverage: Number of audits and audit coverage (cumulative)**

The table below shows the coverage in completed audits (representative and risk based) in terms of the number of beneficiaries, projects as well as the accepted IMI1 contributions.

| | Total population | Audited | Audit coverage |
|---|---|---|---|
| Beneficiaries | 681 | 254 | 37 % |
| Projects | 59 | 58 | 98 % |
| **Contributions accepted by IMI1 (EUR, cumulative)** | **845 715 665**[29] | **134 000 431** | **15.84 %** |

The following table gives an overview of the status of individual audit assignments as of 31 December 2022.

| | Total audits | Audits finalised[30] | Audits ongoing |
|---|---|---|---|
| Representative | 279 | 276 | 3 |
| Risk-based | 23 | 20 | 3 |
| **Total** | **302** | **296** | **6** |

In 2022, nine audits were finalised in total. One sample of representative audits was drawn in June 2022.

**Representative and residual error rates as of 31 December 2022**

At this point, the **cumulative Representative Error Rate** (RepER) resulting from all representative audits finalised by 31 December 2022 is 2.05 % in terms of IMI1 contribution.

The **cumulative Residual Error Rate** (ResER: error remaining in the population after corrections and recoveries) is 0.81 % in terms of IMI1 contribution. The residual error rate is thus below the 2% materiality threshold established in Annex 12 of this report.

**Implementation of audit results**

When an audit report concludes that any amount has been unduly paid to a beneficiary, IHI launches the necessary corrective actions. Where the project is ongoing, the amount is offset against subsequent claims. Where the project is already closed, IHI issues a recovery order to reclaim the amount.

The table below summarises the status of implementation of audit results on a cumulative basis as of the cut-off reporting date of 31 December 2022.

[29] Figure as of 31/12/2022.

[30] An audit is considered finalised when the audit adjustment and the related 'error rate' is final. This comprises of either audits with 'final audit reports' accepted by IHI or if not received or accepted, with a 'pre-final audit report' (after contradictory procedure with the beneficiary) approved by the JU and therefore with a definitive audit adjustment and error rate.

| Number of cases of unduly paid amounts identified in audits | Number of cases implemented | Percentage of cases implemented | Amount implemented (EUR) |
|---|---|---|---|
| 223 | 223 | 100 % | 3 482 962 |

**Extension of audit findings**

When an audit detects findings of a systematic nature, IHI extrapolates them to all other cost claims of the same beneficiary ('extension of audit findings'). The unduly paid amounts thus identified are recovered or offset against subsequent cost claims of the beneficiary.

The status of the implementation of extension of audit findings is shown in the table below.

| Implementation of extension of systematic findings | Beneficiaries |
|---|---|
| Audits finalised | 296 |
| Pre-information letters / letters of conclusion sent | 296 |
| Of which affected by systematic errors[31] | 71 |
| Extrapolation feedback received from beneficiary | 71 |
| Of which implemented | 71 |
| Amount implemented (EUR) | 1 046 622 |

## Ex-post control of operational expenditure under IMI2 (H2020)

As regards the operational expenditure under H2020, the ex-post controls of IMI2 grants are aligned with the harmonised strategy adopted for the entire H2020 programme[32]. The Common Implementation Centre of the European Commission, more specifically its Common Audit Service (CAS), carries out the H2020 audits in accordance with the strategy for all entities implementing the H2020 programme, including IHI. IHI works closely with CAS in the implementation of the common audit strategy, contributes to the relevant working groups, provides inputs during the entire audit cycle from selection of audits to implementation of audit findings, and provides opinions on draft audit reports and extensions of audit findings.

As part of the H2020 programme with a harmonised legal framework, IMI2 cost claims are included in the programme level sampling, notably the H2020 common representative sample (CRS). Accordingly, IHI reports on the error rates drawn from these programme level controls. The extension of findings across the programme also provides an additional element of assurance.

[31] This does not include positive systematic errors and systematic errors below the materiality threshold.

[32] Horizon 2020 Ex-post Audit Strategy (2016 – 2025).

However, as the IMI2 Regulation[33] also establishes a requirement for an individual discharge procedure, this report also contains error rates and other indicators specifically related to the cost claim populations of the IMI2 programme.

**Ex-post control of the H2020 programme globally in 2022**

The H2020 audit campaign started in 2016. At this stage, four common representative samples with a total of 628 expected results have been selected. By the end of 2022, cost claims amounting to EUR 40.8 billion had been submitted by the beneficiaries to the services. The error rates on the H2020 programme level on 31 December 2022 are:

- Cumulative representative detected error rate**:** 2.71%**[34]**,
- Cumulative residual error rate for the R&I Family of DGs: 1.67% (1.71% for DG R&I).

Since H2020 is a multi-annual programme, the error rates, and the residual error rate in particular, should be considered within a time perspective. Specifically, the cleaning effect of audits will tend to increase the difference between the representative detected error rate and the cumulative residual error rate, with the latter finishing at a lower value.

These error rates are calculated on the basis of the audit results available when drafting the Consolidated Annual Activity Report. They should be treated with caution as they may change subject to the availability of additional data from audit results. The effectiveness of the control strategy of the R&I Family can only be measured and assessed fully in the final stages of the EU Framework Programme, once the ex-post audit strategy has been fully implemented, and errors, including those of a systemic nature, have been detected and corrected.

**Ex-post control specific to the IMI2 population in 2022**

By 31 December 2022, IHI had launched eight individual representative samples (one sample of representative audits was drawn in June 2022). Audits were finalised from the first seven samples. A total of 84 representative audits sampled by IHI were finalised. In addition, 10 risk-based audits were finalised by the end of 2022.

**Audit coverage (cumulative)**

The table below shows the coverage in completed audits (representative and risk based) compared to the accepted IMI2 contributions.

| | Total population | Audited | Audit coverage |
|---|---|---|---|
| Contributions accepted by IMI2 (EUR, cumulative) | 641 324 044[35] | 75 148 310 | 11.72 % |

**33** COUNCIL REGULATION (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking; Article 12

**34** Based on the 479 representative results out of the 628 expected in the four Common Representative Samples.

**35** Figure as of 31/12/2022.

The following table gives an overview of the status of individual audit assignments as of 31 December 2022.

| | Total audits | Audits finalised | Audits ongoing |
|---|---|---|---|
| Representative | 103 | 84 | 19 |
| Risk-based | 23 | 10 | 13 |
| **Total** | **126** | **94** | **32** |

In 2022, 21 audits were finalised in total.

**Representative and residual error rates specific to IMI2's population as of 31 December 2022**

At this point, the error rates on IMI2 populations are as follows:

- **Cumulative Representative Error Rate** (RepER) resulting from the 84 finalised audits considered representative is 2.66% in terms of IMI2 contribution.
- **Cumulative Residual Error Rate** (ResER: error remaining in the population after corrections and recoveries) is 0.85% in terms of IMI2 contribution.

**Implementation of negative audit results and extension of audit findings**

Following the finalisation of each audit by CAS, IHI launches the necessary corrective actions to recover or offset against subsequent claims of the same beneficiaries any amounts that have been found to be unduly paid. The table below summarises the status of implementation of audit results for the finalised audits on a cumulative basis, as of the cut-off reporting date of 31 December 2022.

| Number of cases of unduly paid amounts identified in audits | Number of cases implemented | Percentage of cases implemented | Amount implemented (EUR) |
|---|---|---|---|
| 55 | 48 | 87 % | 1 230 794 |

**Extension of audit findings**

The status of the implementation of extension of audit findings is shown in the following table.

| Implementation of extension of systematic findings | Beneficiaries |
|---|---|
| Audits finalised | 94 |
| Pre-information letters / letters of conclusion sent | 94 |

| | |
|---|---|
| Of which affected by systematic errors[36] | 11 |
| Extrapolation feedback received from beneficiary | 8 |
| Of which implemented | 8 |
| Amount implemented (EUR) | 264 576 |

Under H2020, extension of audit findings on IMI2 actions may also be triggered by audits performed by other EU services on IMI2 beneficiaries. For these cases, IHI provides its opinion to the coordinating unit, the Common Audit Service, and implements the correction. As of 31 December 2022, IHI has implemented 13 closed extensions of audit findings triggered by audits performed by other EU services on IMI2 beneficiaries.

**Reporting on the implementation of all audit results and extensions (negative, positive and neutral results)**

Following the adoption of a guidance note on the monitoring of the implementation of ex-post audit results by the CIC Executive Committee in December 2022, the following tables illustrate the common set of data that EU services must use to monitor the implementation of all audit results and extensions: negative, positive and neutral results. Results correspond to a financial audit opinion or a closed extension of systematic audit findings for one beneficiary in one grant.

For implementations done outside the grant management module, therefore outside the audit result implementation Compass workflow (called “AURI”), such as non-joint ECA audits and implementations processed before the entry into service of Compass tools in IMI2 on 24 May 2018, the results are manually added to the statistics produced by Compass.

**Implementation of audit and extension results (cumulative from H2020 start to 31/12/2022)**

| IMI2 JU | Audit results processed | % Audit results processed | Audit results pending | % Audit results pending | Total audit results |
|---|---|---|---|---|---|
| Audits | 134 | 90% | 15 | 10% | 149 |
| Extensions | 45 | 100% | 0 | 0% | 45 |
| **Total** | **179** | **92%** | **15** | **8%** | **194** |

[36] This does not include positive systematic errors and systematic errors below the materiality threshold.

**Time to implement audit and extension results (cumulative from H2020 start to 31/12/2022 as these data are reported for the first time)**

| IMI2 JU | 0-6 months | % total number (0-6 months) | above 6 months | % above 6 months | Total number |
|---|---|---|---|---|---|
| **Closed projects** | **53** | **93%** | **4** | **7%** | **57** |
| Negative adjustments with recovery | 6 | 86% | 1 | 14% | 7 |
| Negative adjustments without recovery | 11 | 85% | 2 | 15% | 13 |
| Positive or zero adjustment | 36 | 97% | 1 | 3% | 37 |
| **Ongoing projects** | **122** | **100%** | **0** | **0%** | **122** |
| Negative adjustments | 30 | 100% | | 0% | 30 |
| Positive or zero adjustment | 92 | 100% | | 0% | 92 |
| **Total** | **175** | **98%** | **4** | **2%** | **179** |

The above figures demonstrate that the JU implements in a timely manner all audit and extensions results enabling IHI to meet all targets set by the EC guidance note on monitoring of the implementation of ex-post audit results.

### 4.1.2 Efficiency of controls ('time to')

In 2022, IHI JU continued to ensure the efficiency and robustness of its granting process as reflected by the three performance indicators described in the following table.

- **Time to Inform (TTI)** represents the time needed by IHI JU to manage the evaluation and selection phase from the call deadline to informing the participants. In 2022, the average TTI was 72 days, against a legal target of 153 days.

- **Time to Grant (TTG)** represents the maximum eight months between the call deadline and grant signature. In 2022, this indicator is not applicable (N/A). IHI started in December 2021 and the first calls were launched in June and December 2022. No grants had been signed by the end of the year.

| Indicators - in days | Target | 2022 |
|---|---|---|
| Total average Time to Inform (TTI) | 153 days | 72 |
| Total average Time to Grant (TTG) | 245 days | N/A [37] |

- **Time to Pay (TTP)** represents the outcome of the process for the payment of costs claimed by beneficiaries. As IHI JU implements the legacy portfolio of IMI1 and IMI2, the table below presents the TTP for those project payments done in 2022.

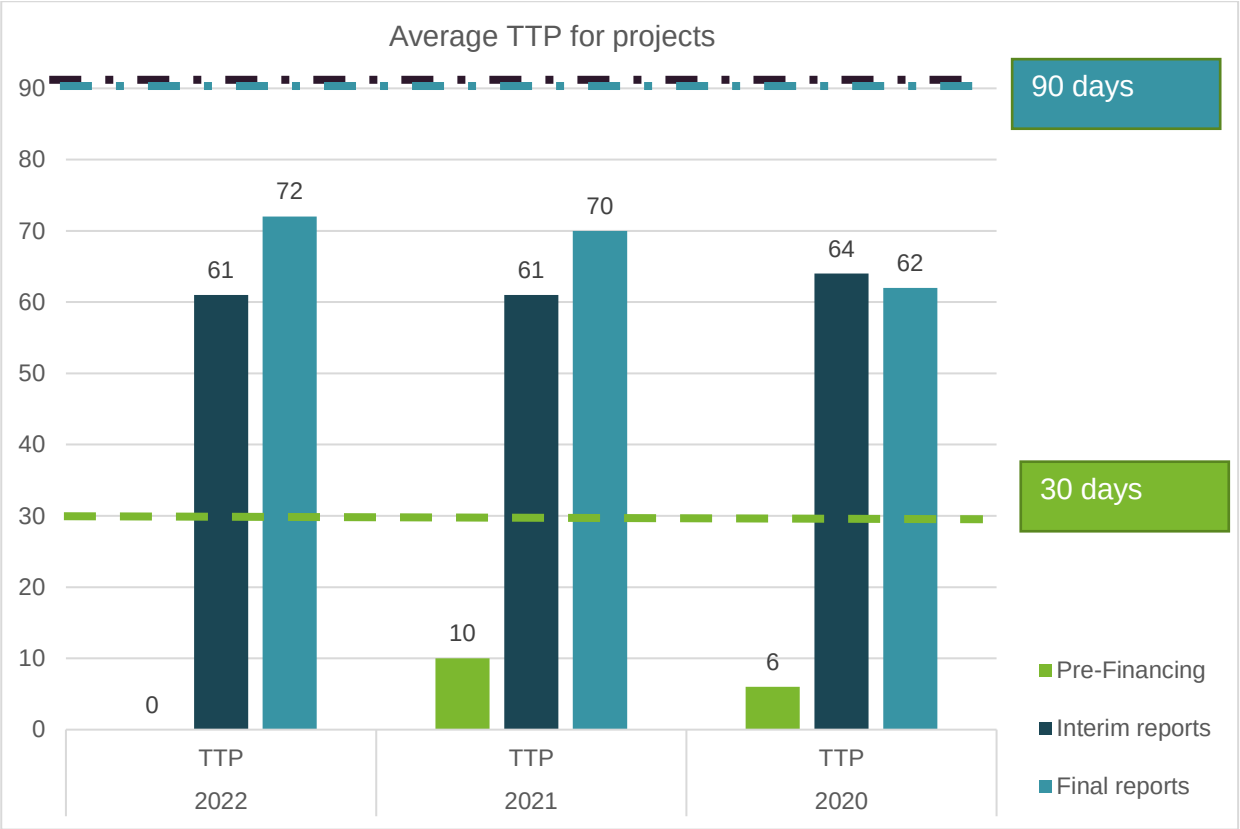
| IMI1 + IMI2<br>Indicators - in days | Target | 2022 | |
|---|---|---|---|
| | | IMI2 | IMI1 |
| Total average Time to Pay (TTP)<br>- for cost-claims and final payments | 90 days | 63 | 59 |

For the IMI2 and IMI1 projects, the actual TTP averages respectively reached 63 and 59 days against a target of 90 days. This demonstrates the efficiency of financial management within the IHU JU.

The graph below demonstrates the efficiency of the Programme Office by meeting all the targets for payments as defined in the Financial Rules[38]. The average TTP results (in days) are below the maximum threshold number of days for all types of operational transactions executed in 2022 and support the efficiency trend.

[37] No IHI grants were signed in 2022.

[38] 30 days for pre-financing, 90 days for interim and final project payments.




In addition to good results of timely project payments, the JU has also demonstrated efficiency in payments to project monitoring experts (under Title 2) and call for proposals evaluation experts (under Title 3). There were no late payments to experts for project monitoring in 2022 and only one late payment for evaluation experts. This confirms that the measures taken to control the workflow were effective.

The average TTP was 10 days for the project monitoring experts which is in line with 9 days for 2021. The average TTP was 18 days for the evaluation experts which is more difficult to compare to 2021, as there was no separation between the two types of experts in 2021. In both cases the average TTP is substantially below the maximum allowed, i.e. 30 days.

**Payments to project monitoring experts**

| Expert payments made in 2022 - Title II | # | % |
|---|---|---|
| # of payments | 50 | 100% |
| # of late payments | 0 | 0% |
| # of payments on time | 50 | 100% |
| Average time to pay (days) | 10 | |
| Total amount paid (EUR) | 85 050 | |

**Payments to evaluation experts**

| Expert payments made in 2022 -Title III | # | % |
|---|---|---|
| # of payments | 47 | 98% |
| # of late payments | 1 | 2% |
| # of payments on time | 46 | 100% |
| Average time to pay (days) | 18 | |
| Total amount paid (EUR) | 153 090 | |

### 4.1.3 Economy of controls

The section below describes the cost-effectiveness of IHI controls related to the overall control cycle (ex-ante controls on call management and evaluation, grant award and project implementation and ex-post controls).

The cost for ex-ante controls represents 1.65 % of operational expenditure in 2022 and can be quantified as EUR 20 thousand per Grant Agreement.

A complete assessment of the cost-effectiveness of the JU's control efficiency (full cost approach) implies a consideration of all costs related to the control of the overall programme life cycle, from submission, evaluation and selection to ex-post audit, including validation of the in-kind contribution provided by industry.

The table below presents the cost-effectiveness ratio of all the controls.

| Cost-effectiveness ratio | 2022 | 2021 |
|---|---|---|
| Cost of controls / Total expenditure 2022 (administrative and operational) | 1.69% | 1.12% |
| Cost of controls / Operational expenditure 2022 | 1.75% | 1.17% |
| Cost of controls / Total accepted costs 2022 (only beneficiaries' cost claims) | 1.80% | 1.27% |
| Cost of controls / Total accepted costs 2022 (both beneficiaries' cost claims and validated industry contribution) | 0.77% | 0.50% |

The different indicators presented above provide an indication of the cost effectiveness of the control system put in place by the JU to ensure a sound financial management of the grant implementation throughout the lifetime of the projects, as well as the monitoring of their scientific progress.

## 4.2 Audit observations and recommendations

### 4.2.1 Internal audit

The Internal Audit Service (IAS) of the European Commission performs the internal audit function for the JU as specified in Article 28 of the Financial Rules.

In line with the International Standards for the Professional Practice of Internal Auditing, the internal auditor has confirmed the organisational independence of the internal audit activity to the Executive Director and the Governing Board.

In 2022 (from June to October), IAS performed an extensive risk assessment covering all IHI JU auditable entities. The risk assessment consisted of on-site visits and remote fieldwork, including meetings and interviews with the IHI JU Governing Board chairperson and vice-chairperson, IHI JU senior management, key process owners, and a subsequent desk review of sample information and documents prepared by the JU.

The risk assessment resulted in the new strategic internal audit plan established for IHI JU for the period of 2023-2025[39].

The annual audit plans of the IAS are coordinated with the European Court of Auditors, the external auditor of all European Union institutions and bodies. The coordination activities aim to avoid duplication and to minimise any overlaps in subjects and areas proposed for audits by internal and external auditors.

### 4.2.2 Audit of the European Court of Auditors

#### Audit on IMI2 JU annual accounts for the financial year 2021

On 15 November 2022, the European Court of Auditors (ECA) published its 'Annual report on the EU Joint Undertakings for the financial year 2021'[40] .

The ECA gave a clean bill of health for IHI JU, issuing an unqualified ('clean') opinion on the reliability of the accounts as well as on the legality and regularity of the revenue and payments underlying the annual accounts.

Without calling into question its 'clean opinion', the ECA also provided some observations in the specific chapter on IHI JU on the following subjects:

- *JUs' employer contributions to the EU pension scheme* – the auditors noted that all JUs (IHI among them) which are only partly financed from the EU budget should pay the part of the employer's contributions to the EU pension scheme corresponding to the ratio of their non-EU subsidised revenues to their total revenues as per Article 83a of the Staff Regulations. The auditors further established that the Commission has neither provided for this expenditure in the JUs' budgets nor formally requested the payments. The auditors have also highlighted that there is a concurrence of different legal provisions (i.e. Staff Regulations and the Single Basic Act) regarding the calculation of the JU's employer contribution with varying financial impact.

[39] Ares(2023)638585 of 27/01/2023

[40] https://www.eca.europa.eu/en/Pages/DocItem.aspx?did=62403

- *Management and control systems* – The ECA audited four randomly sampled Horizon 2020 payments made in 2021, at the level of the final IHI beneficiaries, to corroborate the ex-post audit error rates. In one case, auditors found a systemic error related to personnel costs (EUR 3 381) resulting from the use of incorrect hourly rates that were not based on a completed financial year, and in another case, an error resulting from the lack of appropriate supporting evidence for declared equipment and travel costs (EUR 7 101).

### Audit on IHI JU annual accounts for the financial year 2022

In accordance with Article 54 of the JU Financial Rules, the 2022 annual accounts are audited by the external audit company. The specific contract was signed in 2022 with Baker Tilly Belgium to cover the audit of financial years 2022 and 2023. The audit work for the accounts for 2022 will be completed by issuing an opinion on the final accounts by 15 June 2023.

The Court of Auditors will draw the final audit opinion on the 2022 accounts, revenue and transactions on the basis of the work by independent external auditors as well as the substantial audit work performed by the ECA's dedicated team. The final report is due in November 2023.

### 4.2.3 Follow up of audit recommendations

IHI has implemented the only remaining open action stemming from the audit report on 'Horizon 2020 grant implementation in the Innovative Medicines Initiative 2 Joint Undertaking' issued on 27 January 2021. As recommended by the IAS auditors, IHI adopted a revised anti-fraud strategy reflecting the modalities of funding under the Horizon Europe framework programme and the new related action plan aligned with the horizontal research family approach.

At the end of December 2022, the JU provided evidence on the implementation of the action and requested the IAS team to review and close the recommendation. The conclusions are expected by mid-March 2023.

IHI acted on the ECA's comments on the payment of the employer part of the pension contribution. As soon as the debit note had been received from the Commission services, the due payment was made.

## 4.3 Assessment of internal control systems

IHI JU's internal control framework is designed to provide reasonable assurance regarding the achievement of the following five objectives:

- effectiveness, efficiency and economy of operations;
- reliability of reporting;
- safeguarding of assets and information;
- prevention, detection, correction and follow-up of fraud and irregularities;
- adequate management of the risks relating to the legality and regularity of the underlying transactions, taking into account the multi-annual character of programmes as well as the nature of the payments concerned.

The JU's internal control framework is based on 17 control principles which are aligned with the European Commission control framework. All the principles of the control model are embedded across the JU's organisational structure and rely on a combination of ex-ante and ex-post controls, segregation of duties, documented processes and procedures, control of deviations, control of data quality, promotion of ethical

behaviour and zero tolerance to fraud, prevention of conflict of interest and integrated risk management. The Programme Office at all levels ensures the implementation of the internal control framework.

The self-assessment of the effectiveness of the internal control framework in 2022 is based on the criteria set out in the internal guidance, namely:

- a set of indicators with targets and baselines;
- staff and management surveys and analysis of the results on the functioning of internal control;
- state of implementation of internal control action plan;
- state of implementation of recommendations and observations by internal (Internal Audit Service) and external auditors (independent financial auditors and the European Court of Auditors).

In order to assure that all aspects of the internal control system and business operations were covered by the self-assessment, the 17 control principles have been analysed both individually and as part of the corresponding control component.

### 4.3.1 Fraud prevention, detection and correction

The JU has been implementing the anti-fraud strategy aligned with the Commission Anti-Fraud Strategy (CAFS 2019) and the Common Anti-Fraud Strategy for the Research family (RAFS 2019) which addressed the fraud risks of the entire sector of research in the European Commission. An action plan for detective and preventive measures is linked to this global antifraud strategy, which all stakeholders implement in close coordination with the Commission services. Actions implemented on grants and operational activities are coordinated with DG RTD and other research agencies through a multiannual action plan coordinated by the Fraud and Irregularity in Research (FAIR) Committee.

In addition to the common approach for the research sector, a specific JU-level anti-fraud strategy has been implemented since 2020. A revised IHI JU Anti-Fraud Strategy[41] was adopted in line with the internal audit recommendation. It is based on a dedicated fraud risk assessment last updated in 2022.

In 2022, IHI JU anti-fraud activities were focused on:

- Cooperation with the FAIR Committee activities.
- Increasing staff awareness of anti-fraud, including a specific mandatory training on fraud prevention organised on 6 December 2022 with a speaker from OLAF. As this training was a good opportunity for synergies, it was opened to participants from eight other JUs. A total of 120 staff participated.
- Raising the awareness of staff on cybersecurity risks, including some phishing exercises and trainings.
- Fraud risk assessment exercise. That action was twofold, one embedded in the annual risk assessment cycle and one, more extensive and detailed, to set the basis for the revision of the overall Anti-Fraud Strategy for the new IHI JU.

Additionally, attention was given to cross-cutting issues such as risks linked with conflict of interest, delegation of authority, and segregation of duties.

In 2022 the Programme Office made an internal analysis of a few suspicious cases identified during ex-ante and ex-post controls of its project portfolio. One notification of suspicion of fraud was communicated to OLAF. IHI JU did not receive any enquiries or requests for information from OLAF.

[41] ED decision No 39 of 16 December 2022

### 4.3.2 Assets and information, reliability of reporting

In view of the internal control objective to safeguard assets, the JU has established internal procedures and processes. The inventory check of fixed assets has been performed and relevant write-offs were done. The annual assessment (including declassification decision, calculations of net book value for IT and furniture to be disposed, and SAP bookings) was performed before the year-end operations as set out in the internal procedure.

In view of the objective of reliability of reporting, the JU ensures data quality and accuracy via managerial supervision, segregation of duties, and external reviews and audits. The 2022 annual evaluation (related to financial year 2021) of IHI JU local financial systems was performed by DG BUDG according to Article 25 (d) of the JU Financial Rules. The evaluation did not identify any internal control weakness which would have a material impact on the accuracy, completeness and timeliness of the information required to draft the annual accounts and produce reliable reporting.

On the basis of the available evidence, DG BUDG concluded that the internal control systems are working as intended and that improvements were made as a follow up of some issues raised in 2021.

### 4.3.3 Risk assessment and management

At IHI JU, risk management is a proactive process of identifying, assessing and managing the events that could threaten the implementation of activities planned for the achievement of the JU's objectives. Risk management is an integral element of the strategic planning and monitoring cycle.

To that end, the JU implements a robust enterprise risk management (ERM) process based on the annual risk assessment exercise. This exercise is part of the internal control system and is designed to capture, in a timely way, any new and emerging risks that could potentially influence the achievement of the JU's objectives, as well as to provide timely reflection on the rating and relevance of the existing risks, to ensure that appropriate actions and mitigating measures are put in place. It is also used as a key operational tool for day-to-day management. The risk assessment provides a comprehensive analysis of:

- the weaknesses and risks that might undermine the performance and capacity of the IHI JU to achieve its objectives;
- risks that might be reduced and/or managed through mitigating measures.

Throughout the year, the Programme Office regularly monitored the evolution of the recorded risks and assessed the new emerging risks toward the achievement of the objectives in the Work Programme. To that end, the risk management working group established by the Executive Director reviewed, discussed, and updated the residual risks and corresponding mitigating actions where needed. The regular follow-up ensured that risk management was a continuous, dynamic, and proactive process in view of evolving corporate priorities and emerging risks presenting new threats to the operations and strategy of the JU.

Following the risk assessment exercise carried out by the Programme Office in view of the Work Programme and the objectives planned by IHI JU in 2022, four critical risks were identified and recorded in the corporate register. The critical risks were reported to the GB and the relevant Commission services. Most of these risks were related to the external environment (outside IHI JU), operational processes and human resources. Two of the critical risks were adequately mitigated throughout the first full year of IHI implementation:

- the establishment of the IHI JU governance structures was completed (more details on governance activities can be found under chapter 3);

- the back office arrangements for accounting services were established and the new Accounting Officer for IHI JU was appointed by the Governing Board[42].

The other two critical risks relating to the programme management platform and the uncertainties around key concepts in implementing the research programme were reassessed and transferred to 2023. The key measures of continuous collaboration and dialogue with the Commission horizontal services aim to ensure the maximum level of engagement to mitigate them, and to monitor the impact on the Programme Office and on the business objectives.

### 4.3.4 Prevention of conflicts of interest

In accordance with the IHI JU legal framework, the Executive Director and staff of the Programme Office ensure transparency and compliance with ethical rules including the absence of any conflict of interest with the operational and administrative activities of the JU. A conflict of interests exists where the impartial and objective exercise of the functions of a financial actor or other person is compromised for reasons involving family, emotional life, political or national affinity, economic interest, or any other direct or indirect personal interest.

The objective of controls on the conflicts of interest is to prevent, detect and address any situation that can undermine the reputation of the IHI JU partnership.

The JU has developed a comprehensive set of rules and procedures that are effectively implemented across its entire governance structure, as follows:

- When joining the Programme Office team, each staff member agrees to follow and comply with the Staff Regulations and signs a declaration of honour on the management of conflicts of interest.
- IHI JU applies by analogy, mutatis mutandis, the 'Code of Good Administrative Behaviour' for staff of the European Commission in their relations with the public.
- Conflict of interest procedures are in place for the members of the IHI JU Governing Board as adopted in December 2021 in the scope of the rules of procedure of the GB for the IHI JU[43]. The declarations are made available on IHI JU website. The rules of procedure for IHI State's Representative Group[44] as well as the rules of procedure of the IHI Science and Innovation Panel[45] include explicit requirements for declaration of conflict of interest.
- Specific measures have been implemented for the prevention and management of conflicts of interest of experts in charge of the evaluation of grant applications and of the review of projects and tenders.
- A holistic conflict of interest prevention and detection campaign was conducted within the Programme Office in 2022. All IHI JU staff members were required to submit their up-to-date declarations. Declaring conflicts of interest is a continuous process as any conflicting situations shall be declared within a month and on a proactive basis.

[42] GB Decision No 17 of 30 November 2022

[43] IHI-GB-DEC-2021-01 of 16 December 2021

[44] www.ihi.europa.eu/about-ihi/who-we-are/states-representatives-group

[45] www.ihi.europa.eu/about-ihi/who-we-are/science-and-innovation-panel

### 4.3.5 Conclusion on internal control systems

The JU uses the organisational structure and the internal control system suited to achieving its policy and internal control objectives in accordance with the internal control principles and has due regard to the risks associated with the environment in which it operates.

IHI JU has systematically examined the available control results and indicators as well as the observations and recommendations issued by the internal auditor and the European Court of Auditors. These elements have been assessed to determine their impact on management's assurance about the achievement of the control objectives.

In line with its internal control framework, the JU has assessed its internal control system during the reporting year 2022 and has concluded that it is effective, and the components and principles are present and functioning well. Areas where some further improvements can be made have been identified and will be prioritised in 2023.

## 4.4 Conclusion on the assurance

### 4.4.1 Review of the elements supporting assurance

Reasonable assurance is a judgement by the Executive Director, the Authorising Officer, based on all the information at his disposal.

IHI JU follows the 'three lines of defence' model for assurance and accountability. The Executive Director's assessment is based on the following sources supporting assurance, specifically:

Governance, risk management and internal control framework:

- reporting by the members of the JU management team[46];
- reporting by the internal control officer;
- reports and recommendations by the JU audit manager;
- results of ex-ante and ex-post control
- Governing Board assessment and recommendations.

Findings and opinions from internal and external audits:

- reports and follow up notes by the Internal Audit Service;
- reports by independent financial auditors;
- reports and annual audit opinion by the European Court of Auditors.

External verifications and investigations (when available):

- reports by the EC Accounting Officer;
- reports by the Ombudsman;
- reports by the European Data Protection Supervisor;
- conclusions by the European Anti-fraud Office.

Independent external reviews:

- interim and final evaluation reports;
- project interim review reports;
- socio-economic impact reports;
- bibliometric analysis.

As demonstrated throughout this annual report, the results of the performance and control indicators positively support the statement of the declaration of assurance. Fraud prevention and detection mechanisms in place did not reveal anything that would impair the declaration of assurance. The audit results, the internal control self-assessment and the control indicators did not reveal any significant weaknesses that could have a material impact described in Annex 10. The overall cumulative residual error rate is below 2% for both operational programmes. The control strategy sets out the implementation of further controls during subsequent years designed to detect and correct these errors. The results of grant management operational indicators (time to pay, time to grant, time to sign, time to inform) are well below the legal targets, demonstrating the maturity of our operations and the robustness of our control systems, and supporting the declaration of assurance.

46 Head of Administration and Finance, Head of Scientific Operations, Head of Communications and Institutional Relations

No significant weaknesses were identified or reported under Section 2 (‘Support to operations’) and Section 4 (‘Financial management and internal control’). Furthermore, the management consider that, given the scope of the statement of assurance and taking into account the controls and monitoring system in place, there are no weaknesses that could call into question reasonable assurance as to the use of resources for their intended purpose, in accordance with the principles of sound financial management. The implemented control procedures and results provide the necessary assurance on the legality and regularity of the underlying transactions.

### 4.4.2 Reservations

There are no reasons for introducing any reservations.

### 4.4.3 Overall conclusion

IHI’s management has reasonable assurance that, overall, suitable controls are in place and work as intended; risks are being appropriately assessed, monitored and mitigated; and necessary process improvements and reinforcements are being implemented. The Executive Director, in his capacity as the Authorising Officer, has signed the Declaration of Assurance.

## 4.5 Statement on management reporting

### For the manager in charge of risk management and internal control:

*I declare that in accordance with the IMI2 JU Governing Board decision No 2017-28 on the Revision of the IMI2 JU internal control framework and IHI JU Governing Board Decision No 2021-3, I have reported my advice and recommendations on the overall state of internal control in the IHI JU to the Executive Director. I hereby certify that the information provided in the present Consolidated Annual Activity Report and in its annexes is, to the best of my knowledge, accurate and complete.*

Brussels, 13.06.2023

*Signed*

Elise Oukka, Head of Administration and Finance

### For the manager taking responsibility for the completeness and reliability of management reporting on results and on the achievement of objectives:

*I hereby certify that the information provided in the present Consolidated Annual Activity Report and in its annexes is, to the best of my knowledge, accurate and complete.*

Brussels, 14.06.2023

*Signed*

Hugh Laverty, Head of Scientific Operations

## 4.6 Declaration of assurance

I, the undersigned,

Executive Director ad interim of the Innovative Health Initiative Joint Undertaking

In my capacity as authorising officer

Declare that the information contained in this report gives a true and fair view[47].

State that I have reasonable assurance that the resources assigned to the activities described in this report have been used for their intended purpose and in accordance with the principles of sound financial management, and that the control procedures put in place give the necessary guarantees concerning the legality and regularity of the underlying transactions.

This reasonable assurance is based on my own judgement and on the information at my disposal, such as the results of the self-assessment, ex-post controls, the observations of the Internal Audit Service and the lessons learnt from the reports of the Court of Auditors for years prior to the year of this declaration.

Confirm that I am not aware of anything not reported here which could harm the interests of the Joint Undertaking.

Brussels, 14.06.2023

*Signed*

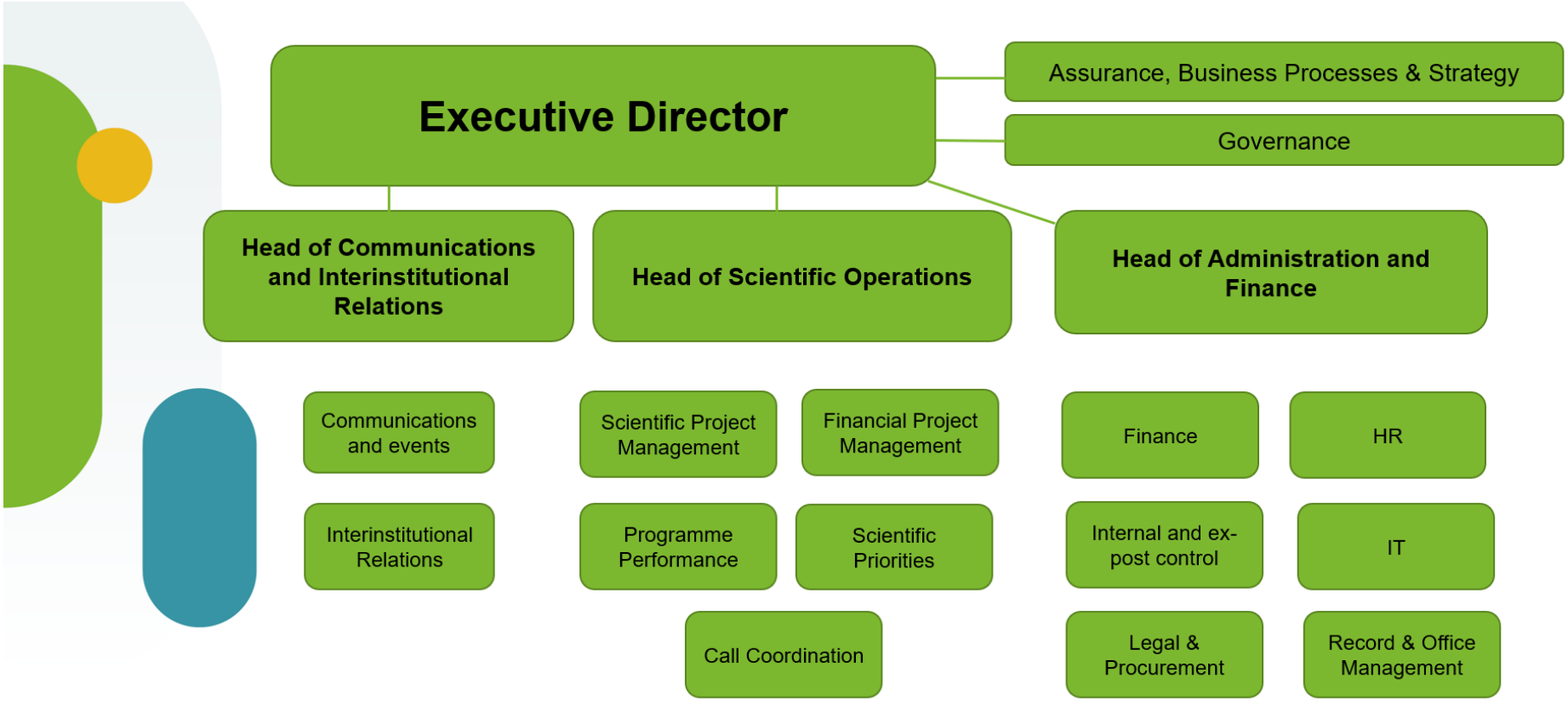
Hugh Laverty

Executive Director ad interim

[47] True and fair in this context means a reliable, complete and correct view on the state of affairs in the Joint Undertaking.

# Annexes

## Annex 1 – Organisational chart



# Annex 2 - Establishment plan and additional information on HR management

| Function group and grade | YEAR 2021 | | | | YEAR 2022 | | | |
|---|---|---|---|---|---|---|---|---|
| | Authorised posts | | Posts actually filled as of 31/12 | | Authorised posts | | Posts actually filled as of 31/12 | |
| | Perm. | Temp. | Perm. | Temp. | Perm. | Temp. | Perm. | Temp. |
| **AD 16** | | | | | | | | |
| **AD 15** | | | | | | | | |
| **AD 14** | | 1 | | 1 | | 1 | | 0 |
| **AD 13** | | 0 | | 0 | | 0 | | 0 |
| **AD 12** | | 2 | | 1 | | 2 | | 1 |
| **AD 11** | | 2 | | 2 | | 2 | | 2 |
| **AD 10** | | 1 | | 2 | | 1 | | 2 |
| **AD 9** | | 7 | | 5 | | 7 | | 4 |
| **AD 8** | | 6 | | 4 | | 6 | | 3 |
| **AD 7** | | 2 | | 4 | | 3 | | 3 |
| **AD 6** | | 11 | | 6 | | 10 | | 6 |
| **AD 5** | | 1 | | 6 | | 2 | | 11 |
| **TOTAL AD** | | **39** | | **31** | | **34** | | **32** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **AST 11** | | | | | | | | |
| **AST10** | | | | | | | | |
| **AST 9** | | | | | | | | |
| **AST 8** | | 1 | | 1 | | 1 | | 1 |
| **AST 7** | | | | | | | | |
| **AST 6** | | | | | | | | |
| **AST 5** | | | | | | | | |
| **AST 4** | | 4 | | 3 | | 4 | | 2 |
| **AST 3** | | | | 1 | | | | 1 |
| **AST 2** | | 1 | | 0 | | | | |
| **AST 1** | | | | | | | | |
| **TOTAL AST** | | **6** | | **5** | | **5** | | **4** |
| **AST/SC 6** | | | | | | | | |
| **AST/SC 5** | | | | | | | | |
| **AST/SC 4** | | | | | | | | |
| **AST/SC 3** | | | | | | | | |
| **AST/SC 2** | | | | | | | | |
| **AST/SC 1** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **TOTAL AST/SC** | | | | | | | | |
| **TOTAL AD+AST+ AST/SC** | | | | | | | | |
| **GRAND TOTAL** | | **39** | | **36** | | **39** | | **36** |

| Contract agents | Authorised | Actually filled as of 31/12/2022 |
|---|---|---|
| **Function Group IV** | 4 | 3 |
| **Function Group III** | 11 | 10 |
| **Function Group III** | 0 | 0 |
| **Function Group I** | 0 | 0 |
| **TOTAL** | **15** | **13** |

| Seconded National Experts | Authorised | Actually filled as of 31/12/2022 |
|---|---|---|
| | 1 | 0 |
| **TOTAL** | **1** | **0** |

## Annex 3 – Project outputs

In order to track progress against the ambitious goals of the IMI programmes, IMI project outputs are categorised according to the following categories:

**New tools/resources for drug discovery & preclinical drug development:** IMI projects are adding to our understanding of disease, as well as delivering tools, resources and platforms to make it easier for researchers to study diseases and identify potential treatments.

**Biomarkers and tools developed to predict clinical outcomes (efficacy and safety):** How do you know which patients are on the path to recovery and which not? How can you identify patients who may be at greater risk of developing complications? How do you know which medicine will be safe and effective for which patients? Answering these questions is a key part of drug development, and requires an understanding of which biological markers ('biomarkers') could provide clues to help researchers answer these questions. Ideally, these biomarkers should be easily obtainable, for example through a simple blood test, scan, or patient-reported outcome (PRO). Ultimately, more reliable predictive tests will help to eliminate ineffective or unsafe compounds earlier in the development process, thereby avoiding unnecessary patient exposure and stopping investments in programmes that will ultimately prove unsuccessful.

**Improved protocols for clinical trial design and processes:** During clinical trials, medicines are tested for the first time in humans, firstly in healthy volunteers (to check that the drug is safe) and then in patients (to check that it works and to determine the best dose). Clinical trials can take years to run and are incredibly expensive. In addition, the results of clinical trials cannot always be extrapolated to the real world, as patients enrolled in a trial may not be fully representative of the wider patient community. IMI projects are investigating ways of improving the way clinical trials are run, so that they can generate reliable results, faster.

**Biomarkers for the efficacy and safety of vaccine candidates:** Vaccines are one of the most effective public health measures out, saving some two to three million lives worldwide every year. During vaccine development, biomarkers are an essential tool to help researchers identify vaccine candidates that will be both safe and effective. Ultimately, these biomarkers will advance the development of new vaccines and contribute to greater public confidence in vaccines.

**New taxonomies of diseases and new stratifications of patient sub-populations:** There is growing evidence that while two patients may be classified as having the same disease, the genetic or molecular causes of their symptoms may be very different. This means that a treatment that works in one patient will prove ineffective in another. In other cases, diseases that are currently defined as separate conditions may share a common molecular basis. There is therefore now broad recognition that the way diseases are classified needs to change. Many IMI projects are working to develop new ways of grouping or stratifying patients into more meaningful groups. In the long term, this will allow researchers to develop more targeted medicines, and increase the chances of patients receiving treatments that work for them.

**Development and use of cohorts, registries and clinical networks for clinical studies and trials:** Behind every clinical trial is a cohort of participants who are selected on the basis of a range of criteria. However, for many disease areas, finding the right number of appropriate patients is far from easy. IMI projects are setting up cohorts and networks of trial sites to facilitate the running of clinical trials in challenging areas such as dementia and antimicrobial resistance.

**Big data solutions to leverage knowledge / implementation of data standards:** Vast amounts of data are generated daily by researchers and in healthcare. If this data can be linked up and analysed, new information and insights can be gathered to further our understanding of diseases and help in the development of new treatments. However, combining data from lots of different sources brings technical

challenges (if file formats and terminology are different) as well as legal and ethical challenges (depending on what permissions were asked of people, like patients, behind the data). IMI projects are devising innovative ways of overcoming these challenges in a number of ways.

**Education and training for new and existing R&D scientists and stakeholders:** If Europe is to stay at the forefront of medical research and drug development, it needs a highly-skilled workforce with a broad understanding of the viewpoints of the different stakeholders involved in the process. IMI's education and training projects have now trained large numbers of new and existing professionals from across Europe and from different sectors, giving them the skills and knowledge to advance in their careers.

**Impact on regulatory framework:** Before medicines can be used by patients, they must be approved by regulatory authorities, such as the European Medicines Agency (EMA). Regulatory authorities assess data on the benefits and risks of a new medicine that is gathered during drug development. Many IMI projects are developing innovative tools and methods of assessing the safety and effectiveness of medicines, and are liaising closely with regulatory authorities to be sure that results based on these are accepted as reliable and valid.

**Implementation of project results inside industry:** The ultimate goal of IMI is to make a very practical, concrete difference to the way new medicines are developed, by delivering tools, knowledge and methods to make the process faster and more efficient. With this in mind, the ultimate test of the significance of a project result is whether or not it has been taken up and used by the project partners, particularly those in industry. With the first IMI projects now closing, it is clear that many results have indeed been taken up by project participants.

**Accessibility of resources/outputs beyond consortium:** Many IMI projects have made their outputs available to researchers outside the consortium, thereby increasing their potential impact on drug development. Results include databases, tools, educational materials, glossaries, compound collections, and cell lines.

The following tables set out IMI project outputs per category. Unless stated otherwise, all projects listed are from IMI2.

## New tools/resources for drug discovery & preclinical drug development

| Project title | Description of result(s) |
|---|---|
| AIMS-2-TRIALS autism | Many genes that code proteins regulating protein synthesis at synapses have been linked to neurodevelopmental disorders such as autism spectrum disorder (ASD). This could be a plausible pathophysiological mechanism for these conditions. For example, mutations in TSC1 and TSC2 (tuberous sclerosis complex 1 & 2) cause tuberous sclerosis, a syndrome whose clinical features include ASD. The project found a specific population of mRNAs (messenger ribonucleic acid) coding synaptic proteins that are regulated by mTOR (target of rapamycin complex 1 (mTORC1) signalling at developing excitatory synapses contacting parvalbumine (PV) interneurons. Among these mRNAs, the autism-associated gene neuroligin-3 (Nlg3) is one of the top candidates regulated, thereby linking two significant susceptibility genes of ASD in the same pathway. The finding opens up new opportunities for target discovery in ASD. The research was published in the journal Science. |
| AIMS-2-TRIALS autism | Mutations within the SHANK (SH3 and multiple ankyrin repeat domains 3) genes are causally associated with ASDs. The consortium generated a Shank2-Shank3 double knockout mouse with severe autism-related core symptoms, as well as a broad spectrum of comorbidities. They then exploited this animal model to identify cortical brain areas linked to specific autistic traits by locally deleting Shank2 and Shank3 simultaneously. Screening of 10 cortical subregions revealed that a Shank2/3 deletion within the retrosplenial area severely impairs social memory, a core symptom of ASD. Notably, DREADD (designer receptors exclusively activated by |

| Project title | Description of result(s) |
|---|---|
| | designer drugs)-mediated neuronal activation could rescue the social impairment triggered by Shank2/3 depletion. The results show the utility of the novel animal model for ASD research and reveal potential new targets for the discovery of treatments for ASD. The research was published in Molecular Psychiatry. |
| BIOMAP<br>skin diseases | The project has integrated experimental results with curated functional information from public repositories to uncover molecular characteristics of psoriasis and identify genes and pathways that are consistently dysregulated in the psoriatic lesion as compared to uninvolved skin.<br>This novel approach, integrating large-scale public data with network analysis, provided an insight into known alterations associated with psoriasis by identifying novel genes which can putatively act as disease biomarkers, and opens the door to new analysis possibilities for psoriasis, and other complex diseases. The findings were published in Human Genomics. |
| BIOMAP<br>skin diseases | To contribute towards a better understanding of the genetic factors that modulate the skin-microbiome interactions, the project performed population-based analyses which suggested that host genetic factors related to innate immunity, environmental sensing and cellular functions are associated with human skin microbiota.<br>The results, which were published in Nature Communications, indicate that host genetics play a role in both the response to and pathogenesis of microbes. This could have implications for understanding the causes of skin conditions and the development of personalised treatments. |
| CARE<br>coronaviruses | Two Syrian hamster infection models were selected, and a protocol developed to investigate drug efficacy, i.e. a prophylactic model and a therapeutic model. After intranasal inoculation of SARS-CoV-2 (B1), high viral loads are detected in the lungs within 4 days causing pathological changes resembling bronchopneumonia observed in human patients.<br>In addition, several *in-vitro* assays were established to investigate the mode of action of coronavirus antiviral hits. |
| COMBINE<br>antimicrobial resistance | The standardisation of *in-vivo* pneumonia models is deemed necessary to improve the robustness and reproducibility of preclinical studies and thus translational research.<br>COMBINE published a review of the state of the art on pneumonia models and the summary of an expert workshop that discussed critical parameters of lung infection models. Both were published in Frontiers in Microbiology.<br>Based on the recommendations of the workshop, COMBINE is developing a standard murine lung infection protocol. This protocol will be used to assess the preclinical efficacy of small molecule antibiotics and contribute to determining the reproducibility of results from lab-to-lab using the standard protocol, and so to improve preclinical-to-clinical translation. |
| ConcePTION<br>safety, pregnancy and breastfeeding | The European Breast Milk Collection is being built with standardised procedures for the collection, shipping, storage of breast milk, standard operating procedures (SOPs) for bioanalytics, including stability tests for demonstration drugs in place. Five demonstration projects studying how five different compounds transfer to breast milk are ongoing to provide more information about the strength and feasibility of different methodological approaches. The first study included over 30 breastfeeding participants using levocetirizine/cetirizine (antihistamine for allergies) donating over 300 milk samples. The samples are being analysed and preliminary lessons from this study showed that women are eager to donate breast milk and social media recruitment works well. The European Breast Milk Collection is presented in more detail in this video. |
| ConcePTION<br>safety, pregnancy and breastfeeding | The project has developed and validated two methods for:<br>1) simultaneous quantification of cetirizine, venlafaxine, and its active metabolite *O*-desmethylvenlafaxine in human breast milk, and<br>2) quantification of metformin in human breast milk and human plasma.<br>These methods, which are described in the Journal of Chromatography B, were developed for high-throughput analysis, with simple sample preparation for minimal loss, and sensitive and rapid liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis. |
| EBiSC2<br>stem cells | EBiSC2 supports third-party research projects in reaching sustainability goals via two new publicly available publications sharing protocols on the 'Scalable expansion of iPSC and their derivatives across multiple lineages' and 'Human iPSC-derived hepatocytes in 2D and 3D |

| Project title | Description of result(s) |
|---|---|
| | suspension culture for cryopreservation and in vitro toxicity studies' informing researchers how to tackle these approaches. |
| ENABLE (IMI1) / GNA NOW<br>antimicrobial resistance | NOSO-502 is a novel antibiotic candidate discovered by a French SME, Nosopharm. It is part of the novel odilorhabdins class and shows potential as a treatment for multidrug resistant infections. The early development of NOSO-502 took place under the IMI1 project ENABLE, where it was progressed to lead candidate status. Its further development is supported by IMI2 project GNA-NOW, which successfully completed the toxicology studies on the compound.<br>Nosopharm is now preparing an application to initiate a phase 1 clinical trial. |
| EUbOPEN<br>drug discovery | With the support of the Michael J. Fox Foundation, EUbOPEN launched a Critical Assessment of Computational Hit-finding Experiments (CACHE) challenge – a community benchmarking competition to predict small molecules (hits) that bind to disease-associated protein targets. The first CACHE challenge aims to predict hits for the WDR domain of LRRK2, the most commonly mutated gene in familial Parkinson's disease. The first challenge comprises 25 participants who will predict 100 compounds each to be tested experimentally by EUbOPEN. |
| EUbOPEN & FAIRplus<br>drug discovery / knowledge management | EUbOPEN aims to create a library of ~ 5 000 well characterised chemical compounds binding to 1 000 proteins. The project is fully committed to open science and aims to publish all its generated data.<br>With help from FAIRplus, the project's compound data has been made accessible and interoperable for end users. In addition, by automating the evaluation of EUbOPEN's complex multiplex compound screens, this work saves researchers weeks of time they can now spend on creating even more data. The way the projects achieved this is described in an online use case. |
| Hypo-RESOLVE<br>diabetes | The project discovered a genetically controlled mechanism that regulates the secretion of glucagon in response to hypoglycaemia. The secretion of glucagon stimulates the production of glucose by the liver, which is the first line of defence against hypoglycaemia. Therefore, this newly identified mechanism sheds light on how hypoglycaemia is sensed by our body and how our body responds to it. The research is published in Molecular Metabolism. |
| iConsensus<br>manufacturing technologies | iConsensus has developed new technologies in mammalian-cell based production of biopharmaceuticals which allow better manufacturing control and are tools to potentially reduce the time and costs of the process.<br>For instance, the project has identified a new application of the holographic cell density quantification NORMA 4S integrated with high-throughput micro-bioreactors allowing a full process automation in mammalian-cell based production of biopharmaceuticals. This is a fully automatic cell counter for high throughput cell culture monitoring (www.iprasense.com/norma-4s/#M%C3%A9dia-Norma-4S). |
| iConsensus<br>manufacturing technologies | The project has developed new methods for the quantification of cell culture components useful to monitor the cultivation process for the production of therapeutic proteins, e.g. amino acids and sugars, in mammalian cell culture by capillary electrophoresis, of which the adaptation to micro-chip format in a stand-alone module has been realised.<br>doi.org/10.1002/biot.202100325<br>doi.org/10.1002/elps.202100213<br>doi.org/10.1155/2022/2819855 |
| iConsensus<br>manufacturing technologies | The project has developed generic models to reliably on-line predict the concentrations of the important metabolites, glucose, lactate and glutamine in CHO cell cultures by Raman probe, calibrated with data from various sites in different companies using different Raman probes and spectrophotometers. The models are described in the journal Sensors. |
| Immune-Image<br>imaging | Therapeutic monoclonal antibodies (mAbs) are used in cancer treatment both in targeted therapy and in immunotherapy. mAbs directly elicit their effect on their target or indirectly through mediation by the immune system. The effectiveness of this therapy is, however, patient specific and the therapy can cause serious side effects. Gaining more insight into the mechanisms of mAbs by tracking them inside the body may improve cancer treatment with mAbs. In addition, as one can obtain only a limited number of blood samples and scans per |

| Project title | Description of result(s) |
|---|---|
| | patient, choosing the optimal time points is important. Zirconium-89-immuno-positron emission tomography (89Zr-immuno-PET) has enabled visualisation of zirconium-89 labelled monoclonal antibody (89Zr-mAb) uptake in organs and tumours *in vivo*. Patlak linearisation of 89Zr-immuno-PET quantification data allows for the separation of reversible and irreversible uptake, by combining multiple blood samples and PET images at different days. The project concluded that the inclusion of a blood sample and PET scan at 24h post-injection improves the accuracy and precision of Patlak results for 89Zr-immuno-PET. The results are published in the journal EJNMMI Research. |
| Immune-Image<br>imaging | The project developed a novel nanobody binding to CD8, a protein that is specifically present on T-cells of the immune system. Modern immunotherapies activate T-cells that will attack tumour cells. With an imaging technique like positron emission tomography (PET) or optical imaging (OI), and the nanobody that is labelled with a radionuclide or a fluorescent group, scientists can assess quickly and safely, without painful procedures, if the T-cells in the tumours have been activated by the immunotherapy. |
| IMP2PACT<br>drug delivery | The project has developed an iPSC (induced pluripotent stem cells) spheroid model to investigate BBB (blood-brain barrier) transport function. In this model, the cells are arranged with astrocytes and neurons forming an inner compact core, surrounded by pericytes and an outer dense layer of brain capillary-like endothelial cells (BCECs). This model is more representative of the physiological state than other models and so it will allow robust and relevant investigation of human BBB transport mechanisms. Further work with the spheroid model is required and if this proves successful, it may be adopted by academia and industry as a BBB transport assay method of choice. |
| imSAVAR<br>autoimmune diseases and cancer | The consortium developed a model to predict hepatotoxic side effects of biologicals. In these test experiments, they were able to replace the hepatocyte cell line with primary hepatocytes obtaining a much better mimic of the liver in vivo environment. |
| ITCC-P4<br>paediatrics, cancer | The consortium worked on adding a wider organoid repertoire to the ITCC-P4 platform, further boosting the patient derived xenograft (PDX) model generation on both rarer entities as well as the liquid tumours, enhancing the *in vivo* testing with innovative combination testing (drug-drug and radiotherapy-drug), and developing the sustainability platform.<br>Over 650 patient derived xenograft (PDX) models are now registered in the IT resource R2. Of these, over 250 are fully established spanning all major paediatric tumour types including rare solid and non-solid entities. By the end of 2022, about 350 of these models were submitted for full molecular characterisation. Molecular data for the first 250 models have been loaded on the R2 platform and will be part of a manuscript to be published. Material (viable cryostocks) for about 350 established PDX models reached the contract research organisations (CROs) and SMEs that are in the consortium for *in vivo* testing. Molecular data contributed to the stratification of the PDX models based on their mutational status and emerging molecular vulnerabilities to inform *in vivo* drug testing across the platform. In particular, this proof-of-concept drug testing has been conducted by defining, for each group of models, a panel of single compounds (standard of care n=3; novel targeted therapies, n=6) or combinations (with each other or with chemo- or radiotherapy).<br>Once completed, these models would be available to be used for preclinical drug testing to prioritise the paediatric development of anticancer drugs that would best target paediatric tumour biology. |
| MAD-CoV 2<br>coronaviruses | MAD-CoV 2 investigated the antiviral activity of recombinant soluble human ACE2 (srhACE2) against SARS-CoV 2 as well as the mechanism behind the function of ACE2. The data demonstrate the power and advantage of srhACE2 as an antiviral compound and will benefit awareness within the research community. The data have been published in high ranked journals, e.g. EMBO Molecular Medicine, eLife, Cell Metabolism, and Cell. |
| MAD-CoV 2<br>coronaviruses | The project validated some newly identified host cell interactors of which one - low density lipoprotein receptor-related protein 1 (LRP1) - turned out to have a dual role (helping both virus attachment and RNA synthesis). The findings are documented in a preprint. |
| MAD-CoV 2<br>coronaviruses | The project found that the Omicron variant of SARS-CoV-2 exhibited a striking gain in resistance against the natural antiviral interferon-alpha. The findings, published in PNAS Nexus, increase our knowledge of SARS-CoV-2, both with respect to a novel host cell |

| Project title | Description of result(s) |
|---|---|
| | interactor (LRP1) as a potential therapeutic target, and a hitherto unrecognised gain of function by SARS-CoV-2 variants of concern. |
| MELLODDY<br>machine learning | MELLODDY has successfully demonstrated that collaborating in artificial intelligence (AI) for drug discovery while maintain confidentiality is possible at industrial scale.<br>Their system was trained on unprecedented level of data from 10 pharma companies.<br>• 10 million annotated small molecules<br>• 1 billion assay biological activity labels<br>The resulting models more accurately predict the pharmacological and toxicological activities of molecules to give better information on which candidate drug molecules to make and test.<br>The technology will now be extended to new fields in healthcare to facilitate privacy-preserving collaboration in AI. |
| PD-MitoQUANT<br>Parkinson's disease | The project established a robust αSyn seeding and toxicity models in induced pluripotent stem cells (iPSC) derived dopaminergic (DA) neurons from a patient harbouring an extra copy of the α-synuclein gene. The study, published in Cell Death and Disease, characterised αSyn aggregation in native and seeded conditions and evaluated its associated cellular dysfunctions. Interestingly, calcium dysregulation and a defect in mitochondrial respiratory chain activity were the first pathological signs detectable in early differentiated DA neuronal cultures. These findings offer a cellular platform to investigate mechanisms of PD and validate candidate inhibitors of native and seeded αSyn aggregation. |
| PD-MitoQUANT<br>Parkinson's disease | The project identified and characterised defects in a primary culture model of αSyn seeding and toxicity using midbrain neurons that contain both dopaminergic and non-dopaminergic neurons. In this more complex mixed culture model, defects in dopaminergic (DA) uptake were the earliest signature of αSyn toxicity. The study was published in the journal Cells. These models developed and the outputs obtained will have a significant impact on the drug development process, delivering new platforms for drug development and molecular target identification. Omics work that employed the models developed has also been performed and is currently being analysed and validated. |
| PHAGO<br>Alzheimer's disease | The project established an improved protocol to generate induced pluripotent stem cell (iPSC)-derived microglia, that was filed as patent by the partner Life and Brain (reference PCT/EP2021/056037). The application is related to 'Up-scaled production of microglia-like/-precursor cells and macrophage cells using mesh macrocarriers'. |
| PREMIER<br>environmental issues | Two *in-silico* models have been generated and published in the scientific literature: a fish PBK model (physiologically-based pharmacokinetic model) and the updated European Pharmaceuticals in the Environment (ePiE) model. The fish PBK model serves to predict API uptake, distribution, metabolism and excretion (ADME), and will be integrated into the overall effects-based models as part of WP2. It is described in a paper in Environmental Science and Technology. The updated ePiE model is used to develop a European spatial exposure modelling framework for APIs and transformation products in surface waters, sediments, soils and biota. It is described in a paper in Environmental Research. |
| RealHOPE<br>drug delivery | The stability of the monoclonal antibody Ipilimumab, used for the treatment of different types of cancer, has been investigated. Renowned protein drug stressors - shaking/temperature, light exposure and dilution - were applied on a 30–45-day series of experiments to observe the physicochemical and biological behaviour of the molecule. The results have been published in the European Journal of Pharmaceutics and Biopharmaceutics. This detailed understanding of Ipilimumab's physicochemical properties, integrity, and stability could ensure the best storage and manipulation conditions for its safe and successful application in cancer therapy. |
| RESCEU<br>respiratory disease | Published in The Lancet a systematic analysis of disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus (RSV) in children younger than 5 years in 2019. An important finding from this work was that globally, RSV was responsible for 101 000 deaths in young children in 2019 alone. |
| RespiriTB | The project showed how studies using the strain *Mycobacterium tuberculosis* H37Rv underestimate the antitubercular potency of Janssen's cytochrome BC1 inhibitors, in contrast to clinical isolates that display a much greater sensitivity to these inhibitors. These findings will |

| Project title | Description of result(s) |
|---|---|
| antimicrobial resistance | lead to a better understanding of how, not only a BC1 inhibitor, but inhibitors in general might behave in the clinic. |
| RTCure<br>rheumatoid arthritis | Results from RTCure contributed to advancing our understanding of the mechanisms underlying rheumatoid arthritis (RA). Results published in Nature Communications describe the presence of clonally expanded CD4+ T cells expressing GPR56 in the synovium of patients with rheumatoid arthritis, which could play a role in the development of the disease. These results could potentially lead to new treatment options. |
| TransQST<br>safety | To minimise unexpected toxicities in early phase clinical studies of new drugs, it is vital to understand fundamental similarities and differences between preclinical test species and humans. To this end, the project investigated species differences in hepatic stress response capacity and published the results as a preprint. These findings are likely to inform the selection of appropriate species for the preclinical safety assessment of drug candidates, based on understanding the mechanisms of toxicity and similarity of animal models to humans. |
| TRISTAN<br>safety | Positron emission tomography (PET) allows the dynamic acquisition of information about the distribution and concentration of drugs in the body, but its application for peptides with long half-lives is limited by the typically used short-lived radionuclides. Alternatives such as Zirconium-89 (89Zr) emerge as candidates for biodistribution studies of long-circulating biomolecules with therapeutic applications in diabetes and obesity.<br>A comparison study was carried out between the biodistribution profiles obtained via 89Zr-PET and the current standard, quantitative whole-body autoradiography (QWBA), which will be valuable for the development of novel peptide drugs. The results were published as part of the ACS Pharmacology & Translational Science virtual special issue 'New Drug Modalities in Medicinal Chemistry, Pharmacology, and Translational Science'. |
| VAC2VAC<br>vaccines | The development and validation of a new and reliable antibody-free targeted liquid chromatography with tandem mass spectrometry (LC-MS/MS) method that is able to identify and quantify the amount of Tetanus neurotoxin (TeNT) present in the bacterial medium during the different production time points up to the harvesting of the TeNT, just before further upstream purification and detoxification is completed. This is important as ensuring the consistency of tetanus neurotoxin (TeNT) production by *Clostridium tetani* could help to ensure consistent product quality in tetanus vaccine manufacturing, ultimately contributing to reduced animal testing. VAC2VAC identified RNA signatures related to consistent TeNT production using standard and non-standard culture conditions. Their findings are published in the journal Toxins. |
| VSV EBOPLUS<br>Ebola and related diseases | VSV EVBOPLUS deciphered the immune and molecular signatures of adult and paediatric responses elicited by the Ervebo® vaccine. This is the first vaccine approved for prevention of Ebola virus disease. The project has improved the computational tool BioFeatS, designed to robustly select the best features in different types of data, especially for large quantities of data from omics and biological datasets, in particular it is used to integrate transcriptomic and reactogenicity data. This tool by itself may be broadly utilised by thousands of laboratories that have to analyse high-throughput datasets. |

## Biomarkers and tools developed to predict clinical outcomes (efficacy and safety)

| Project title | Description of result(s) |
|---|---|
| AB-DIRECT<br>antimicrobial resistance | Built two mathematical models to describe the effects of the novel antibacterial agent gepotidacin over time *in vitro* on bacteria *Escherichia coli* and *Neisseria gonorrhoeae*. The models could play a valuable role in estimating the dosage regimens needed to eradicate these bacteria. |
| AIMS-2-Trials<br>autism | Alterations in γ-aminobutyric acid (GABA)–related pathways have been shown to occur in patients with autism spectrum disorder (ASD). However, the role of GABA signalling modulation on sensory processing remains unclear. The consortium found that visual processing, altered in patients with ASD, could be restored, promoting GABAB receptor activation using arbaclofen and that the drug had different effects in people with ASD versus control 'neurotypical' people. In neurotypicals, sensitivity to visual stimuli was disrupted by 30 mg of arbaclofen, whereas in ASD, it was made more 'typical' and visual processing differences were abolished. Hence, differences in GABAergic function are fundamental to autistic (visual) sensory neurobiology and are modulated by GABAB activity. The results are published in Science Translational Medicine. The consortium is currently running a clinical trial with arbaclofen to study sustained effects on autism related biomarkers (N170) and on measures related to clinical outcomes (VABS-II- ABC) to support the regulatory qualification of both. |
| AIMS-2-TRIALS<br>autism | A longitudinal follow-up study of 483 individuals (204 with ASD and 279 neurotypical individuals, ages 6–30 years), with assessment time points separated by 12–24 months, showed that variation in clinical (adaptive) outcome is associated with both group- and individual-level variation in anatomy of brain regions enriched for genes relevant to ASD. The results, published in the American Journal of Psychiatry, show the possibility to detect neurobiological correlates of changes in adaptive behaviour in autism, linking clinical outcomes to a potential new biomarker. |
| AIMS-2-TRIALS<br>autism | The project studied whether the electrophysiological (EEG) biomarker speed of early-stage face processing (N170 latency) could be used for stratification according to social functioning in a large heterogeneous population of 436 individuals with ASD and controls tested in the multisite European longitudinal study (the Longitudinal European Autism Project, LEAP). Among participants with autism, N170 latency values stratified patients according to socialisation prognosis and improved power in a simulated clinical trial. The results suggest that including N170 evaluation in clinical stratification might help the design and development of patient-specific therapies for autism, and N170 could be useful as a stratification factor to identify biologically and prognostically defined subgroups in ASD. The results are published in Science Translational Medicine. The project is working with the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) towards qualification of N170 as stratification biomarker in autism trials. |
| APPROACH (IMI1)<br>osteoarthritis | Three osteoarthritis (OA) patient endotypes have been identified (low tissue turnover, structural damage, and systemic inflammation) based on baseline biomarker data from APPROACH. The findings are published in the Annals of the Rheumatic Diseases. It is anticipated that, post-project, additional groupings will be characterised during subsequent analysis as more parameters and longitudinal data are included. It is expected that these and future groupings will be utilised clinically to improve therapeutic trials. |
| CARE<br>coronaviruses | The project identified a 'core gene signature' of COVID-19 convalescence (up to 6 months post-infection) associated with a history of thrombotic events, with upregulation of a set of genes involved in neutrophil activation, haematopoiesis, platelet activation, and blood coagulation. This raises the question of the maintenance of prevention measures to avoid thromboembolisms events. Publication In revision in Journal of Clinical Immunology. |
| eTRANSAFE<br>safety | To date, no biomarkers of liver toxicity have been regulatory accepted. eTRANSAFE have designed and implemented a pipeline that uses clinical and preclinical information to explore possible biomarkers. This pipeline uses a series of liver pathology endpoints such as mitosis, single-cell necrosis, haematopoiesis, hypertrophy, hyperplasia, vacuolation and fibrosis and suggests genes that might serve as indicators of the pathological outcome and also inform the mechanisms underlying the adversity. |

| Project title | Description of result(s) |
|---|---|
| eTRANSAFE<br>safety | The eTRANSAFE consortium have developed software that provides an easy-to-use, intuitive user interface for translational safety assessment. The tool is described in the journal Chemical Research in Toxicology. This software can be applied to combine different sources of evidence to obtain a single outcome or conclusion in a translational safety assessment workflow. |
| eTRANSAFE<br>safety | Replacing control animals with data already collected from historical controls has the potential to significantly reduce the number of animals used in *in vivo* toxicity studies.<br>Earlier in the project, eTRANSAFE launched a Virtual Control Group initiative to leverage their database of >5 million data points from historical rat studies and developed tools for data analysis & visualisation.<br>In 2022, approaches to US and European regulators were made to discuss the qualification of the methodology |
| Hypo-RESOLVE<br>diabetes | A mobile phone application, the Hypo-METRICS (Hypoglycaemia—MEasurement, ThResholds and ImpaCtS) app was developed to determine the impact of hypoglycaemia on the daily functioning of diabetes patients. The Hypo-METRICS App was designed through collaboration between psychologists, diabetologists and people with diabetes and may be used as a key outcome in clinical trials evaluating new medications or new technology for diabetes. It may also be used in clinical settings for optimising the care and outcomes for individuals with diabetes. The app is described in the journal BMJ Open. |
| IDEA-FAST<br>digital health | During the IDEA-FAST feasibility study, participants had the option to donate biological samples (blood, urine and stool) to be stored in the IDEA-FAST biobank. Approximately 25% of the participants agreed to donate one or more types of biological sample as part of the study. These samples will continue to be collected during the clinical observational study and will be invaluable for further research into understanding the pathobiology of fatigue and sleep disturbances. |
| IMI-PainCare<br>pain | Published a systematic literature search in the International Journal of Molecular Sciences on pharmacological probes that allow for the validation of functional biomarkers to assess drug-induced effects on nociceptive processing at peripheral, spinal and supraspinal levels using electrophysiological and functional neuroimaging techniques. |
| ImmUniverse<br>autoimmune diseases | Published a position paper in Frontiers in Immunology highlighting the current unmet need for treatments for immune mediated inflammatory diseases. The paper explains how the comprehensive, systems biology-oriented approach employed in ImmUniverse will allow for the identification and validation of tissue and circulating biomarker signatures as well as mechanistic principles. This will provide information about disease severity and future disease progression. |
| imSAVAR<br>autoimmune diseases, cancer | The consortium developed an immune related adverse outcome pathway (irAOP) for CAR-T mediated cytokine release syndrome and assigned cellular key events leading to these immune related adverse events (irAE). To identify molecular biomarkers which can be integrated into improved nonclinical test systems, samples and data sets from 73 patients undergoing CAR-T therapy were collected so far. |
| KRONO<br>coronaviruses | KRONO has developed and validated singleplex assays that use frozen reagent to directly detect SARS CoV-2 from nasal swab eluate and saliva. At the beginning of the project the reagent and method had only been used for blood and this project has delivered a new enzyme mutant (including SOPs for producing it at scale) and a completely new reagent set. This was subsequently taken to full lyophilisation of the reagent, including development of production methods and SOPs which would allow up to 200 000 tests per week delivered. This then supports the pipeline approach for being able to rapidly deploy new assays at scale in response to future outbreaks. |
| KRONO<br>coronaviruses | KRONO has developed, completely from scratch, a new portable instrument capable of detecting COVID-19 in human directly from crude nasal swab eluates in under 45 minutes. The reaction vessel, electronics, heating system, optics, electronics, firmware and software have all been developed during the course of this project. |

| Project title | Description of result(s) |
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| LITMUS<br>liver disease | The project published new data on several potential biomarkers for diagnosing NASH and advanced liver fibrosis using samples from the LITMUS metacohort. The initial data has been published on the proteins TSP2, GDF15 and AKR1B10 (in the journals Hepatology and Science Translational Medicine) and miR34a (in JHEP Reports). |
| PD-MitoQUANT<br>Parkinson's disease | The project identified mitochondrial dysfunction and target drug candidates through the analysis of substantial data generated from functional studies using innovative tools in the fields of bioinformatics, statistical analyses, systems biology, and machine learning. Such tools have the potential to reduce the time required for drug development significantly, and can be applied to other neurodegenerative disorders and metabolic disorders. The research is published in Cell Physiology. |
| RADAR-AD<br>Alzheimer's disease | Published a research article in the Journal of Alzheimer's disease showing that subjective cognitive decline (SCD) may indicate a transitional preclinical stage of Alzheimer's disease (AD) with network changes and brain connectome interruptions. This is the first ever reported study investigating brain connectivity by using the high density-electroencephalography technique in order to explore network changes in subjective cognitive decline in participants while performing visual attention and short-term memory tasks. |
| RESCEU<br>respiratory disease | Showed in a study published in the Journal of Infectious Diseases that seasonal monoclonal antibody (mAb) programmes as a respiratory syncytial virus (RSV) disease prevention strategy are cost-effective over year-round programmes in Norway. As the timing and duration of the cost-effective seasonal programme are sensitive to the pattern of the RSV season in a country, the need to gather RSV surveillance data is essential. |
| RHAPSODY<br>diabetes | In a combined effort, including four cohorts from five countries and combining outputs from four IMI projects (SUMMIT, DIRECT, RHAPSODY and BEAt-DKD), data on 7 000 individuals was studied to quantify liver fat content and body fat mass and distribution. The analysis showed that elevated circulating follistatin is associated with an increased risk of type 2 diabetes, and could be targeted to develop therapies to prevent type 2 diabetes. The research is published in Nature Communications. |
| RHAPSODY<br>diabetes | The consortium identified and studied 25 candidate genes believed to play a role in the development of insulin resistance and/or type 2 diabetes. The genes were analysed using samples from the Servier biocollection. Results from this study indicate that some of the genes believed to play a role in the development of insulin resistance are coregulated in a tissue-specific manner.<br>The results will be combined with additional expression data and published. |
| RHAPSODY<br>diabetes | There is substantial heterogeneity in people with type 2 diabetes (T2D) in terms of disease progression. Prediction algorithms to predict those at high risk of fast disease progression are currently lacking. The RHAPSODY consortium showed that models including clinical risk factors and biomarkers perform reasonably well to predict the time to when treatment with insulin will be required. |
| RHAPSODY<br>diabetes | Gaining insight into progression of T2D following bariatric surgery will enable a more stratified approach to the management of T2D by identifying subgroups who may require different management depending on their likelihood of diabetes progression.<br>In the first ever study to examine longitudinal HbA1c patterns in a bariatric surgery population with T2D, the RHAPSODY consortium showed that longer exposure to hyperglycaemia before surgery, change in HbA1c and insulin-sensitivity in the 1st year after surgery all play a major role in late glycaemic deterioration of T2D patients.<br>This work supports a stratified approach to diabetes management after bariatric surgery, suggesting that people with lower diabetes duration, lower reduction in HbA1c but higher increase in insulin sensitivity between baseline and 1-year will have minimal progression and, therefore, require less invasive glycaemic monitoring and intervention. The research is published in The Lancet Diabetes and Endocrinology. |
| RHAPSODY<br>diabetes | The consortium has studied the 'cost of additional treatment guided by a biomarker' versus 'change in QALY' for 24 of the diabetes biomarkers studies in the project. For example, the |

| Project title | Description of result(s) |
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| | benefit of the additional treatment guided by biomarker ENPP7 and costing up to £103 per year would outweigh the cost. |
| T2EVOLVE<br>advanced therapies, cancer | A key ambition in T2EVOLVE is to assess the currently available preclinical models for evaluating safety and efficacy of engineered T cell therapy and developing new models with higher predictive value for clinical safety and efficacy.<br>T2EVOLVE published two reviews on the gaps and limitations in the current landscape of models and tools to better identify the needs. Both reviews are published in the Journal for ImmunoTherapy of Cancer and are entitled Time to evolve: predicting engineered T cell-associated toxicity with next generation models and Time 2EVOLVE: predicting efficacy of engineered T-cells – how far is the bench from the bedside? |
| TransBioLine<br>safety | The project has established a pipeline (miND pipeline) to facilitate microRNA biomarker discovery studies. The miND pipeline aims to streamline the bioinformatics processing of small RNA next-generation sequencing data by standardising the processing from raw data to a final, comprehensive, and reproducible report. The pipeline is described in the journal F1000Research.<br>Meanwhile the raw data from the clinical samples that were used for establishing the miND pipeline for microRNA biomarker discovery studies, are uploaded and available at the Gene Expression Omnibus public repository. |
| TransQST<br>safety | Renal toxicity is one of the major causes of drug attrition, yet no translational model for drug-induced kidney injury (DIKI) had been developed to date. The TransQST team developed a prototype of a kidney quantitative systems toxicology (QST) model based on the newly generated dose-response and time-course toxicity data from cisplatin in rats. The model can predict the degrees of lesions on renal proximal tubules associated to serum and urinary injury biomarkers in rats while these findings can also be translated to humans by applying species-specific physiological parameters. Potential applications of the kidney QST model include study design support (e.g. dose selection and prediction of recovery time) and renal injury biomarker monitoring in human patients. The model has been made available through the BioModels repository. |
| TransQST<br>safety | A novel cardiovascular systems (CVS) model was developed based on pressure-volume loop theory using atenolol as proof-of-concept drug. Both systems- and drug-specific parameters of this CVS-contractility (CTR) model could be identified without cardiac output (CO) data. Hence, the absence of CO data does not limit the application of this model to data from other species. It is expected that the incorporation of pressure-volume loop theory will provide the mechanistic basis to apply the developed CVS-CTR model for inter-species scaling. It has the potential to be integrated into a translational modelling platform to support CVS safety evaluations. The research is published in CPT: Pharmacometrics & Systems Pharmacology. |
| VALUE Dx<br>antimicrobial resistance, diagnostics. | The project is developing a novel method for *S. pneumoniae* serotyping, involving amplicon sequencing with second- and third-generation sequencing technology. This method would make it possible to study the penicillin-binding proteins of this organism in order to predict potential non-susceptibility to beta-lactam antibiotics. This novel technique, in combination with 16S rRNA gene sequencing would make it possible to further characterise the oro- and nasopharyngeal microbiome of patients enrolled in the clinical studies.<br>Another technique currently undergoing evaluation is a highly multiplexed quantitative RT-PCR with capability to target more than 20 viral and bacterial pathogens. The use of this assay in combination with the metagenomic approach would make it possible to elucidate the patients' aetiology.<br>VALUE Dx is also validating a high-throughput multiplex assay for the measurement of cytokines, chemokines and growth factors performed using the meso scale discovery platform, starting with the selection of the most relevant and promising biomarkers based on the previous studies in patients infected with different pathogens (various strains of SARS-CoV-2, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, etc.). |
| VHFMODRAD<br>Ebola and related diseases | VHFMODRAD developed an optimised Crimean Congo Haemorrhagic Fever Virus (CCHFV) human immunoglobulin G (IgG) serological assay without using clinical positive samples (for bio-hazard reasons), an artificial positive control was created from immunised rabbit serum. |

| Project title | Description of result(s) |
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| VSV EBOPLUS<br>Ebola and related diseases | Molecular signatures induced by rVSV-ZEBOV vaccination were analysed in adult cohorts in Europe, Africa and North America as reported in The Lancet Microbe. These signatures will aid in the rational development, testing, and evaluation of novel vaccines and will allow evaluation of the effect on responses to vaccines of host factors such as age, co-infection, and comorbidity. |

## Improved protocols for clinical trial design and processes

| Project title | Description of result(s) |
|---|---|
| AB-DIRECT<br>antimicrobial resistance | Improved the protocol for measurement of gepotidacin concentrations in human tissue by microdialysis. The process was optimised by reducing probe flow rates as much as possible. The efficiency of the new procedure was confirmed by complementary experiments in rats. Microdialysis is the only *in vivo* sampling technique that can continuously monitor drug concentrations in the extracellular fluid.<br>The project also continued the recruitment of patients for a phase 1 human clinical study to investigate the tissue distribution of the novel antibiotic gepotidacin, with 32 of 60 patients recruited so far.<br>This study involves an ex-vivo (outside a living organism) microdialysis procedure, using tissues removed during tonsillectomy and prostatectomy surgery. ClinicalTrials.gov Identifier: NCT04484740. |
| AMYPAD<br>Alzheimer's disease | Published a state-of-the-art review in the European Journal of Nuclear Medicine and Molecular Imaging covering the tools and measures available for amyloid positron emission tomography (PET) quantification used for detecting brain changes in Alzheimer's disease (AD) pathogenesis. |
| AMYPAD<br>Alzheimer's disease | Identified three spatial-temporal trajectories of amyloid accumulation, referred to as frontal, parietal, and occipital. These subtypes are distinctly associated with Alzheimer's Disease risk factors and concomitant vascular burden. These results, published in Brain Communications, further support trial stratification. |
| c4c<br>paediatrics, clinical trials | The Strategic Feasibility Advice process was further tested with an increased number of advice requests received from industry and academic c4c partners (covering any clinical, methodology and patient and public involvement aspects of paediatric drug development).<br>In total since this process became operational, 40 advice requests have been received of which 26 have been completed. A couple of these experts' advices have been used by sponsors when discussing their paediatric investigation plan with the Paediatric Committee at the European Medicines Agency (EMA).<br>The database was expanded in 2022 and include more than 400 clinical and methodological paediatric experts and 135 patients, parents and Young Person's Advisory Group experts. These experts are divided into 24 expert groups based on paediatric subspecialties and medical-scientific expertise and one public and patient involvement (PPI) expert group. |
| c4c<br>paediatrics, clinical trials | The c4c expert groups developed two white papers published in the British Journal of Clinical Pharmacology addressing important aspects of the paediatric drug development: use of omics in paediatric drug development and pharmacokinetics extrapolation and optimisation of study protocols for small molecules and monoclonal antibodies in children. |
| c4c<br>paediatrics, clinical trials | Held the second multistakeholder meeting on atopic dermatitis involving regulatory agencies, academic experts, clinicians, paediatricians and industry representatives and aiming to discuss scientific and/or regulatory challenges encountered in the field of paediatric atopic dermatitis and to agree on a new development path. A publication on the meeting content and the proposed strategy is in preparation. |

| Project title | Description of result(s) |
|---|---|
| CARE<br>coronaviruses | Improvement of developed working instructions for the conduct of phase 1 and 2 drug trials in acute COVID-19. These documents enable the consortium partners to rapidly set up a clinical trial in a situation where compounds need to be assessed with minimum organisational delay. |
| EBOVAC3<br>Ebola and related diseases | The project produced theoretical and practical demonstrations of biases in the conventional test negative design under outbreak and pandemic conditions (i.e. when testing is an active response element). Identified modifications to data collection to remedy the issue (i.e. capture the reason for conducting the test), and proposed a new hybrid design combining test-negative and cohort studies. Published in the International Journal of Epidemiology. |
| EU-PEARL<br>clinical trial design | Finalised interim reports on the master protocols and regulatory requirements for the four disease areas that EU-PEARL disease-specific work packages are focusing on, namely major depressive disorder (MDD), tuberculosis (TB), liver disease non-alcoholic steatohepatitis (NASH), and neurofibromatosis (NF). |
| H2O<br>digital health | A feasibility study protocol was developed by the project to assess and compile recommendations for sustainable growth of health outcomes observatories and create guidelines for the implementation process for data collection and storage of core outcome sets. |
| Hypo-RESOLVE<br>diabetes | Glucose levels and hypoglycaemia can be recorded by a sensor called a continuous glucose monitoring (CGM) device, but the actual symptoms of hypoglycaemia vary between and within patients with diabetes. The protocol of the multicentre clinical study Hypo-METRICS (Hypoglycaemia—MEasurement, ThResholds and ImpaCtS) is designed to define the threshold and duration of sensor (CGM) glucose that provides the optimal sensitivity and specificity for events that people living with diabetes experience as hypoglycaemia. The study will improve our understanding of the clinical, psychological and health economic impacts of both symptomatic and asymptomatic hypoglycaemia in diabetes patients. The protocol of the Hypo-METRICS study was published in the journal Diabetic Medicine. |
| IDEA-FAST<br>digital health | Despite the COVID pandemic, the IDEA-FAST feasibility study was successfully concluded. This study used several wearables and other devices and aimed to identify candidate digital parameters of fatigue and sleep disturbances to be further tested in a larger study. The study was performed across four centres in six different disease populations: Parkinson`s disease, rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, inflammatory bowel disease, and Huntington's disease. A total of 146 participants were recruited, including 42 healthy controls. The results were used to develop the protocol for the larger clinical observational study considering also input from the European Medicines Agency.<br>As part of the IDEA-FAST feasibility study, a polysomnography sub-study was conducted in order to identify the most suitable devices for sleep assessment. 28 participants were observed over 2 nights using the following digital devices:<br>• Dreem head band (measures brain activity head movements during sleep);<br>• VTT bed sensor (measures movements and breathing rate);<br>• Everion (measures heart rate, heart rate variability, inter-beat-interval, blood pulse wave, blood oxygen levels, skin temperature, skin blood perfusion, respiration rate, sweat and energy expenditure);<br>• Axivity (contains a 3D accelerometer and a temperature sensor);<br>• McRoberts (a movement sensor worn on the lower back);<br>• Byteflies devices (measure brain activity (EEG) and electrical activity of the heart (ECG)).<br>As with the main feasibility study, the results were used to develop the protocol for the larger clinical observational study (COS) including input received from the European Medicines Agency. |
| IDEA-FAST<br>digital health | IDEA-FAST is investigating whether digital solutions based on mobile or wearable technology could better quantify fatigue and sleep disturbances.<br>In 2022, the project's main clinical observation study started. The study involves 15 clinical sites across Europe that will recruit 2000 participants with rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, Crohn's disease, ulcerative colitis, Parkinson's Disease, and Huntington's disease.<br>Registration: drks.de/search/en/trial/DRKS00027946<br>Patient information: idea-fast.eu/patient-information/ |

| Project title | Description of result(s) |
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| IMI-PainCare<br>pain | Published in Trials the protocol for a randomised, double-blind, placebo-controlled, crossover, multi-centre trial in healthy subjects to investigate the effects of lacosamide, pregabalin, and tapentadol on biomarkers of pain processing observed by peripheral nerve excitability testing (NET). |
| IMI-PainCare<br>pain | Published in Trials the protocol for a randomised, double-blind, placebo-controlled, crossover, multicentre trial in healthy subjects to investigate the effects of lacosamide, pregabalin, and tapentadol on biomarkers of pain processing observed by non-invasive neurophysiological measurements of human spinal cord and brainstem activity. |
| IMI-PainCare<br>pain | Published a systematic literature review in the Journal of Pain assessing the use of patient reported outcome measures (PROMs) in chronic neuropathic pain. The results show that there is still a high degree of heterogeneity, highlighting the need for a standardised core set of outcome domains and PROMs to improve comparability of clinical trials and neuropathic pain treatment. |
| MACUSTAR<br>eye disease | Showed that chart-based assessments of visual function (VF) can be used as potential measures for clinical trial end points for age-related macular degeneration. Standard operating procedures for visual function testing developed within MACUSTAR are also freely available in this open access article as supplementary information. |
| Mobilise-D<br>digital health | Published in PLoS ONE the protocol of the clinical validation study (CVS) to demonstrate the clinical validity of measuring digital mobility outcomes in the real world. The four disease cohorts studied within Mobilise-D CVS are Parkinson's disease (PD), multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD) and proximal femur fracture (PFF).<br>Through this study, the project will provide the first-ever systematic approach to mobility determination that is standardised, codified, and freely available to industry, extending patient measurement systems that have utility across all aspects of patient care, from research through intervention development to routine large scale patient care. It provides a model for future studies in the field of digital health assessment. |
| PERISCOPE<br>vaccines | An outpatient controlled human infection study was initiated to confirm results obtained previously in in-patient studies and evaluate risk of asymptomatic transmission to household contacts. |
| PharmaLedger<br>blockchain | PharmaLedger released their eConsent for remote clinical trials module. This module uses a transparent blockchain-based platform that can connect all stakeholders in the clinical trial ecosystem and also allows patients to better control and manage who can access their personal data. The project's use case on electronic consent is presented in this video. |
| PRISM 2<br>neurological disorders | The PRISM 2 clinical study protocol that will make it possible to validate and extend the novel digital and neurobiological biomarkers for social dysfunction across schizophrenia, Alzheimer's disease, and major depressive disorder patients, was finalised. Following the local institutional review board (IRB) approval received in the spring of 2022, 4 sites were issued the green light to begin recruitment. In 2022, a total of 54 patients were recruited. |
| PROTECT-Trial<br>cancer | PROTECT-trial aims to compare the clinical outcomes of proton therapy and state-of-the-art photon radiotherapy for locally advanced oesophageal cancer, with the goal of improving outcomes for this group of patients.<br>The consortium published in Radiotherapy & Oncology a study on "Treatment planning comparison in the PROTECT-trial randomising proton versus photon beam therapy in oesophageal cancer: Results from eight European centres". The study aimed to compare treatments across eight European centres to ensure consistency in the project's phase-III trial<br>The main findings were:<br>• All centres met the first priority constraints for the nominal treatment plans.<br>• There is large variability in dose to organs at risk (OAR) between 8 centres.<br>• Robustness of treatment plans towards anatomical changes is also variable.<br>The conclusion is that very strict quality assurance (QA) guidelines will be needed for the PROTECT-trial. |

| Project title | Description of result(s) |
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| PROTECT-Trial<br>cancer | In 2022, the PROTECT-Trial consortium received regulatory approval and recruited their first patients for their pan-European PROton versus photon Therapy for Esophageal Cancer –study (PROTECT), which aims to compare the clinical outcomes of proton therapy and state-of-the-art photon radiotherapy for locally advanced oesophageal cancer. |
| Trials@Home<br>digital health | In March 2022, the Trials@Home consortium used the new Clinical Trials Information System (CTIS) to submit the protocol for the project's RADIAL study. This study is a multi-country, parallel-group, open-label, multi-centre study that investigates the feasibility of running decentralised clinical trials in 6 European countries. Approvals for all countries (Germany, Poland, Italy, Spain, Denmark and, separately, UK) were received by the end of 2022 and the study will begin in 2023. EUCTEUCT number 2022-500449-26-00. |
| TRIC-TB<br>antimicrobial resistance | Successful completion of Phase I clinical trials with BVL-GSK098, the analysis of preliminary, blinded data from the first time in human studies show a favourable safety, tolerability and pharmacokinetic profile of BVL-GSK098 at therapeutically effective doses in healthy volunteers. The positive result has enabled TRIC-TB to transition to a Phase IIa clinical study in patients with pulmonary TB to test the Early Bactericidal Activity (EBA), safety, tolerability and pharmacokinetics of ethionamide (Eto) alone and in combination with BVL-GSK098. This Phase 2 study is supported by the European & Developing Countries Clinical Trials Partnership (ECDPT2). |
| UNITE4TB<br>antimicrobial resistance | The setting-up of the innovative adaptive phase 2 clinical trial has started with the development of a clinical trial master protocol for phase 2B/C. Overall trial design, compounds and combinations to be included in the first wave of the phase 2B/C trial have been identified. |

## Biomarkers for the efficacy and safety of vaccine candidates

| Project title | Description of result(s) |
|---|---|
| FLUCOP (IMI1)<br>vaccines | Current vaccination strategies against influenza focus on generating an antibody response against the viral haemagglutination surface protein, however there is increasing interest in neuraminidase (NA) as a target for vaccine development. A critical tool for development of vaccines that target NA or include an NA component is validated serology assays for quantifying anti-NA antibodies. Additionally, serology assays have a critical role in defining correlates of protection in vaccine development and licensure. Standardisation of these assays is important for consistent and accurate results. FLUCOP validated a harmonised enzyme-linked lectin assay (ELLA)- neuraminidase inhibition (NI) standard operating procedure for N1 influenza antigen and demonstrated the assay was precise, linear, specific and robust within classical acceptance criteria for neutralization assays for vaccine testing. The results are published in Frontiers in Immunology. |
| PERISCOPE<br>vaccines | An assay to measure cellular responses to pertussis in whole blood was qualified in readiness for deployment in three infant pertussis vaccination studies. Nasal sampling was established as a non-invasive mucosal sampling method and this diagnostic specimen was assessed for use in various quantitative and functional antibody assays to measure immunity to pertussis. This enables large-scale and repeated immune monitoring of vaccines in populations normally difficult to sample, including infants. |
| PERISCOPE<br>vaccines | Within the PERISCOPE project, a biomarker discovery platform has been established to investigate the immune response to pertussis, with a clear focus on clinical development. In total, 14 novel immunological assays have been developed, either for use in central laboratories for centrally stored samples, or for local use at the clinical sites for samples that needed to be analysed freshly. These assays were designed to measure crucial aspects of immunity to pertussis, including quantification of serum and mucosal antibodies and their functional properties (bactericidal activity, complement deposition, inhibition of bacterial adherence to epithelial cells, pertussis toxin neutralization, etc), as well as cellular immune responses to pertussis in blood, focusing on antigen-specific T- and B-cells. In the final year of PERISCOPE, biomarker assays |

| Project title | Description of result(s) |
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| | were applied to clinical samples obtained from the maternal-infant vaccination studies, as well as the BERT, Immfact and the Phase B challenge studies. |
| VSV EBOPLUS<br>Ebola and related diseases | The project identified and cross-validated immune-related transcriptomic signatures induced by rVSVΔG-ZEBOV-GP vaccination in four cohorts of adult participants from different genetic and geographical backgrounds. These signatures will aid in the rational development, testing, and evaluation of novel vaccines and will allow evaluation of the effect of host factors such as age, co-infection, and comorbidity on responses to vaccines. The research is published in The Lancet Microbe. |

## New taxonomies of diseases and new stratifications of patient sub-populations

| Project title | Description of result(s) |
|---|---|
| LITMUS<br>liver disease | LITMUS has utilised (1) liver transcriptomic analysis with circulating proteomic analysis, and (2) genetic analysis through polygenic risk scores to identify potential novel disease subtypes that go beyond the simplistic routine stratifiers currently used in clinical practice. These continue to be studied for further validation within LITMUS and through external collaborations, but offer potentially important insights into disease heterogeneity that have implications both for routine clinical care and addressing variation in patient outcomes within clinical trials, and also metabolomic profiling to identify disease subtypes and patterns of progression. |
| LITMUS<br>liver disease | The LITMUS project has created a European NAFLD Registry and associated sample biobank. It includes 13 483 event records across 8,984 individual patients and is supplemented by extra data & samples from 1 878 patients from EFPIA partners.<br>These well-characterised patient cohorts can be used to develop better biomarkers and novel therapies. |
| LITMUS<br>liver disease | Identification of hepatocyte ballooning underpins regulatory approval for non-alcoholic steatohepatitis (NASH) medications. LITMUS researchers have shown that ballooning is too subjective for its presence or complete absence to be unequivocally determined by pathologists as a trial endpoint. In an article in the Journal of Hepatology, they propose AI-based approaches as a more reliable way to assess the range of injury recorded as hepatocyte ballooning. |
| SOPHIA<br>obesity | Federated database of observational studies and clinical trial cohorts set up, including the necessary computational infrastructure (database and tools) at each local site. 14 clinical cohorts aligned to a standard data model (OMOP common data model) have become accessible for statistical analysis through the system, representing around 63 000 patients. The federated database contains over 60 000 mapped clinical variables covering demographics, laboratory measurements, observational (e.g. questionnaire) data and medications. |
| VITAL<br>vaccines | VITAL has enriched their biobank, which can be used for current and future studies of immunological mechanisms of vaccine responses. This can be used to support system vaccinology approaches and identification of correlates of protection. Current data linked to the dataset are data from cell subsets present at baseline and changing upon vaccination after influenza vaccination as well as after pneumococcal vaccination. VITAL novel hierarchical cluster analyses can help to enhance stratification (in addition to age) of the population and may contribute to biomarker profiles to be used to predict vaccine response in specific populations. Inflammageing profiles have been generated which showed different patterns for specific markers and will further add to these stratifications. |
| VITAL<br>vaccines | Development of a static disease model, VITALO, that evaluates the total infection disease burden under the different aspects of demography, age-groups, sex, multidimensional poverty index, infection rates, and healthcare offering. Impact of vaccination against respiratory diseases has been assessed expressed in cost-effectiveness evaluation. |

## Development and use of cohorts, registries and clinical networks for clinical studies and trials

| Project title | Description of result(s) |
|---|---|
| AIMS-2-TRIALS<br>autism | Phelan-McDermid Syndrome (PMS, also known as 22q13 deletion syndrome) and neurexin 1 (NRXN1) deletions (NRXN1ds) are two synaptopathies associated with autism spectrum disorder (ASD). However, large heterogeneity exists between the conditions which need better understanding. The consortium published in Frontiers in Neuroscience the study design and methodology of the Synaptic Gene (SynaG) study which comprehensively assesses these two syndromic forms of ASD including information on the necessary adaptations made during the global COVID-19 pandemic. The paper describes the demographics of the data collected thus far, including 25 PMS, 36 NRXN1ds, 33 idiopathic autism (iASD), and 52 neurotypical development (NTD) participants, and presents an interim analysis of autistic features and adaptive functioning. The publication is a very important resource for progressing the development of treatments for these two rare forms of ASD. |
| AIMS-2-TRIALS<br>autism | The project published in Frontiers in Psychiatry the study protocol of the phase 2 randomised, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of arbaclofen administered for the treatment of social function in children and adolescents with autism spectrum disorders: (AIMS-2-TRIALS-CT1). AIMS-CT1 is an international, multi-site, double-blind, parallel group Phase II randomised clinical trial in males and females aged 5:0–17:11 years, with a diagnosis of ASD and fluent speech, The primary outcome is the effect on social function from weeks 0 to 16 measured on the socialisation domain of the Vineland Adaptive Behaviour Scales, 3rd edition. Genetic and electrophysiological markers (e.g. N170) are examined as potential stratifiers for treatment response. Exploratory novel digital technologies are also used to measure change, examining simultaneously the validity of digital biomarkers in natural environments. The trial has now completed successfully enrolment at all seven sites for a total of 124 participants. Though the teams do not know yet which participants have taken arbaclofen and which have taken the placebo, all of the reported side effects have been mild. The initial results of the trial are expected to be ready for Spring 2023. The study protocol is very closely aligned with a parallel Canadian trial of 90 participants (ARBA Study, US NCT number: NCT03887676) to allow for secondary combined analyses. |
| AIMS-2-TRIALS<br>autism | There is still no approved medication for the core symptoms of autism spectrum disorder (ASD). The consortium did a network meta-analysis of pharmacological and dietary-supplement treatments for ASD and analysed data for 41 drugs and 17 dietary-supplements, from 125 randomised clinical trials (RCTs) (n = 7 450 participants) in children/adolescents and 18 RCTs (n = 1 104) in adults. Most of the studies were inadequately powered (sample sizes of 20–80 participants), with short duration (8–13 weeks), and about a third focused on associated symptoms. Conclusions are that evidence on their efficacy and safety is preliminary, some medications could improve core symptoms, although this could be likely secondary to the improvement of associated symptoms. Thus routine prescription of medications for the core symptoms cannot be recommended, which is an important information for patients. The research is published in Molecular Autism. |
| AMYPAD<br>Alzheimer's disease | Published an article in Alzheimer's & Dementia presenting the baseline features of participants in the diagnostic and patient management study (DPMS) which aims to investigate the clinical utility and cost-effectiveness of amyloid-PET in Europe. The findings reported support the representativeness of the study sample to a wider European memory clinic population, suggesting that the results of DPMS will be generalisable. |
| AMYPAD<br>Alzheimer's disease | Completed enrolment in the prognostic and natural history study (PNHS, EudraCT NUMBER: 2018-002277-22). 1 856 participants from 17 sites in 7 countries were contacted to take part. 1321 participants consented to take part of whom 1 192 were scanned. In addition, 227 scanned participants received a follow-up scan. All parent cohorts shared their historical data, resulting in a total of ~2 700 scans of the PNHS at the end of the study. |
| c4c<br>paediatric clinical trials | To test the viability of the paediatric network, the non-industry proof of viability (PoV) studies are ongoing:<br>• TREOCAPA (paracetamol in premature babies; as of the end of December 2022: 389 out of the 794 children recruited in the phase III)<br>• KD-CAAP (Kawasaki disease coronary artery aneurysm prevention trial; at the end of December 2022: 40 patients recruited, 41 screened out of 262) |

| Project title | Description of result(s) |
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| | • In addition, two industry PoV studies started:<br>• Operetta 2 (for children and teenagers living with relapsing-remitting multiple sclerosis (RRMS)<br>• Fiona (chronic kidney disease and proteinuria).<br>All countries represented in the network are involved in these PoV trials. |
| COMBACTE-CARE (IMI1)<br>antimicrobial resistance | Site initiations were completed on 16 September 2022 for the Phase 3 REVISIT clinical trial, that aims to evaluate the efficacy and safety of aztreonam-avibactam (ATM-AVI) for treating serious infections caused by Gram-negative, carbapenem-resistant bacteria (NCT03329092). As of December 2022, 138 global sites were activated for enrolment, 68 of which were from the COMBACTE Clin-net network and more than 98% of the patients have been already randomised. (418 patients randomised globally out of the 425 targeted, of which 197 are from the COMBACTE Clin-net network). |
| COMBACTE-CDI<br>antimicrobial resistance | Results of the COMBACTE-CDI study have been published highlighting the burden that undiagnosed *Clostridium difficile* infections (CDI) places on healthcare systems, whereby lack of clinical suspicion and testing in adults who present with diarrhoea in the hospital or community setting was found to ultimately lead to further hospital admissions. Increased awareness by both patients and healthcare professionals of CDI in the community, in adults with either known predisposing risk factors or in those with prolonged days of diarrhoea, is required to reduce transmission rates and potential further healthcare burden. |
| COMBACTE-CDI<br>antimicrobial resistance | The team found that potato is a food commonly contaminated with *C. difficile*, although the positivity rates across countries varied substantially. The absence of clonal clusters indicates that there are no clearly successful clonal strains. However, the prevalent PCR ribotypes detected (014/020, 078/126, 010) overlap with the *C. difficile* population that is found in humans, animals and soil. Further large studies are needed to fully understand the role of food in *C. difficile* transmission chains. The research is published in Eurosurveillance. |
| COMBACTE-MAGNET (IMI1)<br>antimicrobial resistance | The project continued setting up the EPI-Net excellence centres network for epidemiology which aims to connect healthcare centres across Europe to facilitate high-level international projects on antimicrobial resistance. The EPI-Net Excellence Centres currently includes 16 healthcare centres from 9 European countries as members.<br>EPI-Net network will continue through the Horizon 2020 project ECRAID. |
| COMBACTE-MAGNET (IMI1)<br>antimicrobial resistance | A study showed a high prevalence (33.6%), of multidrug resistant *Pseudomonas aeruginosa* within European ICUs as well as wide intercountry variability determined by the dissemination of extensive drug resistance high-risk clones, thus arguing for the need to reinforce infection control measures (Journal of Antimicrobial Chemotherapy).<br>Another study showed that the gut can act as a reservoir for resistant *P. aeruginosa* with potential for translocation to the lung. These findings suggest that reducing intestinal colonisation of *Pseudomonas* may be an effective way to prevent lung infections in critically ill patients, Nonetheless, resistance was primarily shown to be driven by parallel evolution in the gut and lung coupled with organ specific selective pressures (Nature Communications).<br>Another study aimed for the rapid identification of *P. aeruginosa*-derived host markers to enable an early detection of *P. aeruginosa* VAP (VAP-PA) in easily accessible patient samples such as urine. Using metabolomics, the authors identified 58 metabolites that were significantly elevated or uniquely present in VAP-PA compared to the VAP–non-PA and pre-infection groups (Biomarker Insights). These, if further validated, could serve as highly specific diagnostic biomarkers of VAP-PA, thereby stewarding antibiotic use and improving clinical outcomes. |
| COMBACTE-MAGNET (IMI1)<br>antimicrobial resistance | Results from the EVADE study, a phase 2, randomised, parallel-group, double-blind, placebo-controlled study of MEDI3902 in mechanically ventilated patients with *Pseudomonas aeruginosa* (PA) lower respiratory tract colonisation have been published in the journal Critical Care. Although the bivalent, bispecifc monoclonal antibody MEDI3902 (gremubamab) did not reduce PA nosocomial pneumonia incidence in PA-colonised mechanically ventilated subjects, whether MEDI3902 could help prevent PA pneumonia, with higher doses or in more specific patient populations, would require additional studies. The study contributed to further build the COMBACTE-NET networks i.e. Clin-NET, LAB-NET and STAT-NET. (Clinicaltrials.gov NCT02696902; EudraCT 2015-001706-34) |

| Project title | Description of result(s) |
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| COMBACTE-NET (IMI1)<br>antimicrobial resistance | The patient enrolment in HONEST-PREPS study ended on 1 May 2022. A total of 2 165 patients were included from sites spread out through mostly Eastern Europe (Serbia, Czech Republic, Romania, Croatia, Albania, and France). Further to the database lock, analysis is now ongoing to determine the incidence, microbiological aetiology (including antibiotic resistance), management and outcome of hospital acquired and ventilator associated pneumonia (HAP/VAP) in the intensive care unit (ICU).<br>HONEST-PREPS sites who performed well had the opportunity to transit to the EU-funded ECRAID-Base Perpetual Observational Study into Ventilator Associated Pneumonia (POS-VAP) with the prospect of joining future randomised controlled trials controlled trials and other clinical trials related to prevention, diagnosis or treatment of VAP in ICUs. Eight out of the 40 selected sites previously participated in HONEST-PREPS. |
| COMBACTE-NET (IMI1)<br>antimicrobial resistance | First patient enrolled in SAATELLITE-2 trial in Limoges, France on September 6, 2022. As of 30 November 2022, 11 subjects have been randomised, all in sites from the Clin-Net network.<br>SAATELLITE-2 is a phase 3, randomised, double-blind, placebo-controlled, single-dosed trial, to evaluate the safety and efficacy of the monoclonal antibody suvratoxumab in the prevention of *S. aureus* infections in intubated and ventilated patients. The SAATELLITE-2 study will be conducted in over 500 patients at approximately 100 European Clin-Net and 100 non-European sites. EudraCT Number: 2021-004979-14 |
| COMBACTE-NET (IMI1)<br>antimicrobial resistance | Results from ARTHR-IS retrospective study, which aimed to determine the risk factors associated with *S. aureus* prosthetic joint infections (SA-PJI), the healthcare utilisation and the incidence and predictors of treatment failure of SA-PJI after a primary hip and knee arthroplasty have been published. (). Rates of treatment failure were high, with significant rates of loss of function, especially after prosthesis removal. Anaemia and obesity were identified among the risk factors for treatment failure while the probability of treatment success was increased when surgical cleaning without prosthesis removal was performed early, and when the antibiotic rifampicin was used in combination with another antibiotic. These findings were published in Infectious Diseases and Therapy.<br>Preoperative and perioperative risk factors have also been identified and predictive risks-scoring for *S. aureus*-PJI developed and validated in an external cohort. Information on the incidence and use of healthcare resources was collected. The results were published in Clinical Microbiology and Infection.<br>Overall, these results help to better understand the global burden of prosthetic infection due to *S. aureus* and better identify high-risk patients in whom targeted interventions and trials would be more efficient and improve the medical prognosis of this disease. |
| DRIVE<br>vaccines | For the final 2021/22 influenza season, 13 sites were chosen from 8 different European countries, covering 21 hospitals and approximately 1 125 general practitioners for the test negative design studies and 1 nation-wide register-based cohort study in Finland participated in the DRIVE study. Low influenza circulation (in comparison to pre-pandemic flu seasons) was observed, and the flu season was influenced by several factors: 1) interference with the Omicron variant COVID-19 pandemic wave from November 2021 to February 2022, and 2) a late influenza epidemic peak surging in many European countries in March-April 2022. Despite the low influenza circulation, the DRIVE study was conducted smoothly, and brand-specific IVE estimations were obtained for 8 out of the 12 influenza vaccines marketed in Europe in the season 2021/22. This highlights the ability of the study network to cover the variety of influenza vaccine brands administered in Europe. Annual detailed reports are available for download from the project website. |
| EBOVAC3<br>Ebola and related diseases | A core part of EBOVAC3 is the conduct of EBL2007, a phase 2 clinical trial to evaluate the immunogenicity and safety of the Ebola vaccine regimen in health care providers, in the Democratic Republic of the Congo (DRC).<br>In 2022, the project published in the journal Vaccines a paper on the challenges, mitigations and lessons learned from setting up the Ebola vaccine trial in a remote location in DRC. The paper can be downloaded for free (open access).<br>The project also published a paper in Epidemiology on biases in the conventional test-negative design under outbreak and pandemic conditions. |
| EHDEN<br>big data | In a paper published in British Medical Journal studying the association of Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis and covid-19 vaccines, EHDEN researchers analysed data from > 22 million people from Spain and the UK and found no association between COVID-19 vaccines and these neuroimmune conditions. |

| Project title | Description of result(s) |
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| FLUCOP (IMI1)<br>vaccines | A standard protocol to promote consistent haemagglutination inhibition (HAI) testing methods across laboratories was developed and results were published in mSphere. For both HAI and virus neutralisation (VN) methods, an external quality assessment (EQA) was performed to further assess the variability of HAI and VN methods across a wider range of laboratories including both FLUCOP and non-FLUCOP partners. For that purpose, participating laboratories were asked to test a serum panel of 30 samples with four seasonal influenza viruses. Data were collected from 13 laboratories for HAI and from 7 laboratories for VN. The results showed that the use of standards (calibrators, reference reagents) is beneficial and consistently reduced variation between laboratories across assays (HAI and VN) and between virus types and subtypes. |
| H2O<br>digital health | The Health Outcomes Observatory established three new national health observatories Austria, Spain, and The Netherlands. Denmark has been selected to serve as the pan-European hub. |
| Hypo-RESOLVE<br>diabetes | A cross-sectional, multi-country, web-based study investigating the impact of hypoglycaemia on the quality-of-life patients with diabetes and their partners was performed as part of this project. The study is called “YourSAY (Self-management And You): Hypoglycaemia”. Results of this study among patients with type 1 diabetes show that that hypoglycaemia has a negative impact in most domains of life, (including leisure activities, physical health, emotional well-being, spontaneity, independence, work/studies) with sleep being the most negatively affected domain. The results are published in the Journal of Diabetes and its Complications. |
| iABC (IMI1)<br>antimicrobial resistance | The Phase I Murepavadin study in healthy subjects sponsored by Spexis completed the run-in phase part of the PK and safety study in healthy subjects (Part A) as well as the Part B (randomised, double-blind, placebo-controlled single-ascending dose study) successfully with a total of 30 subjects dosed. Initial results show that the murepavadin, delivered via the oral inhalation route is well tolerated and no adverse effects have been reported and the concentration profile of murepavadin after inhalation was favourable. These data support moving forward to phase 2 in cystic fibrosis and non-cystic fibrosis bronchiectasis lung infection. |
| iABC (IMI1)<br>antimicrobial resistance | Patient recruitment is progressing in the phase 2 study sponsored by Novartis to explore the efficacy and safety of QBW251 in patients with bronchiectasis. 16 clinical sites have been initiated, 64 patients have been screened and 20 randomised out of the 72 planned. *(clinicalTrials.gov* NCT04396366*)*. |
| IMMUcan<br>cancer | IMMUcan intends to understand how the immune system and tumours interact, and the impact of therapeutic interventions. To achieve this goal, the project is accessing patient biological material and linked clinical data to be analysed. Via the EORTC platform called SPECTA, 153 principal investigators from 88 clinical sites from 18 countries have been authorised to recruit patients as of December 2022. In addition, the consortium has access to 8 clinical studies, cohorts or archival material collections outside EORTC SPECTA platform. |
| INNODIA / INNODIA HARVEST<br>diabetes | The unique type 1 diabetes (T1D) clinical trial network established in INNODIA is continuing to prove its strength with more than 50 accredited clinical centres in over 13 European countries (21 clinical INNODIA centres with additional national satellite centres).<br>The consortium has succeeded in completing recruitment for the IMPACT study in collaboration with the SME Imcyse in the context of INNODIA HARVEST (106 randomized patients). In addition, the INNODIA clinical trial network is successfully running the phase II MELD-ATG trial in INNODIA (currently 102 people with newly diagnosed T1D screened, 72 randomised) and the phase II Ver-A-T1D trial in INNODIA HARVEST (currently 92 people with newly diagnosed T1D screened, 61 randomised), both promising full recruitment in 2023 and 2024 respectively. These ongoing trials offer access to different clinical interventions and disease modifying therapies in various European countries for newly diagnosed T1D patients. |
| NEURONET<br>neurodegenerative disease | NEURONET has continued to maintain its NEURO Cohort, representing the open network of 40 research active clinical sites in Europe, representing 13 countries and 25 000 participants. Moreover, it has worked to maintain collaboration with other cohort initiatives, such as EPND (European Platform for neurodegenerative diseases) and the Davos Alzheimer’s Collaborative Cohort.<br>The NEURO Cohort has the potential to become a unique asset, in Europe and worldwide, that unites neurodegeneration research and clinical sites in an attempt to overcome research fragmentation, helping accelerate innovative research in an unprecedented way. |

| Project title | Description of result(s) |
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| PROMISE<br>respiratory disease | Set up the case-control validation study to validate biomarkers from the RESCEU infant case-control study and infant cohort study (PROMISE builds on the work of RESCEU). The study population consists of previously healthy infants with respiratory syncytial virus (RSV) of different severity (ventilated infants, hospitalised non-ventilated infants, medically attended non-hospitalised infants and healthy controls without RSV). As of the end of 2022, 55 infants have been recruited. |
| RADAR-AD<br>Alzheimer's disease | Successfully completed recruitment in a clinical study to assess the utility and feasibility of using remote monitoring technologies such as smartphones or wearable devices to assess function and cognition in a real-world setting. Participants were selected from memory clinics and ongoing observational studies and included in three study Tiers (227 participants were enrolled in Tier 1, 45 in Tier 2, and 40 and Tier 3).<br>• Tier 1 devices to be deployed across the whole cohort will be highly scalable. These devices, such as smartphone apps or wearables, will be set up when participants make a clinic visit.<br>• Tier 2 devices will be those that require a home visit for setup. For example, power socket monitors may involve setup procedures (such as local Wi-Fi connections), which may be too complex for participants to handle independently.<br>• Tier 3 for sensors where physical installation is too disruptive for short-term study, these devices will be trialled only in an existing smart-home environment. |
| STOPFOP<br>rare / orphan diseases | The aim of the STOPFOP clinical study (Saracatinib Trial TO Prevent FOP (STOPFOP) - EudraCT: 2019-003324-20; ClinicalTrials.gov: NCT04307953) is to investigate the efficacy and safety of the drug AZD0530 (saracatinib) for treating patients with fibrodysplasia ossificans progressiva (FOP). FOP is one of the rarest, most disabling genetic conditions, which causes bone to form in muscles, tendons, ligaments, and other connective tissues. 14 patients out of 20 foreseen in total have already enrolled in the clinical study. Although the STOPFOP study has not been finalised yet, the first data coming from the patients that completed the trial are promising. If positive, this study will provide data to treat a very serious condition for which no treatment currently exists. |
| VALUE DX<br>diagnostics | A clinical algorithm for diagnosing the aetiology of the community-acquired acute respiratory tract infections (CA-ARTIs) is necessary to limit inappropriate antibiotic prescribing in primary care and consequently curb antibiotic resistance emergence. Although there is no shortage of clinical algorithms (CA) for detecting bacterial aetiology of CA-ARTIs in the literature, they are all mainly derived from local data, prevalence at the time of the study, available diagnostic tools, and type of population. The VALUE-Dx heuristic algorithm is designed to be able to select an optimal CA for any particular out-patients setting, i.e. list of available point of care diagnostic tests, their performance and cost, and disease prevalence. The CA is a binary decision tree, with nodes corresponding to the index tests and edges to the test outcomes. |
| VALUE DX<br>diagnostics | The PRUDENCE Trial (Platform Randomised Controlled Trial of Point of Care Diagnostics for Enhancing the Quality of Antibiotic Prescribing for Community Acquired Acute Respiratory Tract Infection [CA-ARTI] in Ambulatory Care in Europe) will assess the effectiveness of CA-ARTI diagnostics (Dx) in terms of both reductions in antibiotic prescribing and patient recovery. The trial will explore whether adding a CA-ARTI-Dx to usual primary care has: effects on antibiotic prescribing; effects on antibiotic use; effects on patient recovery and safety, including complications and hospitalisation; effects on use of medications other than antibiotics; effects on clinician's decision-making process regarding diagnosis and treatment; effects on patients' perceived ability to understand and cope with their illness; is cost-effective.<br>The PRUDENCE Trial has received approvals and opened to recruitment in 7 Primary Care Networks and 2 Long Term Care Facility Networks, with 450 participants having been randomised (the recruitment target is 2 500). |

## Big data solutions to leverage knowledge / implementation of data standards

| Project title | Description of result(s) |
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| BIGPICTURE<br>artificial intelligence | BIGPICTURE aims to generate a repository of 3 million whole slide images (WSIs) for the development of AI algorithms and the acceleration of computational pathology.<br>In 2022, the first clinical dataset was successfully submitted to the platform – a major milestone. The dataset includes 80 WSIs of 8 melanoma patient cases. |
| BIGPICTURE<br>artificial intelligence | The BIGPICTURE consortium has developed and publicly released software tools to allow for the easy conversion of a range of existing whole slide image (WSI) file formats to the digital imaging and communications in medicine (DICOM) standard:<br>• wsidicomizer is a Python library for converting files WSI files to DICOM using opentile or openslide;<br>• wsidicom is a python package for reading DICOM WSI file sets;<br>• opentile is a python library for reading tiles from WSI tiff-files. |
| BIGPICTURE<br>artificial intelligence | BIGPICTURE has published a report on the legal rules applicable to the contributors of whole slide images for 8 countries (AT, BE, FI, DE, IT, NL, SE, UK). This report will be the basis of setting up local procedures for GDPR-compliant data sharing, within the project while still adhering to all applicable laws and regulations. |
| c4c<br>paediatric clinical trials | The development of the Paediatrics User Guide, in collaboration with CDISC has been completed after going through public consultation. This Paediatrics User Guide provides advice and examples on how to implement CDISC data standards for data collection and data tabulation for use in paediatric studies. |
| CARE<br>coronaviruses | Using big data and AI to do hit enrichment. A machine learning artificial intelligence approach was established that uses information from various screening efforts to virtually screen large libraries with the aim of finding hits from these libraries with a high likelihood of showing antiviral activity against coronaviruses (hit enrichment). |
| CARE<br>coronaviruses | Using AI coupled with a structure-based approach to identify compounds with high potential. The project set up AI structure-based generative modelling to identify potent, antiviral small molecule inhibitor of identified targets, to accelerate and optimise the identification of target inhibitors. |
| CARE<br>coronaviruses | By colocalisation of 300 genetic association maps, the project provided evidence of >5 000 molecular links to COVID-19 associated genomic loci. Hundreds (>200) of gene candidates for COVID-19 risk and severity were identified. By interrogation of different tissue, cells and stimuli contexts, the project pinpointed potentially relevant COVID-19 biological contexts of origin. Presented in BOG 2022. |
| ConcePTION<br>medicines safety | The team worked on an inventory of 90 European data sources across 14 countries that can be used to study neurodevelopment following maternal medication exposure. This inventory, which is published in PLoS ONE, is a useful resource for researchers for evaluating perinatal and long-term childhood neurodevelopmental risks associated with in-utero exposure to medication. |
| EHDEN<br>big data | The EHDEN consortium added 22 data partners from 13 countries to its data network in the final data partner call (Call 7). This call was held in collaboration with HDR UK and has resulted in an overall network of 187 from 29 countries mapping ~830 million records to the OMOP common data model. |
| EHDEN<br>big data | The EHDEN Real World Data Portal offering findable, standardised data at scale was opened in June 2022. This portal provides a one-stop-shop for study planning, data access, standardised analysis & reporting with free access to the research community.<br>It is currently populated with 160 million patient records from 20 countries, and will grow to include the complete EHDEN network of ~830 million patient records. |
| EHDEN<br>big data | EHDEN and the Uppsala Monitoring Centre (UMC) held a joint event to evaluate the feasibility and utility of using the EHDEN data network to support of UMC's preliminary medicine side effect assessment process. The 'evidence-a-thon' event assembled more than 30 participants from the |

| Project title | Description of result(s) |
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| | UMC, EHDEN, DARWIN EU, and EHDEN data partners. Data from electronic health records, hospital, and registry data from Spain, the UK, Finland, Serbia, the Netherlands, and Norway were analysed, and 9 new drug-event combinations were identified. This study showed that an analysis in 6 countries can be run in 15 minutes. |
| FAIRplus & Combine<br>knowledge management and antimicrobial resistance | Many data from antimicrobial resistance research cannot be reused due to lack of interoperability standards leading to duplication of work. With the IMI COMBINE project, FAIRplus researchers developed a new approach for the standard application of metadata for *in-vivo* experiments, greatly enhancing the usability of the data and potential reducing animal use in AMR research. The use case is published online. |
| FAIRplus & EUbOPEN<br>knowledge management and drug discovery | In a joint project with FAIRplus, a large amount of EUbOPEN imaging data (> 35 000 files) has been uploaded to BioImage Archive. These data, which originate from testing chemogenomic compounds on three model cell lines, are now freely available to the community. |
| Gravitate Health<br>digital health | Gravitate Health aims to give patients access to trusted and up to date electronic product information (ePI) tailored to their individual needs. Building on existing EU developments, Gravitate Health has started a collaboration with the EMA and HL7 (FHIR) to develop an interoperable standard for ePI that is suitable for global use. |
| H2O<br>digital health | H2O started a new research collaboration with the International Consortium of Health Outcomes Measurement (ICHOM) with the aim of transforming healthcare systems by creating a mind-set of focus on patient outcomes and continuous learning and improvement.<br>In 2022, H2O also started research collaborations with Aarhus University Hospital, Gesundheit Österreich GmbH, and the Ludwig Boltzmann Institute with the aim of increasing awareness and support for the vision and goals of H2O. |
| H2O<br>digital health | The Health Outcomes Observatory developed six patient-reported standardised outcome sets. The outcome sets for lung cancer and breast cancer were published in the journals Lung Cancer and Breast Cancer Research and Treatment respectively. The metastatic breast cancer outcome set has also been accredited by ICHOM.<br>Publications describing the outcomes sets for inflammatory bowel disease, diabetes types 1 and 2, as well as a generic outcomes set, are under preparation. |
| HARMONY / HARMONY PLUS<br>big data, cancer | HARMONY and HARMONY PLUS, big data projects focused on blood cancers, continue organising datasets in the platform according to the observational medical outcomes partnership (OMOP) standard format for observational data, capable of admitting any information independently of its origin. HARMONY has expanded existing vocabularies, terminologies, and coding schemes. Communication channels and data curation procedures have been maintained with data providers to warrant the harmonisation quality assurance process. Approx. 150 000 patients' datasets had already been identified by December 2022. |
| IDEA-FAST<br>digital health | IDEA-FAST published the clinical and sensor data standards that will be used in their fatigue and sleep disturbances observational study. These standards will provide a common reference for health-related quality of life (HRQOL) and activities of daily living (ADL) related clinical studies, and could facilitate and enhance data sharing, integration and cross-study analysis in other studies. |
| PIONEER<br>big data, cancer | Expansion of the PIONEER Big Data Platform collection of datasets featuring patients affected by prostate cancer.<br>PIONEER has welcomed 8 new data providers from 5 different countries in 2022, with a further 4 datasets actively being mapped to OMOP common data model and 3 others in the pipeline. |
| RADAR-CNS<br>neurological disorders | In a study on patient engagement with remote sensing technologies, RADAR-CNS monitored 547 people with a history of depression for ~ 541 days using Fitbit devices and mobile app questionnaires. The consortium found no evidence for the effect of depression on perceived usability of Fitbits or questionnaires completed, demonstrating that, despite the challenges of |

| Project title | Description of result(s) |
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| | living with depression, participants effectively engaged with remote sensing technologies. The research is published in the Journal of Affective Disorders. |
| RADAR-CNS<br>neurological disorders | Researchers from the RADAR-CNS project have found that geolocation data from smartphones can be used to predict worsening of depression symptom severity in people with Major Depressive Disorder. Data from 290 participants with MDD were collected for 2 years in UK, the Netherlands and Spain. Analysis showed that, in the two weeks prior to when they reported symptoms of depression, participants who experienced a worsening of depressive symptoms spent more time at home and less average time spread across different locations. The study is published in the journal JMIR Mental Health. |
| RADAR-CNS<br>neurological disorders | The RADAR-CNS consortium performed a survey of 1006 healthcare professionals, including hospital physicians, GPs & nurses to assess how remote measurement technologies (RMTs) could be integrated into everyday practice. Questions included:<br>• types of data considered useful,<br>• preferred methods of accessing the data,<br>• benefits and challenges to RMT implementation,<br>• impact of RMT data on clinical practice.<br>> 70% respondents indicated their service would benefit from the implementation of RMT in patient care plans, however, the time available to review the information is still an important problem.<br>The research is published in BMC Medical Informatics and Decision Making. |

## Education and training for new and existing R&D scientists and stakeholders

| Project title | Description of result(s) |
|---|---|
| c4c<br>paediatrics, clinical trials | The c4c Academy Platform continue to offer multiple short training courses and accredited advanced courses. The project designed 3 new short courses (on developmental pharmacology, innovative trial design, and gene therapy trials), as well as 2 competence development GCP courses on informed consent and assent, and auditing and inspection readiness. All these courses are still currently internal to the c4c consortium and staff involved in the national hubs sites to build capacity of the network.<br>In addition the consortium launched the online catalogue of relevant external paediatric training courses that are available. |
| ConcePTION<br>safety | Results of a qualitative study conducting in women during preconception, pregnancy, or nursing were published in BMC Pregnancy and Childbirth. The study showed that a learning healthcare system (LHS) approach could be a viable alternative to generate evidence on medication safety in pregnancy and breastfeeding, and provide insights for the development of a sustainable and ethically responsible LHS. |
| EBiSC2<br>stem cells | EBiSC2 has engaged with four national and three international research funders to provide grant applicants with information on how to build sustainability for iPSCs into projects from the onset, resulting in funder-led networking meetings, a blog post and the recommendation of EBiSC as a key resource for iPSC researchers. |
| EBOVAC3<br>Ebola and related diseases | The EBL2005 clinical trial (EBOVAC Infant Study) is a Phase 2 study to evaluate the safety, reactogenicity, and immunogenicity of the Janssen 2-dose vaccination regimen against Ebola virus disease in infants aged 4-11 months in Guinea and Sierra Leone.<br>Existing and new clinical study staff in Guinea and Sierra Leone attended the site initiation visit and specific training sessions on the latest protocol and standard operating procedures as well as staff engagement meetings, in order to ensure compliance and quality. |

| Project title | Description of result(s) |
|---|---|
| EHDEN<br>big data | In 2022, several additional courses were added to the EHDEN academy including a series of courses for non-experts and courses on health technology assessment and open science & FAIR principles.<br>Over 2 000 users accessed the academy in 2022 and 1 500 courses were completed. |
| FAIRplus<br>knowledge management | The FAIRplus fellowship programme, which started in May 2021, concluded in 2022. 18 fellows from academia, SMEs and EFPIA partners were trained to get a better understanding of:<br>• what FAIR means for their institutions;<br>• when FAIR is 'FAIR enough';<br>• why FAIR data is so essential to today's life science industry;<br>• how to transform or initiate a FAIRification process in their organisations;<br>• how to advise to internal departments and teams to make their data FAIR.<br>The training consisted of a series of modules combining online learning, training on the job and face-to-face meetings. |
| GetReal (IMI1) / GetReal initiative<br>relative effectiveness | The GetReal Institute is an independent, member-led, not-for-profit organisation resulting from the GetReal and The GetReal Initiative projects (to date 25 members (public, non-governmental organisation, academia, business). The Institute through the GetReal Academy continued offering the courses open to all in 2022 on real-world evidence in medicine development as well as on structured benefit–risk assessment of medicinal products. |
| HARMONY<br>HARMONY PLUS<br>big data, cancer | Regular monthly training sessions and videoconferences have been organised for data scientist and biostatistician teams of different partners participating in the analysis of the data in the platform. These sessions included understanding OMOP vocabulary and CDM format, approaches to data modelling, model complexity and data availability, introduction to data analytics using Apache Zeppelin platform-based notebook, and harmonisation quality assurance processes. |
| PIONEER / EHDEN<br>big data, cancer | European Common Data Model training: PIONEER has trained an additional 3 EAU (European Association of Urology) Guidelines Associates with regards to the concepts of the European common data model as well as how to map clinical data to OMOP via the EHDEN Academy in 2022.<br>PIONEER also built a training thread into the second studyathon throughout the entire 5 days. The aim of this training component was to expand the skills base of consortium members with regards to phenotype development, building and executing feasibility and study packages and in critical analysis of results. A total of 12 researchers were trained across the 5 days. |
| PREMIER<br>environmental issues | Published a science-based opinion paper on 'GREENER pharmaceuticals for more sustainable healthcare'. The paper describes an approach to identify and meet important environmental criteria, which will help reduce the impact of medicinal residues on the environment.<br>Examples include criteria like effect reduction by avoiding non-target effects or undesirable moieties, exposure reduction via lower emissions or environmental (bio)degradability, no PBT (persistent, bioaccumulative, and toxic) substances, and risk mitigation. The paper was published in Environmental Science and Technology Letters where it received the accolade of Editor's choice due to its broad public interest. |

## Impact on regulatory framework

| Project title | Description of result(s) |
|---|---|
| ARDAT<br>advanced therapies | Published an article in Cell & Gene Therapy Insights providing an overview of the current regulatory landscape for conducting shedding and biodistribution studies of gene therapy products. This work illustrates the clear need for regulatory harmonisation across different regions. |
| EHDEN<br>big data | The EMA's Data Analysis and Real World Interrogation Network (DARWIN EU) aims to deliver real-world evidence on diseases, populations & use of medicines. It is also an early flagship 'pathfinder' for the European Health Data Space. The EHDEN project has funded the data mapping of most of DARWIN EU's initial data partners – fast-tracking the network. |
| LITMUS<br>liver disease | LITMUS has had successful submissions and interactions with both the EMA (Europe) and the FDA (USA).<br>With the FDA, following a Critical Path Innovation Meeting (CPIM), formal submissions of Letters of Intent have been accepted by the FDA to address: (a) Diagnostic [DDTBMQ #000095] and (b) Prognostic [DDTBMQ #000106] contexts of use. These letters each contained two exemplar biomarker panels (single/composite, including imaging) and mean LITMUS is well placed to proceed with qualification of biomarkers for NAFLD for use in clinical trials.<br>With the EMA, following an Innovation Task Force (ITF) meeting, LITMUS has had formal Scientific Advice and Qualification Advice interactions with the EMA.<br>Together, these mean the consortium is ready to submit formal qualification packages in Europe and the US, pending completion of ongoing data acquisition and analysis. |
| MACUSTAR<br>eye disease | The EMA issued a second letter of support for MACUSTAR based on the cross-sectional part of the clinical study which focused on the technical evaluation of functional, structural and patient-reported candidate outcomes. The letter supported MACUSTAR's interpretation of the results and encouraged the ongoing validation of functional, structural and patient-reported endpoints in age-related macular degeneration. |
| NECESSITY<br>Sjögren's syndrome | The NECESSITY project has developed the Sjögren's Tool for Assessing Response (STAR) to improve the assessment of drug efficacy on all aspects of Sjögren's. STAR was published in Annals of Rheumatic Diseases and is freely available to the scientific community for analysis of completed and future trials.<br>The EMA issued a Letter of Support for STAR as a tool to improve the assessment of drug efficacy on all aspects of Sjögren's after reviewing the methodology for development and results. This shows that the EMA recognises the need for such a tool and that it agrees with the overall development process. Such a recognition will facilitate the use of STAR in future academic- and industry-led clinical studies.<br>STAR is used as primary endpoint in the NECESSITY trial which include a network of 34 sites in 8 countries for a total of 300 randomised patients. In 2022, 13 sites have opened and 17 randomised patients have already been recruited in the study. |
| NEURONET<br>neurodegenerative disease | In 2022, NEURONET updated its Regulatory and Health Technology Assessment (HTA) Engagement Decision Tool, which was published on April 2022 in the NEURONET Knowledge Base . The updated tool outlines key processes and procedures for engaging with regulatory, HTA bodies, and payers, and will help IMI projects identify relevant procedures, based on the project's stage of research and asset developed. |
| PIONEER<br>big data, cancer | HTA workshop: A workshop was held in December 2022 to prioritize prostate cancer evidence challenges of interest to payers and HTA agencies that could be used as use cases to pilot within the PIONEER platform, therefore testing the utility of the platform to regulatory and HTA authorities. The workshop group identified 2 possible research questions that could be used as a proof-of-concept to demonstrate the utility of the PIONEER platform to decision makers. |
| PREFER<br>Patient involvement in R&D | The European Medicines Agency adopted a qualification opinion for PREFER framework with points to consider for methods selection for a patient preference study in May 2022, endorsing them as a comprehensive reference document for planning and conducting patient preference studies (PPS). |

| Project title | Description of result(s) |
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| | The PREFER framework can be used by industry, regulators and health technology assessment bodies who want to know how to use patient preferences as input in medical product decision making. Regulatory experience with PPS is currently limited and therefore this achievement is contributing to advance the field of integrating patient perspectives in decisions by regulatory agencies, health and technology assessment bodies and industry. |
| RAPID-COVID<br>coronaviruses | The consortium submitted for CE IVD approval a robotic platform automation system to decrease hands-on time required for assay setup and developed a software prototype, conforming to ISO13485 and IEC62304 standards, to automatically analyse test results. These tools enable automatic analysis of quantitative polymerase chain reaction (qPCR) data to be carried out at medium and high throughput (500 to 3000 analyses/day) and could be used for many areas of human diagnostics beyond SARS COV-2 as well as for research and development (R&D) activities. |
| VAC2VAC<br>vaccines | Extensive work was carried out to implement and validate the European Pharmacopoeia (Ph. Eur) method “Monocyte Activation Test (MAT)” for pyrogenicity testing of Encepur, a vaccine against tick-borne encephalitis virus. This is the first method within VAC2VAC to reach regulatory acceptance and implementation and thus represents an important milestone in their effort to implement the consistency approach. Pharmacopoeia is working on the replacement of the rabbit pyrogen test in all monographs including tick-borne encephalitis virus (TBEV), with implications beyond VAC2VAC. |
| VAC2VAC<br>vaccines | Development of a roadmap for achieving meaningful change in regulatory policy through replacement of in vivo methods with in vitro methods with practical considerations and best practices for developing a strategy to encourage adoption and implementation of non-animal methods by industry partners and regulatory agencies worldwide. |

## Implementation of project results inside industry

| Project title | Description of result(s) |
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| BEAt-DKD<br>diabetes | The replicated project results have shown that insulin resistant type 2 diabetes (T2D) patients are more likely to progress towards renal decline. BEAt-DKD partner Eli Lilly knew that a drug in the company’s development pipeline, tirzepatide, was able to substantially increase insulin sensitivity, and that other incretin drugs with less of an effect on insulin resistance also slowed renal decline in T2D patients. Therefore, an ad hoc analysis of tirzepatide in the SURPASS-4 trial was performed to determine the effect of this drug on renal loss T2D patients. The results of this study, published in the Lancet Diabetes and Endocrinology, showed a positive outcome of Tirzepatide (now branded Mounjaro) in slowing renal loss in T2D patients. These results may lead to a new prospective clinical trial, and eventually, to a new indication for an existing drug. |
| COMBACTE-NET (IMI1)<br>antimicrobial resistance | Based on the findings of the observational studies EXPECT-1 and 2 conduced in the COMBACTE-NET project that aimed at collecting information from participants who were hospitalised with an invasive disease caused by Extraintestinal pathogenic *E. coli* (ExPEC), Janssen Vaccines was able to design and start the Phase 3 clinical vaccine efficacy study E.mbrace trial.<br>Over 40 clinical sites from Clin-Net network are participating in the study. |
| EBiSC2<br>stem cells | EBiSC2 developed a fully human assay combining neurogenin2 (NGN2)-inducible neurons co-cultured with iPSC-derived astrocytes. The assay was published in Stem Cell Research. Subsequently, Janssen is using the NGN2 protocol in R&D activities in the neuroscience department and exploring its potential in early toxicology assessments. |
| EBiSC2<br>stem cells | EBiSC2 completed a dual centre study on bulk cryopreservation of hiPSCs in therapeutically relevant cell numbers and immediate bioreactor seeding upon thawing towards closed workflows in manufacturing processes. |

| Project title | Description of result(s) |
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| | Outside EBiSC2, Novo Nordisk have used core principles from this work to inform and lay the foundation for bulk cryopreservation of cells internally. |
| EBiSC2<br>stem cells | EBiSC2 partners worked together to agree and implement industry standard QC regimes for large scale production of iPSCs and four iPSC-derived cells (neurons, astrocytes, cardiomyocytes and hepatocytes). QC regimes are applied to EBiSC products which are then used by industry partners. The EBiSC QC regime set standards which have been used by Novo Nordisk internally to benchmark processes. Janssen is using the QC pipeline set up and piloted by the EBiSC2 consortium (including external partners) for R&D projects involving iPSC lines received from third parties. |
| EBOVAC3<br>Ebola and related diseases | The safety and immunogenicity results generated in the EBL2005 phase 2 study support the administration of the Janssen vaccine regimen (Ad26.ZEBOV, MVA-BN-Filo) against Ebola Virus Disease (EVD) to infants under 1 year of age, which is one of the most vulnerable populations affected by EVD. Indeed, younger children have shorter times from symptom onset to hospitalisation and from symptom onset to death, and the highest mortality rate. It is therefore important to evaluate any vaccine for Ebola for safety and immunogenicity in this population. |
| LITMUS<br>liver disease | LITMUS has further developed a disease-specific patient-reported outcome measure: NASH-CHECK. This tool measures NASH F1-F3 and F4 patients, is freely available, and has already been implemented in clinical trials by LITMUS industry partners is now being adopted by companies outside of the consortium. |
| LITMUS<br>liver disease | The data generated through LITMUS has provided substantial new insights into the performance of multiple biomarkers (blood-based, and imaging) that have helped to shape industry strategy for clinical trial pre-screening and inclusion within studies. These have led to tangible changes in the conduct of trials by several LITMUS partners. |
| VSV EBOPLUS<br>Ebola and related diseases | The project is providing relevant information for the industry, analysing the immune and molecular signatures, elicited by rVSV-ZEBOV vaccination in adults and children and determining the dynamic transcriptomic and metabolomic profiles of the human immune response to VSV-ZEBOV vaccination at multiple time points. |

## Accessibility of resources/outputs beyond consortium

| Project title | Description of result(s) |
|---|---|
| 3TR<br>autoimmune diseases | A tool that allows the molecular characterisation of individual systemic lupus erythematosus (SLE) patients, called MyPROSLE, has been produced and is available online. This tool is an algorithm using transcriptome data that detects disease activity or long-term remission of patients with SLE, and therefore, can support precise therapeutic decisions. The tool is described in the journal Briefings in Bioinformatics. |
| APPROACH (IMI1)<br>osteoarthritis | Details on the APPROACH study and database parameters have been posted to the FAIRplus database' This provides a public view of project details and contact information for others to inquire about data access. The APPROACH consortium plans to make the entire data set public via FAIRplus within 5 years after the end of the APPROACH project. |
| BigData@Heart<br>big data, cardiovascular disease | The CODE-EHR Minimum Standards Framework was proposed by BigData@Heart and the European Society of Cardiology to improve the design of studies, enhance transparency, and develop a roadmap towards more robust and effective utilisation of electronic health records (EHRs) in clinical research. It was simultaneously published at The European Heart Journal, The BMJ, and The Lancet.<br>Research using these data is a crucial component of future health-care evaluation and administration and will have an increasingly important role in decisions regarding patient care made by regulatory, governmental, and health-care agencies in every medical specialty. |

| Project title | Description of result(s) |
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| | The consortium contacted the top journals in the field to ask them to join the initiative; 4 of them already added or agreed to include this checklist as a recommendation or requirement for new publications. |
| BIOMAP<br>skin diseases | A first disease map comprising mechanisms linking biomarkers of psoriasis severity, psoriatic arthritis and treatment response to the onset and development of the disease has been made publicly available. The disease map is freely accessible, and can be both used as a reference for future related research projects and for educational purposes. |
| COMBACTE-NET (IMI1)<br>antimicrobial resistance | The Lab-net network with its central coordinating laboratory at the University of Antwerp has been involved in a number of studies by providing training to laboratories of clinical sites, sample kits and sample collection & management manual, as well as helping in the site selection process.<br>VACCELERATE studies: AGED and BOOSTAVAC on COVID-19 as well as CoVacc in paediatric subjects.<br>Microbiology sub-study in the Paediatric Community Acquired Pneumonia (PediCAP) project funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) that have started recruiting. Lab-net will also perform the sample analysis. |
| COMBINE<br>antimicrobial resistance | Developed a new ontology that will enable researchers to convert unstructured bioassay protocol data into structured machine-readable formats thereby promoting their overall reusability. The Bioassay Protocol Ontology (BPO) allows to accurately describe in-vivo efficacy study metadata for antibiotic agents.<br>The ontology has been made publicly available for reuse (creative commons CC4.0) and is accessible here. |
| ConcePTION<br>pregnancy and breastfeeding | The availability of the ConcePTION common data model (CDM) has already been used in several external EMA tendered safety research projects related to risk minimisation measurement for pregnancy prevention programs, COVID-19 vaccines and pregnancy in COVID-19 through the European Pharmacoepidemiology & Pharmacovigilance research network for the following projects:<br>• Retinoids risk minimisation studies in 6 Data Access Providers (DAPs) EUPAS31095<br>• Valproate risk minimisation studies with 5 DAPs EUPAS31001<br>• ACCESS, background rates of COVID-19 adverse events of special interest in 10 DAPs (European Union electronic Register of Post-Authorisation Studies registration number (EUPAS) 37273)<br>• CONSIGN, Medicines use and effects to treat COVID-19 in pregnant women (9 DAPs) (EUPAS39226, EUPAS39438, EUPAS40317)<br>• Early Covid Vaccines Monitor with four DAPs (EUPAS40404)<br>• Covid Vaccines Monitoring with 10 DAPs (EUPAS 42504) • Effectiveness of heterologous and homologous COVID-19 vaccine effects.<br>The CDM is also adopted by the Vaccine Monitoring Collaboration for Europe (VAC4EU), and used in studies to monitor COVID-19 vaccines safety<br>• COVID-19 Vaccine AstraZeneca PASS (EUPAS43593)<br>• COVID-19 Vaccine Moderna/Spikevax PASS (EUPAS44424)<br>• COVID-19 Vaccine Pfizer-BioNTech/Comirnaty PASS (EUPAS41725)<br>• COVID-19 Vaccine Janssen PASS (EUPAS45461).<br>The SIGMA consortium, a collaboration of pharmacoepidemiology centres, has adopted the ConcePTION CDM. |
| DRIVE<br>vaccines | In DRIVE's 5 seasons (2017 to 2022), data from more than 35 000 patients, approximately 60 variables and 13 influenza vaccines has been collected. The DRIVE partners consider that this valuable database could be leveraged and further utilised for various reasons, such as research and development activities for new generation of influenza vaccines, and a contribution to the worldwide efforts to enhance global surveillance network for respiratory viruses and associated diseases and monitor related vaccines performance. This is the reason why DRIVE developed an open access to research data and secondary use framework, allowing the secondary use of the data generated since the 2018/19 season. |
| EBiSC2<br>stem cells | The consortium finalised: |

| Project title | Description of result(s) |
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| | • The collection of clinical data for 21 donors in line with the fast healthcare interoperability resources standard. Data included 64 comorbidities, 180 medications and 53 treatments and was annotated with SNOMED CT and disease ontology terms.<br>• The complete characterisation of 1 'healthy' cardiac cell product.<br>• The optimisation of protocol development for one cardiac disease cell product and one astrocyte cell product.<br>• The collection of 5 new iPSC from clinically relevant cohorts, including rare diseases, for incorporation into EBiSC.<br>• The progressed deposition of 13 iPSC cohorts from a variety of research projects including IMI-PHAGO, totalling >100 new iPSC lines expected for external distribution in 2023.<br>• The complete deposition of 12 new iPSC lines with extensive genomic and clinical datasets available for researcher use.<br>• The implementation of new functionality to enable researchers to build tailored induced pluripotent stem cell (iPSC) line cohorts representative of patient sub-populations through 'gene of interest' search functionality in 127 iPSC lines where open access whole genome sequence data is available. New functionality in the EBiSC catalogue enables researchers to filter cell lines further by karyotype categories in 621 lines.<br>EBiSC2 has enabled, via the update of the ethical governance framework, the ethically compliant collection of iPSCs from a myriad of sources using many variable consent templates, into the EBiSC centralised repository. This impacts researchers worldwide, providing them with access to safeguarding newly generated iPSC resources. |
| EBiSC2<br>stem cells | Human pluripotent Stem Cell registry (hPSCreg) continues to be the entry point for newly incoming EBiSC induced Pluripotent Stem Cell (iPSC) lines. Its use has enabled registration of >75 new EBiSC iPSC lines, providing standard identifiers and enabling a standard pipeline for data management through to the EBiSC catalogue. |
| EBiSC2<br>stem cells | The project has engaged with 6 different external research groups to advise them on how EBiSC2 can support with iPSC reprogramming, gene editing, differentiation and/or quality control. EBiSC2 has also provided 3 different letters of support for external third-party funding applications. Service provision activity for EFPIA has been completed, demonstrating application of EBiSC2 quality control standards to User banked lines. |
| EBiSC2<br>stem cells | To improve user experience and FAIRness (i.e., increase findability, accessibility, interoperability, and reusability) of the EBiSC collection, EBiSC2 has improved ontology mapping in the EBiSC catalogue by introducing three new tools (ROBOT, OLS and OxO), which simplifies search functionality and improves the user experience of searching for specific characteristics and identifying their cell line(s) of choice. |
| EBiSC2<br>stem cells | Continued provision of EBiSC2 iPSC lines via publicly searchable catalogue for a non-profit fee per vial. >360 vials have been distributed in 2022, covering >15 different diseases plus healthy controls and fulfilling >140 separate orders across four continents.<br>Anonymised clinical data related to 20 EBiSC iPSC lines is available upon request in .csv format for free. Clinical metadata for 20 iPSC lines is also openly searchable via the EBiSC catalogue. Updated protocols, publications, frequently asked questions and webinars are also all freely accessible via the EBiSC catalogue including 2 new publications and 3 new protocols, supporting Users to introduce and use iPSCs within their research activities.<br>Improved accessibility to linked clinical data and iPSC tools accelerates disease research. |
| EBiSC2<br>stem cells | EBiSC2 project results supported the research community enabling in 2022 at least 27 publications by external researchers using EBiSC iPSCs.<br>pubmed.ncbi.nlm.nih.gov/35805069/<br>pubmed.ncbi.nlm.nih.gov/35895133/<br>pubmed.ncbi.nlm.nih.gov/35456571/<br>pubmed.ncbi.nlm.nih.gov/36179692/<br>pubmed.ncbi.nlm.nih.gov/34932569/ |
| EPND<br>neurodegenerative diseases | The goal of EPND is to develop an infrastructure facilitating access to samples and data to support the acceleration of biomarker research in neurodegeneration. Targeted engagement with |

| Project title | Description of result(s) |
|---|---|
| | the neurodegenerative disease cohort community has resulted in an initial release of the Cohort Catalogue to support information exchange and connectivity across the community. |
| ESCulab<br>drug discovery | The European Lead Factory (ELF; currently funded through the ESCulab project) is a screening service with a vast chemical library that can be used by researchers to boost their drug discovery programmes. During the first year of the COVID-19 pandemic, the ELF prioritised COVID-19-related proposals through a fast-track procedure. The aim was to identify novel small-molecule inhibitors of viral entry into host cells as a prophylactic and therapeutic option for SARS-CoV-2 infection. The programme resulted in high-quality hits (chemical compounds with inhibitory activity) and associated biological data which have been used as the basis for a successful proposal to access the medicinal chemistry services available within EU-OPENSCREEN, ensuring thus continuation of the programme towards hit-to-lead phase outside the ESCulab project. This will allow the study of the precise mode of action along with the assessment of potency and affinity to variants of concern. EU-OPENSCREEN is a not-for-profit European Research Infrastructure Consortium (ERIC) which supports all stages of a chemical tool development project, including assay adaptation, high-throughput screening, and chemical optimisation of the 'hit' compounds. The ELF and EU-OPENSCREEN are complementary initiatives with common focus on the discovery and development of small molecule compounds. |
| ESCulab<br>drug discovery | ELF has launched a partnering initiative for charities and foundations, which will contribute to the sustainability efforts of the project. Through this initiative, the charities and foundations that enter into a collaboration with the ELF (outside of the project's frame), will gain access to a high-quality library of 535,000 chemical compounds, industry-standard ultra-high-throughput and high content screening facilities. The ELF platform for this service is now publicly available. |
| eTRANSAFE<br>safety | Flame, the predictive modelling and compound similarity search framework previously developed by eTRANSAFE has been released as stand-alone, open-source software. Flame allows users to easily develop machine-learning models, (e.g. QSAR) starting from collections of chemical compounds and is freely available. A manuscript describing this software has been published in the Journal of Cheminformatics. |
| EUbOPEN<br>drug discovery | EUbOPEN aims to facilitate new drug discovery programmes by providing starting points for under-researched drug targets. To date, they have publicly released:<br>• a dataset of 1.1 million compounds with over 10.9 million bioactivity data points<br>• comprehensive datasets on 41 freely-available high quality chemical probes for a variety of targets<br>• over 500 small molecules that cover a larger target space (albeit with less stringent criteria). |
| EUbOPEN<br>drug discovery | Several screening platforms have been set up to help identify chemical starting points for novel drug discovery programmes including:<br>• 8 DNA glycosylase assays including the following targets: OGG1, NEIL1/2/3, UNG, TDG, SMUG1, MPG;<br>• a GPCR screening panel (ADGRF1, ADRA2A, ADRB2, AGTR1, APLNR, C5AR1, CX3CR1, FPR2, FFAR4, GLP1R, GPR119, GPR35, S1PR1);<br>• a differential scanning fluorimetry (DSF) panel which contains 110 representative kinases (1/5 of the kinome);<br>• a kinome-wide cellular screening platform which allows for the screening of nearly 200 kinases in a cellular system.<br>Freely available at: www.eubopen.org/protocols-reagents |
| EUbOPEN<br>drug discovery | EUbOPEN manufactured 384 unique high quality protein samples from the 'druggable genome' – high potential drug targets that are difficult to study. The consortium also deposited 174 crystal structures from 87 different protein targets into the publicly available Protein Data Bank. |
| FAIRplus<br>knowledge management | One of the key outputs of the project, the FAIRplus 'cookbook' has been greatly updated via monthly 'bookdashes'. The cookbook is a practical guidance to help make and keep data findable, accessible, interoperable and reusable (FAIR). It currently includes over 50 recipes contributed by over 50 professionals from 30 organisations (including ELIXIR UK, EBI, Luxemburg, Switzerland, Netherlands, and Spanish ELIXIR nodes); cross-links have been added to several resources and registries in the ELIXIR ecosystem. The cookbook has also become an |

| Project title | Description of result(s) |
|---|---|
| | official service of the ELIXIR UK and Luxembourg Nodes; and IHI is recommending other project consortia to use it. |
| FAIRplus<br>knowledge management | When FAIRifying datasets, it is important to assess the level of FAIRness achieved. FAIRplus have developed a FAIR Evaluator tool for datasets.<br>This tool can be used both before and after a FAIRification process to check how successful the process has been. It is broken down into 5 maturity levels from 'Single Use Data', with no potential for reuse, up to 'Managed Data Assets', which are optimally managed at an enterprise level.<br>The tool is available as a recipe in the FAIRplus cookbook. |
| iABC (IMI1)<br>antimicrobial resistance | A number of pharmaceutical companies have been in contact with the EMBARC registry team to get support for clinical trial feasibility and/or to identify potential sites for clinical studies into bronchiectasis. |
| iConsensus<br>manufacturing technologies | The project has developed a new assay kit, the PA-301 aggregation screening assay kit for antibody in cell culture. Therapeutic antibody aggregation can cause immune reaction after being injected in the body. Quantification of antibody aggregation is a very important information, which is typically detected by methods such as on High Performance Liquid Chromatography (HPLC). Instead, the project has developed a simple high-throughput method. The kit can be ordered for fee to PAIA BIOTECH GMBH. |
| LITMUS<br>liver disease | The LITMUS project has published an atlas of histological images and guidelines for diagnosis and scoring. This atlas aims to provide a set of histological images useful to diagnose and score non-alcoholic fatty liver disease (NAFLD) in a consistent manner and is available online. |
| NeuroDeRisk<br>safety | The project succeeded at delivering a set of validated solutions for predicting neurotoxicity – many of which have been integrated into the NeuroDeRisk *in-silico* toolbox.<br>The toolbox includes a method for screening chemical structures and drug candidates against a panel of neurotoxicophore models, which scientists can use to predict adverse neurotoxic effects. It also includes data mining tools and a database of all the data generated and acquired during the project. One can also use the toolbox to draw a molecular structure and get structure-based alerts – even before the compound is synthesised. The NeuroDeRisk *in-silico* toolbox is available to anyone who wants to know about a compound's potential risks to the nervous system. |
| NEURONET<br>neurodegenerative disease | NEURONET has maintained its Knowledge Base, which represents the public publication of outputs from the IMI neurodegenerative portfolio. To date, the Knowledge Base represents the assets, deliverables, publications and tools of 24 projects. Since its launch, it has received just 27 423 page views and 4 397 users.<br>The most popular KB module, the Asset Map, represents 100 project assets, and is designed to provide a comprehensive overview of the assets from the IMI neurodegeneration portfolio, categorised by R&D stage (non-clinical, clinical, regulatory and real-world evidence) and type. |
| PIONEER<br>big data, cancer | The project ran a second studyathon in October 2022. The aim was to identify, amongst patients with metastatic hormone-sensitive prostate cancer (mHSPC) treated according to approved treatment plans, which patients will experience progression and death during an established follow-up period. During the 5-day event, a group of 55 participants defined study cohorts and the features that would facilitate treatment prediction by clinicians.<br>A total of 95 181mmunorent phenotypes were identified, and a sophisticated prediction model developed. To date, 15 data contributors have contributed data to the studyathon. Resources from the studyathon are available online here and here.<br>Access to the development tools, analytics environment and material can be granted upon request. |
| PREFER<br>patient involvement in R&D | The PREFER Recommendations – Why, when and how to assess and use patient preferences in medical product decision-making – have been released.<br>These PREFER Recommendations, with its strong input from regulators and HTA bodies, allow future sponsors of patient preference studies to design and execute the studies in a way that it addresses key aspects which are of high relevance for the stakeholders who intend to use the preferences for decision-making. These recommendations are accompanied by an operational |

| Project title | Description of result(s) |
|---|---|
| | Guidance that consists of 9 templates to utilise in the development and execution of a patient preference study.<br>In addition to the PREFER recommendations and operational Guidance, the consortium released a set of 16 webinars on the PREFER YouTube channel to further assist anyone who is interested in the development and execution of patient preference studies. Links to the webinars can also be found here.<br>The 2022 Report of the CIOMS Working Group XI Council for International Organisations of Medical Sciences (CIOMS) on The Patient involvement in the development, regulation and safe use of medicines encourages the use of the PREFER recommendations. |
| RAPID-COVID<br>coronaviruses | The project (which aimed to develop a rapid diagnostic for differential diagnosis of COVID-19 versus other respiratory infections) has made available on Mendeley (here and here) the data generated by the project that is relevant for addressing the public health emergency presented by the COVID-19 pandemic. |
| RESOLUTE<br>drug development | The project has kept generating numerous new tools and knowledge that boosts research on solute carriers (SLCs), and, ultimately, will facilitate their use as targets for drug development.<br>So far, the project has generated tools including: 894 codon-optimised human SLC sequences inserted in a plasmid compatible with the gateway cloning system; 1 197 lentiviral CRISPR/Cas9 vectors to generate knock-out (k.o.) cell lines; 1 090 inducible SLC expression vectors to generate two types of overexpression cell lines; 446 BacMam vectors for SLC expression and purification studies; 40 BioID vectors to generate cells for proximity proteomics studies; 3 plasmid libraries; 1 077 cell lines overexpressing tagged SLCs; k.o. cell line clones for 315 SLCs; 26 SLC proteins purified and reconstituted in proteoliposomes / detergents for *in vitro* assays or binder generation.<br>The project's public outputs can be accessed via the project website:<br>• tools & reagents: re-solute.eu/resources/reagents<br>• data generated by RESOLUTE or gathered form public repositories: re-solute.eu/resources/datasets<br>• transcriptomics and imaging datasets in visualisation dashboards: re-solute.eu/resources/dashboards |
| RESOLUTE<br>drug development | The project developed 25 assays to test the effect of different chemical compounds on individual SLC function for future use in drug discovery by the pharmaceutical industry and small/medium-sized biotech companies. These assays have been optimised and adapted to high throughput and medium throughput platforms for drug screening. The protocols and first results have been shared in the open access repository PubChem. |
| REsolution<br>drug development | REsolution has compiled publicly available data on genetic variation in solute carrier (SLC) genes and their association to diseases which can be visualised in the project's portal. This allows the quantification and comparison of the variants across SLCs, which is a tool for scientists for the exploration of human SLC genetics.<br>REsolution aims at maximising the chances that SLC transporters will become successful drug targets and uses the growing amount of data becoming available on genetic variations and disease association to assign pathophysiological relevance to individual transporters. |
| REsolution<br>drug development | A genetic score was established based on genetic assessments for the entire SLC family and visualised in the web portal. The scoring algorithm allows users to quantify and compare the variants across all SLCs, which should assist researchers in a tailored exploration of human SLC genetics. |
| SOPHIA<br>obesity | Produced and made available online the Bariatric Weight Trajectory Prediction tool, a calculator for predicting five-year weight trajectories after bariatric surgery. |
| TransQST<br>safety | The development and enhancement of tools that help to decipher and quantify toxic mechanisms is a key achievement of the project. Most of these tools have already been published and are openly accessible. To facilitate the access, the consortium has made them available through the open-source platform bio.tools, allowing their use in other projects and by the wider scientific community. |

| Project title | Description of result(s) |
|---|---|
| VAC2VAC<br>vaccines | 12 monoclonal antibodies (mAbs) that were selected based on the results obtained during the VAC2VAC project are available as purified mAbs from the National Institute for Biological Standards and Control in the UK. The antibodies are intended for use in the further development and validation of immunoassays for human diphtheria, tetanus and acellular pertussis (DtaP) vaccines and veterinary tetanus vaccines, for which proof of concept was demonstrated in VAC2VAC. |
| VALUE Dx<br>antimicrobial resistance, diagnostics | VALUE Dx has published on their website a report on Recommendations for innovative fit for purpose pricing and funding models for community-acquired acute respiratory tract infections (CA-ARTI) diagnostics. VALUE Dx proposed a total of 15 recommendations targeted at policymakers; 10 of them have been clustered in the policy areas of health technology assessment (HTA), pricing and procurement, and funding. Five additional recommendations refer to overarching aspects that are conducive to the successful implementation of policies stressing the importance of communication and stakeholder involvement, collaborative approaches (also across countries), and monitoring and evaluation as essential components of policy implementation. |
| VITAL<br>vaccines | A searchable catalogue web application was developed, allowing an easy and fast view of existing data sources for specific infectious diseases (ID) known for their high disease burden in aging adults. This catalogue is an interesting tool in preclinical drug development for those interested in knowing the extent of specific ID burden. The database has been made publicly available. |

## Miscellaneous

| Project title | Description of result(s) |
|---|---|
| DRAGON<br>coronaviruses | In partnership with the U-BIOPRED Alliance and the Paediatric Asthma Alliance, DRAGON established Precision Medicine BioPharmaX. This collaborative partnership brings together different disciplines, stakeholders, initiatives and disease domains such as asthma, COPD, and COVID-19 to advance the concept of precision medicine. The new organisation will help to secure the sustainability of DRAGON's results. |
| ENABLE (IMI1)<br>antimicrobial resistance | The success of ENABLE motivated a group of institutes to set up the ENABLE-2 Drug Development Platform with funding from the Swedish government. ENABLE-2 is an antibacterial drug discovery platform with focus on the early stages of antibiotic discovery and development with the hope that they will successfully 'graduate' to other initiatives that focus more on the later stages. |
| EQIPD<br>data quality | EQIPD developed the EQIPD Quality System (EQIPD QS), which sets out a systematic approach to improving the quality of preclinical research data as well as tools and resources to further support researchers who want to follow best practice in this important field.<br>In 2022, the Guarantors of EQIPD e.V. (GoEQIPD) announced the formation of a registered association to provide the legal framework for future activities and ensure the preservation and further development of the legacy of the EQIPD project. In addition to keeping the EQIPD resources up to date, GoEQIPD aims to oversee the EQIPD certification process, and provide training to the research community on the generation of quality research. |
| EUbOPEN<br>drug discovery | As a result of the work performed in EUbOPEN, an SME, CELLinib, has been established. This company offers profiling of small molecules for a representative fraction of the kinome in living cells using the Promega NanoBRETTM technology. |
| INNODIA / INNODIA HARVEST<br>diabetes | An international non-profit association called INNODIA iVZW (internationale vereniging zonder winstoogmerk) based in Leuven, Belgium has been established to ensure that the projects' legacy will continue after the IMI funding period.<br>The organisation aims at facilitating the sharing of expertise in the European type 1 diabetes research space and empower people living with type 1 diabetes in clinical trials. At the core of |

| Project title | Description of result(s) |
|---|---|
| | INNODIA iVZW's work is the unique pan-European clinical trial infrastructure for type 1 diabetes that the projects have created. |
| RAPID-COVID coronaviruses | The two diagnostic panels to detect and differentiate the causative pathogens in patients who present with COVID-like symptoms (SARS-CoV-2 alongside 17 common causes of upper-respiratory tract infections and 11 common causes of pneumonia), CE marked in the previous period received regulatory approval for sale in the EU, with planned transition into in vitro diagnostic regulation (IVDR) compliance by 2025). In the coming years, these kits should support treatment decisions for several respiratory diseases whilst maintaining surveillance on SARS COV-2, supporting potential control measures for SARS COV-2 positive patients and allow rapid identification of potential localized outbreaks of COVID-19. |
| RESCEU respiratory disease | An article published in the Journal of Infectious Diseases co-authored by both researchers and patient experts summarises the history, current role, and future aims of the RSV Patient Advisory Board in the RESCEU project as an advocate to improve patient involvement in research. |
| RTCure rheumatoid arthritis | The consortium evaluated importance and effectiveness of involving patients and members of the public in rheumatology research actions. The results, published in BMC Rheumatology, confirm patient and public involvement had a positive impact on the RTCure project, by enhancing the integration of different perspectives and ensuring that the research is relevant and meaningful for patients. The study also highlights the importance of early involvement, engagement, and compensation of the patient and public partners. |

# Annex 4 – Publications from projects

### Hot publications in 2022

Hot publications are those that received enough citations to place in the top 0.1% of papers in their research field.

- Trubetskoy, Vassily et al. (2022) Mapping genomic loci implicates genes and synaptic biology in schizophrenia, Nature 604: 502
- Vangeel, Laura et al. (2022) Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern, Antiviral Research 198: n/a
- Xie, Chenglong et al. (2022) Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow, Nature Biomedical Engineering 6: 76
- D'Agostino, Mattia et al. (2022) Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project, Journal of Clinical Oncology 40: 3406

### 2022 publications featured in the top 10 Journals by JIF (journal impact factor)

- Walma, David A. Cruz et al. (2022) Ubiquitin ligases: guardians of mammalian development, NAT REV MOL CELL BIO 23: 350-367
- Aliberti, Stefano et al. (2022) Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations, LANCET RESP MED 10: 298-306
- Kachroo, Priyadarshini et al. (2022) Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma, NAT MED 28: 814-822
- Li, Xintong et al. (2022) Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis, BMJ-BRIT MED J 376:
- Jones, Philip S. et al. (2022) IMI European Lead Factory – democratizing access to high-throughput screening, NAT REV DRUG DISCOV 21: 245-246
- Bernabei, Roberto et al. (2022) Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project), BMJ-BRIT MED J 377:
- Vianello, Eleonora et al. (2022) Transcriptomic signatures induced by the Ebola virus vaccine rVSV Delta G-ZEBOV-GP in adult cohorts in Europe, Africa, and North America: a molecular biomarker study, LANCET MICROBE 3: E113-E123
- Sartore-Bianchi, Andrea et al. (2022) Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial, NAT MED
- Liew, Felicity et al. (2022) Inhaled corticosteroids: not just for asthma, but for COVID-19? Comment, LANCET RESP MED 10: 526-527
- Mila-Aloma, Marta et al. (2022) Plasma p-tau231 and p-tau217 as state markers of amyloid-beta pathology in preclinical Alzheimer's disease, NAT MED 28: 1797-+
- Mackensen, Andreas et al. (2022) Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus, NAT MED 28: 2124-2132
- Buergel, Thore et al. (2022) Metabolomic profiles predict individual multidisease outcomes, NAT MED 28: 2309-+
- Oakley, Bethany F. M. et al. (2022) Advances in the identification and validation of autism biomarkers COMMENT, NAT REV DRUG DISCOV 21: 697-698
- Kotecha, Dipak et al. (2022) CODE-EHR best practice framework for the use of structured electronic healthcare records in clinical research, BMJ-BRIT MED J 378

- Surendran, Praveen et al. (2022) Rare and common genetic determinants of metabolic individuality and their effects on human health, NAT MED 28: 2321
- Rech, Juergen et al. (2022) Towards preventive treatment of rheumatoid arthritis, LANCET 400: 253-255
- Feldman, Eva L. et al. (2022) Amyotrophic lateral sclerosis, LANCET 400: 1363-1380
- Kieh, Mark et al. (2022) Randomized Trial of Vaccines for Zaire Ebola Virus Disease, NEW ENGL J MED
- Li, You et al. (2022) Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis, LANCET 399: 2047-2064

### Highly cited publications in 2022

Highly cited publications have received enough citations to place in the top 1% of papers in their research field.

- Kalkman, Shona et al. (2022) Patients and public views and attitudes towards the sharing of health data for research: a narrative review of the empirical evidence, J MED ETHICS 48: 3-13
- Xie, Chenglong et al. (2022) Amelioration of Alzheimer's disease pathology by mitophagy inducers identified via machine learning and a cross-species workflow, NAT BIOMED ENG 6: 76
- Masoodi, Mojgan et al. (2022) Disturbed lipid and amino acid metabolisms in COVID-19 patients, J MOL MED 100: 555-568
- Chen, Jun et al. (2022) JAS-GAN: Generative Adversarial Network Based Joint Atrium and Scar Segmentations on Unbalanced Atrial Targets, IEEE J BIOMED HEALTH 26: 103-114
- Gawish, Riem et al. (2022) ACE2 is the critical in vivo receptor for SARS-CoV-2 in a novel COVID-19 mouse model with TNF- and IFN gamma-driven immunopathology, ELIFE 11
- Shannon, Ashleigh et al. (2022) A dual mechanism of action of AT-527 against SARS-CoV-2 polymerase, NAT COMMUN 13
- Luukkonen, Panu K. et al. (2022) Distinct contributions of metabolic dysfunction and genetic risk factors in the pathogenesis of non-alcoholic fatty liver disease, J HEPATOL 76: 526-535
- Whiteley, William et al. (2022) Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, or thrombocytopenic events: A population-based cohort study of 46 million adults in England, PLOS MED 19
- Gutmann, Clemens et al. (2022) Association of cardiometabolic microRNAs with COVID-19 severity and mortality, CARDIOVASC RES 118: 461-474
- Balboa, Diego et al. (2022) Functional, metabolic and transcriptional maturation of human pancreatic islets derived from stem cells, NAT BIOTECHNOL 40: 1042
- Aliberti, Stefano et al. (2022) Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations, LANCET RESP MED 10: 298-306
- van Kessel, Robin et al. (2022) Digital Health Paradox: International Policy Perspectives to Address Increased Health Inequalities for People Living With Disabilities, J MED INTERNET RES 24
- Obeid, Michel et al. (2022) Humoral Responses Against Variants of Concern by COVID-19 mRNA Vaccines in Immunocompromised Patients, JAMA ONCOL 8
- Petersen, Elina Larissa et al. (2022) Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme, EUR HEART J 43: 1124-1137
- Kachroo, Priyadarshini et al. (2022) Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma, NAT MED 28: 814-822
- Li, Xintong et al. (2022) Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population-based cohort and self-controlled case series analysis, BMJ-BRIT MED J 376
- Trubetskoy, Vassily et al. (2022) Mapping genomic loci implicates genes and synaptic biology in schizophrenia, NATURE 604: 502

- Nan, Yang et al. (2022) Data harmonisation for information fusion in digital healthcare: A state-of-the-art systematic review, meta-analysis and future research directions, INFORM FUSION 82: 99-122
- Schweighauser, Manuel et al. (2022) Age-dependent formation of TMEM106B amyloid filaments in human brains, NATURE 605: 310
- Vangeel, Laura et al. (2022) Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern, ANTIVIR RES 198
- Bernabei, Roberto et al. (2022) Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project), BMJ-BRIT MED J 377
- Oakley, Bethany F. M. et al. (2022) Alexithymia in autism: cross-sectional and longitudinal associations with social-communication difficulties, anxiety and depression symptoms, PSYCHOL MED 52: 1458-1470
- Mackensen, Andreas et al. (2022) Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus, NAT MED 28: 2124-2132
- Dagostino, Mattia et al. (2022) Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project, J CLIN ONCOL 40: 3406
- Li, You et al. (2022) Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis, LANCET 399: 2047-2064
- Codd, V et al. (2022) Measurement and initial characterization of leukocyte telomere length in 474,074 participants in UK Biobank, NATURE AGING 2: 170

## Annex 5 – Patents from projects

Since the start of the IMI2 programme, projects have been patenting developed technologies. The statistics below encompass 7 patent/trademark/registered design applications and 12 patents/trademarks awarded from the beginning of IMI2 until 31 December 2022.

FILODAG – 1 patent application on ‘superparamagnetic particles modified with samarium, gadolinium and yttrium for use in the detection of Ebola virus’.

MOFINA – 1 registered design and 1 trademark application on ‘Alere Q filovirus detector’.

EBOVAC 1 – 1 patent awarded on ‘methods and compositions for enhancing immune responses’ and 2 patents awarded on ‘methods and compositions for inducing protective immunity against filovirus infection’.

PHAGO – 1 patent awarded on ‘TREM2 cleavage modulators and uses thereof’ and 1 patent awarded on ‘up-scaled production of microglia-like/-precursor cells and macrophage cells using mesh macro carriers’.

PEVIA – 2 patent applications on ‘mélanges d’epitopes t cd8 immunogènes du virus Ebola’ and ‘peptides 188mmunogens issus de la nucléoprotéine du virus Ebola’.

EbiSC2 – 2 trademark applications for the EbiSC trademark.

TRIC-TB – 6 patents awarded for ‘novel compounds’.

GRAVITATE-HEALTH – 1 trademark awarded on “G-lens”, a digital health information tool.

There are no patent applications nor patents awarded under IHI due to the recent launch of the programme.

# Annex 6 – Scoreboard of Horizon 2020 legacy key performance indicators (KPIs)

This annex contains the scoreboards relating to the IMI2 programme, which was part of Horizon 2020. Note that in the interests of space, we have deleted the rows of the tables that are no longer relevant, such as those relating to the launch and evaluation of Horizon 2020 calls for proposals.

## KPIs specific to the Innovative Medicines Initiative 2 (IMI2) programme

Reporting methodology: cumulatively reporting from the beginning of IMI2 until 31/12/2022.

These KPIs are for the IMI2 programme only. However, many of them are also relevant for IMI1. In these cases, the results for IMI1 + IMI2 are given in a separate column. The goal here is to provide readers with an overview of the results of the entire IMI programme, since its launch in 2008. In cases where the KPI is not relevant for IMI1, the IMI1 + IMI2 column is marked 'not applicable' (n/a).

| KPI | Definition | Comment | Relates to | IMI2 target | IMI2 results | IMI1 + IMI2 results |
|---|---|---|---|---|---|---|
| 1 | Number of relevant priority areas in the WHO "Priority Medicines for Europe and the World 2013 Update" reflected in the IMI2 Strategic Research Agenda (SRA) and addressed by IMI2 projects. | Based on the SRA and including the WHO priority medicines therapeutic areas:<br>- Expressed as a number of areas reflected in the IMI2 portfolio.<br>- Complemented by the number and budget of grant agreements that delivered them. | IMI2 Regulation objective b1:<br>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' | 12 | 11 out of 12 SRA priority areas are addressed by IMI2 projects<br>Number of projects: 80<br>Budget committed:<br>EUR 2 225 485 225 | n/a |
| 2 | The number of project developed assets that completed a significant milestone during the course of an IMI2 project. | Assets are defined as new drug or diagnostic candidates, targets, biomarkers or other tools that can be shown to have reached a significant milestone or pass a significant stage gate. | IMI2 Regulation objectives b1, b2, b4, b5 and b6:<br>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'<br>b2: 'reduce the time to reach clinical proof of concept in medicine development…'<br>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to | 50 | 439 | 590 |

| KPI | Definition | Comment | Relates to | IMI2 target | IMI2 results | IMI1 + IMI2 results |
|---|---|---|---|---|---|---|
| | | | clinical relevance and approved by regulators'<br>b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks'<br>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products' | | | |
| 3 | New or improved guidelines, methodologies, tools, technologies or solutions accepted by regulatory authorities for use in the context of R&D, specifically for:<br>- new tools for preclinical drug development,<br>- biomarkers and tools developed to predict clinical outcomes,<br>- improved protocols to design and process of clinical trials,<br>- new biomarkers developed for the efficacy and safety of vaccine candidates. | - Measured by the number of the formal qualification procedures completed (letters of support, qualification opinions received).<br>- Complemented by number of qualification procedures launched.<br>- Expressed as net figure.<br>- Complemented by the number and budget of grant agreements that delivered them. | IMI2 Regulation objectives b1, b2, b4, b5 and b6:<br>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'<br>b2: 'reduce the time to reach clinical proof of concept in medicine development…'<br>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'<br>b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks'<br>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products' | 10<br>(for completed procedures) | 24 completed procedures:<br>-CE mark: 4<br>-Inclusion in regulatory guidelines: 6<br>-Regulatory letter of support: 2<br>-Regulatory qualified opinion : 10<br>-Submission for qualification opinion: 2<br>Number of projects: 17<br>Projects' budget: EUR<br>410 510 810 | 44 completed procedures:<br>-CE mark: 4<br>-Inclusion in regulatory guidelines: 17<br>-Regulatory letter of support: 6<br>-Regulatory qualified opinion : 12<br>-Submission for qualification opinion: 5<br>Number of projects: 32<br>Projects' budget: EUR<br>1 056 497 669 |
| 4 | New taxonomies of diseases and new stratifications (such as the definition of patient | - Expressed as net figure.<br>- As published and/or implemented by industrial | IMI2 Regulation objectives b3 and b4:<br>b3: 'develop new therapies for diseases for which there is a high unmet need…' | 30 | 46<br>Number of projects: 17<br>Projects' budget: EUR | 62<br>Number of projects: 24<br>Projects' budget: EUR |

| KPI | Definition | Comment | Relates to | IMI2 target | IMI2 results | IMI1 + IMI2 results |
|---|---|---|---|---|---|---|
| | subpopulations, development, validation and use of new diagnostics) developed. | partners and evidenced in annual reporting.<br>- Complemented by the number and budget of grant agreements that delivered them. | b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' | | 461 627 565 | 842 492 641 |
| 5 | Contribution (in-kind or in-cash) from non-pharma actors (e.g. non-pharma industries, foundations, charities, professional organisations). | Expressed as total amount in EUR. | IMI2 Regulation objective a:<br>a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'<br>and IMI2 Regulation recital 8:<br>'The initiative should consequently seek to involve a broader range of partners, including mid-caps, from different sectors, such as biomedical imaging, medical information technology, diagnostic and animal health industries.' | EUR 300 million | EUR 269.8 million<br>(AP: EUR 202.7 million<br>Partners in Research: EUR 67.1 million) | n/a |
| 6 | Share of IMI projects whose resources/outputs are made accessible beyond the consortia partners (with or without fee), such as major databases, bio-banks, in silico tools, training materials, clinical trial networks, guidance etc. | - Complemented by the number and budget of grant agreements that delivered them.<br>- Accessibility to be evidenced by online availability (with or without fee), and documented by project reports. | IMI2 Regulation objectives a, b2 and b6:<br>a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'<br>b2: 'reduce the time to reach clinical proof of concept in medicine development'<br>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products' | 50% | 58.26%<br>Number of projects: 67<br>Projects' budget: EUR<br>1 881 777 705 | 65.12%<br>Number of projects: 112<br>Projects' budget: EUR<br>3 509 603 388 |
| 7 | Co-authorships and cross-sector publications between | - Expressed as net figure<br>- Complemented by the number and budget of grant | IMI2 Regulation objective a:<br>a: 'to support… the development and implementation of pre-competitive research | 1 500 | 2 167 | 5 993 |

| KPI | Definition | Comment | Relates to | IMI2 target | IMI2 results | IMI1 + IMI2 results |
|---|---|---|---|---|---|---|
| | European researchers on IMI2 projects (sectors include academia, small and mid-sized companies, pharma, regulators, patient organisations, etc.). | agreements that delivered them. | and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…' | | | |
| 8 | New tools and processes generated by IMI2 projects that have been implemented by the industry participants of IMI projects. | - New tools and processes: e.g. animal models, standards, biomarkers, SOPs, use of screening platforms and clinical trial networks.<br>- Expressed as net figure.<br>- Complemented by the number and budget of grant agreements that delivered them.<br>- Assessment based on yearly reporting by industrial partners until the project close-out meetings. | IMI2 Regulation objectives a, b2 and b6:<br>a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'<br>b2: 'reduce the time to reach clinical proof of concept in medicine development'<br>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products' | 50 | 524<br>Number of projects: 56<br>Projects' budget: EUR<br>1 263 451 582 | 838<br>Number of projects: 96<br>Projects' budget: EUR<br>2 769 524 178 |
| 9 | Share of projects involving patient organisations and healthcare professionals' associations (as consortium partners, members of advisory boards, members of stakeholder groups etc.). | - Complemented by the number and budget of grant agreements that delivered them. | IMI2 Regulation objectives a, and b1:<br>a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'<br>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' | 80 % | 63.16%<br>Number of projects: 72<br>Projects' budget: EUR<br>2 183 490 806 | 59.06%<br>Number of projects: 101<br>Projects' budget: EUR<br>3 079 374 335 |
| 10 | Support to SMEs: share of SMEs participating as formal | - To be complemented by the number of SMEs benefitting | H2020 priority;<br>IMI2 Regulation recital 9 | 20 % | Participations: 16.1%<br>(370 out of 2 300) | Participations: 16.2%<br>(571 out of 3 524) |

| KPI | Definition | Comment | Relates to | IMI2 target | IMI2 results | IMI1 + IMI2 results |
|---|---|---|---|---|---|---|
| | IMI project beneficiaries. | from IMI project support in other ways. | '(…) should seek to foster the capacity of smaller actors such as research organisations, universities and SMEs for participating in open innovation models and to promote the involvement of SMEs in its activities, in line with its objectives' | | (IMI2 cumulative figures as of 31/12/2022, beneficiaries receiving EU funding only) | (IMI1 and IMI2 cumulative figures as of 31/12/2022, beneficiaries receiving EU funding only) |

## Horizon 2020 Key Performance Indicators common to all JTI JUs[48]

| | Correspondence to general Annex 1 | Key Performance Indicator | Definition / responding to question | Type of data required | Target at the end of H2020 | Results in 2022 |
|---|---|---|---|---|---|---|
| Industrial Leadership | 12 | SME – Share of participating SMEs introducing innovations new to the company or the market (covering the period of the project plus three years) | Based on Community Innovation Survey. Number and % of participating SMEs that have introduced innovations to the company or to the market | Number of SMEs that have introduced innovations | 50% | n/a |
| | 13 | SME – Growth and job creation in participating SMEs | Turnover of company, number of employees | Turnover of company, number of employees | To be developed based on FP7 ex-post evaluation and /or first H2020 project results | n/a |
| Societal Challenges | 14 | Publications in peer-reviewed high impact journals | The percentage of papers published in the top 10 % impact ranked journals by subject category | Publications from relevant funded projects (DOI: Digital Object Identifiers); Journal impact benchmark (ranking) data to be collected by commercially available bibliometric databases. | [On average, 20 publications per EUR 10 million funding (for all societal challenges)] | 28.23% |
| | 15 | Patent applications and patents awarded in the area of the JTI | Number of patent applications by theme; Number of awarded patents by theme | Patent application number | On average, 2 per EUR10 million funding (2014 – 2020) RTD A6 | 7 patent applications<br>12 patents awarded |

[48] This table shows the H2020 KPIs which apply to JTI JUs, both under Industrial Leadership and Societal Challenges (H2020 Key Performance Indicators. Annex II - Council Decision 2013/743/EU). In this and the following table, the numbers attributed to the indicators correspond with those in the H2020 indicators approved by the RTD Director-General and agreed by all the research family DGs (according to Annexes II and III - Council Decision 2013/743/EU). The missing numbers correspond to KPIs not applicable to the JUs. KPIs and indicators that correspond to those approved by the RTD Director-General are presented with a white background in the tables. KPIs and monitoring indicators in tables I and II which do not correspond to those approved by the RTD Director-General are presented with a green background in the tables.

| | Correspondence to general Annex 1 | Key Performance Indicator | Definition / responding to question | Type of data required | Target at the end of H2020 | Results in 2022 |
|---|---|---|---|---|---|---|
| | 16 | Number of prototypes testing activities and clinical trials[49] | Number of prototypes, testing (feasibility/demo) activities, clinical trials | Reports on prototypes, and testing activities, clinical trials | [To be developed on the basis of first Horizon 2020 results] | Since the start of IMI2 programme, cumulatively:<br>Prototypes: 136<br>Testing Activities: 164<br>Clinical Trials: 252 |
| | 17 | Number of joint public-private publications in projects | Number and share of joint public-private publications out of all relevant publications | Properly flagged publications data (DOI) from relevant funded projects | [To be developed on the basis of first Horizon 2020 results] | 811<br>27.82% |
| | 18* | New products, processes, and methods launched into the market | Number of projects with new innovative products, processes, and methods | Project count and drop down list allowing to choose the type processes, products, methods | [To be developed on the basis of first Horizon 2020 results] | Since the start of IMI2 programme, cumulatively:<br>New Products: 45<br>New Processes: 31<br>New Methods: 37 |

[49] Clinical trials are IMI specific.

## Indicators for monitoring H2020 cross-cutting issues common to all JTI JUs[50]

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| 2 | Widening the participation | 2.1 Total number of participations by EU-28 Member State | Nationality of H2020 applicants & beneficiaries (number of) | YES | Eligible proposals:<br>Applications: 7 495<br>Applicants: 2 628<br>Beneficiaries: 2 714 |

| Country | Participations (Participants) |
|---|---|
| Austria | 59 (26) |
| Belgium | 258 (80) |
| Bulgaria | 2 (2) |
| Croatia | 4 (4) |
| Czechia | 12 (7) |
| Denmark | 96 (32) |
| Estonia | 6 (3) |
| Finland | 44 (13) |
| France | 314 (122) |
| Germany | 435 (155) |
| Greece | 11 (7) |
| Hungary | 8 (5) |
| Ireland | 35 (19) |

[50] This table presents all indicators for the monitoring of cross-cutting issues which apply to JTI JUs (Annex III - Council Decision 2013/743/EU). In this table and the previous one, the numbers attributed to the indicators correspond with those in the H2020 indicators approved by the RTD Director-General and agreed by all the Research family DGs (according to Annexes II and III - Council Decision 2013/743/EU). The missing numbers correspond to KPIs not applicable to the JUs. KPIs and Indicators that correspond to those approved by the RTD Director-General are presented with a white background in the tables. KPIs and monitoring indicators in tables I and II, which do not correspond to those approved by the RTD Director-General, are presented with a green background in the tables.

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 | |
|---|---|---|---|---|---|---|
| | | | | | Italy | 182 (93) |
| | | | | | Latvia | 1 (1) |
| | | | | | Lithuania | 1 (1) |
| | | | | | Luxembourg | 35 (6) |
| | | | | | Netherlands | 319 (101) |
| | | | | | Poland | 9 (7) |
| | | | | | Portugal | 28 (27) |
| | | | | | Romania | 3 (3) |
| | | | | | Slovenia | 8 (6) |
| | | | | | Spain | 178 (79) |
| | | | | | Sweden | 125 (33) |
| | | | | | United Kingdom[51] | 541 (146) |
| | | | | | Total EU-28 | 2 714 (978) |
| | | | | | (Cumulative figures as of 31/12/2022) | |
| | | 2.2 Total amount of EU financial contribution requested by EU-28 Member State (EUR millions) | Nationality of H2020 beneficiaries and corresponding EU financial contribution | YES | Country | IHI contrib., M EUR (%) |
| | | | | | Austria | 38.7 (2.9%) |
| | | | | | Belgium | 75.6 (5.6%) |
| | | | | | Bulgaria | 0.2 (0%) |
| | | | | | Croatia | 0.2 (0%) |
| | | | | | Czechia | 3.1 (0.2%) |
| | | | | | Denmark | 22.1 (1.6%) |
| | | | | | Estonia | 2.7 (0.2%) |
| | | | | | Finland | 19.3 (1.4%) |
| | | | | | France | 134.6 (10%) |

[51] To ensure easy comparisons with reports of previous years, the UK is kept with the EU-27 in the H2020 / IMI2 KPIs.

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| | | | | | Germany 164.4 (12.2%)<br>Greece 3.7 (0.3%)<br>Hungary 3.3 (0.2%)<br>Ireland 25.4 (1.9%)<br>Italy 75.3 (5.6%)<br>Latvia 0.4 (0%)<br>Lithuania 0.1 (0%)<br>Luxembourg 12.5 (0.9%)<br>Netherlands 272.6 (20.3%)<br>Poland 1.7 (0.1%)<br>Portugal 9.8 (0.7%)<br>Romania 1.6 (0.1%)<br>Slovenia 1.3 (0.1%)<br>Spain 113.4 (8.4%)<br>Sweden 54.3 (4%)<br>United Kingdom 309.4 (23%)<br>Total EU-28 1 345.7<br>(Cumulative figures as of 31/12/2022) |
| NA | | Total number of participations by Associated Countries | Nationality of H2020 applicants & beneficiaries (number of) | YES | Eligible proposals:<br>Applications: 590<br>Applicants: 246<br>Beneficiaries: 256<br>Country — Participations (Participants)<br>Iceland 1 (1)<br>Israel 22 (12)<br>Norway 28 (13)<br>Serbia 4 (4)<br>Switzerland 199 (52)<br>Turkiye 2 (2)<br>Total Assoc. countries: 256 (84) |

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| | | | | | (Cumulative figures as of 31/12/2022) |
| NA | | Total amount of EU financial contribution by Associated Country (EUR millions) | Nationality of H2020 beneficiaries and corresponding EU financial contribution | YES | Country / IHI contrib., M EUR (%)<br>Iceland 0.1 (0.1%)<br>Israel 3.6 (4.6%)<br>Norway 11 (14.2%)<br>Serbia 1.1 (1.4%)<br>Switzerland 62.1 (79.7%)<br>Turkiye 0 (0%)<br>Total Assoc. countries: 77.9<br>(Cumulative figures as of 31/12/2022) |
| 3 | SMEs participation | 3.1 Share of EU financial contribution going to SMEs (Enabling & industrial tech and Part III of Horizon 2020) | Number of H2020 beneficiaries flagged as SME<br>% of EU contribution going to beneficiaries flagged as SME | | Participations: 370 out of 2 300 (16.1%)<br>Participants: 249 out of 989 (25.2%)<br>EU funding: €176.5m (12.1%)<br>(Cumulative figures as of 31/12/2022, beneficiaries receiving EU funding only) |
| 6 | Gender | 6.1 Percentage of women participants in H2020 projects | Gender of participants in H2020 projects | YES | 53% of the total workforce working in IMI2 projects is female. |
| | | 6.2 Percentage of women project coordinators in H2020 | Gender of MSC fellows, ERC principal investigators and scientific coordinators in other H2020 activities | YES | 31 women out of 117 project coordinators in IMI2 projects in 2022 |
| 7 | International cooperation | 7.1 Share of third-country participants in Horizon 2020 | Nationality of H2020 beneficiaries | YES | Eligible proposals:<br>Applications: 242<br>Applicants: 162 |

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| | | | | | Beneficiaries: 133<br>Country \| Participations (Participants)<br>Australia 2 (2)<br>Benin 1 (1)<br>Brazil 1 (1)<br>Burkina Faso 1 (1)<br>Canada 7 (7)<br>China (People's Republic of) 1 (1)<br>Congo (Democratic Republic of) 1 (1)<br>Gabon 2 (1)<br>Japan 2 (2)<br>Senegal 2 (1)<br>Sierra Leone 3 (2)<br>Singapore 1 (1)<br>South Africa 3 (3)<br>Tanzania (United Republic of) 1 (1)<br>United States 105 (53)<br>Total for third countries 133 (79)<br>(Cumulative figures as of 31/12/2022) |
| | | 7.2 Percentage of EU financial contribution attributed to third country participants | Nationality of H2020 beneficiaries and corresponding EU financial contribution | YES | Country \| IHI contrib. M EUR (%)<br>Australia 0.3 (0.7%)<br>Benin 0.6 (1.4%)<br>Brazil 0.3 (0.7%)<br>Burkina Faso 3.8 (9.1%)<br>Canada 0.4 (1.1%)<br>China (People's Republic of) 0 (0%) |

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| | | | | | Congo (Democratic Republic of) 3 (7.3%)<br>Gabon 0.9 (2.1%)<br>Japan 0 (0%)<br>Senegal 0.4 (0.9%)<br>Sierra Leone 20.2 (48.8%)<br>Singapore 0 (0%)<br>South Africa 1.5 (3.7%)<br>Tanzania (United Republic of) 0.5 (1.2%)<br>United States 9.5 (23.1%)<br>Total for third countries 41.4<br>(Cumulative figures as of 31/12/2022) |
| NA | | Scale of impact of projects (High Technology Readiness Level) | Number of projects addressing TRL[52] between (4-6, 5-7) | | 2 projects TRL 4<br>3 projects TRL 5<br>1 project TRL 6<br>3 projects TRL 7<br>1 projects TRL 8<br>6 projects TRL 9 |
| 11 | Private sector participation | 11.1 Percentage of H2020 beneficiaries from the private for-profit sector | Number of and % of the total H2020 beneficiaries classified by type of activity and legal status | | Participations:<br>1 196 out of 3 104 (38.53%)<br>Participants:<br>428 out of 1 141 (37.5 %) |
| | | 11.2 Share of EU financial contribution going to private for-profit entities | H2020 beneficiaries classified by type of activity; corresponding EU contribution | | €197.8 million out of €1 465.0 million (13.5%) |

[52] TRL: Technology Readiness Level.

| Correspondence in the general Annex 2 | Cross-cutting issue | Definition / responding to question | Type of data required | Direct contribution to ERA | Results in 2022 |
|---|---|---|---|---|---|
| | | (Enabling & industrial tech and Part III of Horizon 2020) | | | |
| 12 | Funding for PPPs | 12.1 EU financial contribution for PPP (Art 187) | EU contribution to PPP (Art 187) | | 2022 EU cash contribution EUR 155 095 000 |
| | | 12.2 PPPs leverage: total amount of funds leveraged through Art. 187 initiatives, including additional activities, divided by the EU contribution | Total funding made by private actors involved in PPPs<br>- in-kind contribution already committed by private members in project selected for funding<br>- additional activities (i.e. research expenditures/investment of industry in the sector, compared to previous year) | | EFPIA and Associated Partners contribution (EUR 1 499.4 million) divided by EU contribution (EUR 1 452.1 million)<br>= leverage of 103% |
| 13 | Communi-cation and dissemination | 13.3 Dissemination and outreach activities other than peer-reviewed publications – [Conferences, workshops, press releases, publications, flyers, exhibitions, trainings, social media, websites, communication campaigns (e.g. radio, TV)] | A drop down list allows to choose the type of dissemination activity. Number of events, funding amount and number of persons reached thanks to the dissemination activities | YES | Total number of events: 173 588<br>Total funding amounts: EUR 10 733 316 |
| NA | Participation of RTOs and universities | Participation of RTOs[53] and Universities in PPPs (Art 187 initiatives) | Number of participations of RTOs to funded projects and % of the total<br>Number of participations of universities to funded projects and % of the total<br>% of budget allocated to RTOs and to universities | YES | Participations:<br>Research org: 566 (18.2%)<br>HES: 991 (31.9%)<br>% budget allocated:<br>Res. Org: EUR 349.2 million (23.8%)<br>HES: EUR 771.0 million (52.6%) |

[53] RTO: Research and Technology Organisation.

## Annex 7 – Scoreboard of Horizon Europe common key impact pathway indicators (KIPs)

IHI launched 3 calls for proposals in 2022: two single stage calls (IHI call 1 and call 3) and one two-stage call (IHI call 2). There were no Grant Agreements signed in 2022, therefore these projects will start in 2023 and will have their first reporting period in 2024.

| Key Impact Pathway[54] | Short-term | Medium-term | Longer-term | Detail per action or globally for 2022 |
|---|---|---|---|---|
| **Towards scientific impact** | | | | |
| 1-Creating high-quality new knowledge | Publications – Number of peer-reviewed scientific publications resulting from the Programme | Citations – Field-weighted citation index of peer-reviewed Publications resulting from the Programme | World-class science – Number and share of peer-reviewed publications resulting from the projects funded by the Programme that are core contribution to scientific fields | |
| 2-Strengthening human capital in R&I | Skills -Number of researchers involved in upskilling (training, mentoring/coaching, mobility and access to R&I infrastructures) activities in projects funded by the Programme | Careers – Number and share of upskilled researchers involved in the Programme with increased individual impact in their R&I field | Working conditions – Number and share of upskilled researchers involved in the Programme with improved working conditions, including researchers' salaries | |
| 3-Fostering diffusion of knowledge and open science | Shared knowledge – Share of research outputs (open data/publication/software etc.) resulting from the Programme shared through open knowledge infrastructures | Knowledge diffusion – Share of open access research outputs resulting from the Programme actively used/cited | New collaborations – Share of Programme beneficiaries which have developed new transdisciplinary/transsectoral collaborations with users of their open access research outputs resulting from the Programme | |
| **Towards societal impact** | | | | |
| 4-Addressing Union policy priorities and global challenges through R&I | Results – Number and share of results aimed at addressing identified Union policy priorities and global challenges | Solutions – Number and share of innovations and research outcomes addressing identified Union | Benefits – Aggregated estimated effects from use/exploitation of results funded by the Programme on tackling identified Union policy priorities and global challenges (including | |

54 NB: For some KIPs the data will not be available in the short or even medium term.

| | | | |
|---|---|---|---|
| | (including SDGs) (multidimensional: for each identified priority)<br>Including: Number and share of climate-relevant results aimed at delivering on the Union's commitment under the Paris Agreement | policy priorities and global challenges (including SDGs) (multidimensional: for each identified priority)<br>Including: Number and share of climate-relevant innovations and research outcomes delivering on Union's commitment under the P'ris Agreement | SDGs), including contribution to the policy and law-making cycle (such as norms and standards) (multidimensional: for each identified priority) Including: Aggregated estimated effects from use/exploitation of climate-relevant results funded by the Programme on delivering on the Union's commitment under the Paris Agreement including contribution to the policy and law-making cycle (such as norms and standards) |
| 5-Delivering benefits and impact through R&I missions | R&I mission results – Results in specific R&I missions (multidimensional: for each identified mission) | R&I mission outcomes – Outcomes in specific R&I missions (multidimensional: for each identified mission) | R&I mission targets met – Targets achieved in specific R&I missions (multidimensional: for each identified mission) |
| 6-Strengthening the uptake of R&I in society | Co-creation – Number and share of projects funded by the Programme where Union citizens and end-users contribute to the co-creation of R&I content | Engagement – Number and share of participating legal entities which have citizen and end-users engagement mechanisms in place after the end of projects funded by the Programme | Societal R&I uptake – Uptake and outreach of co-created scientific results and innovative solutions generated under the Programme |
| **Towards technological / economic impact** | | | |
| 7-Generating innovation-based growth | Innovative results – Number of innovative products, processes or methods resulting from the Programme (by type of innovation) & Intellectual Property Rights (IPR) applications | Innovations – Number of innovations resulting from the projects funded by the Programme (by type of innovation) including from awarded IPRs | Economic growth – Creation, growth & market shares of companies having developed innovations in the Programme |
| 8-Creating more and better jobs | Supported employment – Number of full time equivalent (FTE) jobs created, and jobs maintained in participating legal entities for the project funded by the Programme (by type of job) | Sustained employment - Increase of FTE jobs in participating legal entities following the project funded by the Programme (by type of job) | Total employment – Number of direct & indirect jobs created or maintained due to diffusion of results from the Programme (by type of job) |

| | | | |
|---|---|---|---|
| 9- Leveraging investments in R&I | Co-investment – Amount of public & private investment mobilised with the initial investment from the Programme | Scaling-up – Amount of public & private investment mobilised to exploit or scale-up results from the Programme (including foreign direct investments) | Contribution to ‘3 % target’ – Union progress towards 3 % GDP target due to the Programme |

## Annex 8 – Scoreboard of common indicators for Horizon Europe partnerships

IHI launched 3 calls for proposals in 2022: two single stage calls (IHI call 1 and call 3) and one two-stage call (IHI call 2). There were no Grant Agreements signed in 2022, therefore these projects will start in 2023 and will have their first reporting period in 2024.

| N° | Criterion addressed | Proposed common indicators | Baseline | Results for2022 | Target 2027 |
|---|---|---|---|---|---|
| 1 | Additionality | Progress towards (financial and in-kind) contributions from partners other than the Union – i.e. committed vs. actual | | | |
| 2 | Additionality/ Synergies | Additional investments triggered by the EU contribution, including qualitative impacts related to additional activities[55] | | | |
| 3 | Directionality | Overall (public and private, in-kind and cash) investments mobilised towards EU priorities | | | |
| 4 | International visibility and positioning | International actors involved | | | |
| 5 | Transparency and openness | Share & type of stakeholders and countries invited/engaged | | | |
| 6 | Transparency and openness | No and types of newcomer members in partnerships and their countries of origin (geographical coverage) | | | |
| 7 | Transparency and openness | No and types of newcomer beneficiaries in funded projects (in terms of types and countries of origin) | | | |
| 8 | Coherence and synergies | Number and type of coordinated and joint activities with other European Partnerships | | | |

55 For this indicator, quantitative data will hopefully become available as of 2023 or later. For qualitative inputs, please elaborate it in 1.7.2, as relevant.

| | | |
|---|---|---|
| 9 | Coherence and synergies | Number and type of coordinated and joint activities with other R&I Initiatives at EU /national/regional/sectorial level |
| 10 | Coherence and synergies | Complementary and cumulative funding from other Union funds (Horizon Europe, National funding, ERDF, RRF, Other cohesion policy funds, CEF, DEP, LIFE, other) |
| 11 | International visibility and positioning | Visibility of the partnership in national, European, international policy/industry cycles |

## Annex 9 – Scoreboard of KPIs specific to IHI

IHI launched three calls for proposals in 2022: two single stage calls (IHI call 1 and call 3) and one two-stage call (IHI call 2). There were no Grant Agreements signed in 2022 therefore these projects will start in 2023 and will have their first reporting period in 2024. At this stage there are no progresses to report against IHI specific KPIs.

| KPI name | Unit of measurement | Baseline[56] | Target[57] 2023 | Target 2025 | Target 2027 | Ambition >2027 | Status |
|---|---|---|---|---|---|---|---|
| **Resources, processes and activities (inputs)** | | | | | | | |
| 1.1. Involvement of multiple health care stakeholders | Share of projects involving more than two types of health care stakeholders [research higher or secondary education organisations (private or public), small & medium enterprise (SME), large company (for-profit legal entity), non-governmental organisations (NGOs), healthcare professional organisation/healthcare provider, patient / citizen organisation, regulators or regulatory body, notified body, health technology assessment body (HTA), health care payer, charity and foundation, public authority] as project participants or advisors | 50% | 55% | 60% | 65% | 70% | 100% |
| 1.2. Cross-sectoriality of the partnership | Share of projects bringing together private members and/or contributing partners (or their affiliated or constituent entities) from two or more technology sectors[58] | 25% | 70% | 80% | 85% | 90% | 100% |
| 1.3. Engagement of regulators | Number of projects interacting with regulators[59] to contribute to new or improved guidelines or methodologies | 13 | 0 | 5 | 10 | 20 | |
| **Outcomes** | | | | | | | |

[56] Baselines are derived (where possible) from the Innovative Medicines Initiative (IMI2) as predecessor to IHI.

[57] Reporting methodology: cumulatively reporting from the beginning of IHI until 31/12/2030.

[58] The IHI private members COCIR, EFPIA, EuropaBio and MedTech Europe have members from several technology sectors. Contributing partners might also cover further technology sectors.

[59] In this document, the term 'regulators' refers to the different bodies involved in the processes regulating medical products (e.g., scientific assessment, production of scientific guidelines, scientific advice to manufacturers, granting/refusal/suspension of marketing authorisations, post-market surveillance, withdrawing/recalling of devices put on the market, authorisation and oversight of clinical trials). It includes the European Commission, National Competent Authorities (NCA), the Medical Device Coordination Group (MDCG), and the European Medicines Agency (EMA). Notified Bodies (NB), while designated to perform a regulatory function (verification of medical device/in-vitro diagnostics conformity), cannot be considered as regulators in the strict sense of this definition. However, the potential input and expertise of Notified Bodies may still be relevant for the design and implementation of the activities of the proposed initiative.

| KPI name | Unit of measurement | Baseline[56] | Target[57] 2023 | Target 2025 | Target 2027 | Ambition >2027 | Status |
|---|---|---|---|---|---|---|---|
| 2.1. Cross-stakeholders' collaboration | Share of multi-stakeholders' publications identified through bibliometric data analysis [research / higher or secondary education organisations (private or public), small & medium enterprise (SME), large company (for-profit legal entity), non-governmental organisations (NGOs), healthcare professional organisation / healthcare provider, patient / citizen organisation, regulators or regulatory body, notified body, health technology assessment body (HTA), health care payer, charity and foundation, public authority] | 65% | 65% | 66% | 67% | 70% | |
| 2.2. Public-private collaboration | Share of publications across public and private stakeholders identified through bibliometric data analysis (academic, pharmaceutical, biopharmaceutical, medical technologies, biotechnologies) | 65% | 65% | 66% | 67% | 70% | |
| 2.3. Project outputs for use in clinical practice and health research development and innovation (R&D&I) | Number of:<br>• new tools for studying new potential drug targets such as new pharmacological tools, therapeutic modalities, and patient-derived assays available to the scientific community<br>• new tools to test diagnostically and/or therapeutically relevant hypotheses in pre-clinical models and/or clinically in uncharted areas of disease biology<br>• new tools for prediction, prevention, interception, surveillance, diagnosis, treatment, and management options to prepare for major epidemic outbreaks<br>• new biomarkers of disease (relevant for diagnosis, efficacy, safety, or prevention) identified and experimentally validated<br>• new taxonomies of disease or new stratifications to define patient sub-populations | 100 | 0 | 50 | 120 | 150 | |
| 2.4. Integrated health care solutions considering end-users' needs | Number of project outputs that combine people-centred integrated solutions (pre-competitive tools, methods, solutions as well as products/services or combined products) | No baseline available | 0 | 3 | 7 | 10 | |
| 2.5. Methodologies for value assessment of integrated solutions | Number of Methodologies for the assessment of the added value of combinations of products/services or combined products (including development of patient reported outcomes / experience measures and statistical methods/tools), submitted to health care authorities and organisations[60] | No baseline available | 0 | 2 | 3 | 5 | |

[60] Health care authorities and organisations to which it is referred here are HTA bodies, and Regulatory Authorities, Payers and Public Authorities

- HTA agencies/bodies: http://www.adhophta.eu/toolkit/assets/tools/AdHopHTA_toolkit_tool24_document.pdf; https://www.eunethta.eu/about-eunethta/eunethtanetwork/)

| KPI name | Unit of measurement | Baseline[56] | Target[57] 2023 | Target 2025 | Target 2027 | Ambition >2027 | Status |
|---|---|---|---|---|---|---|---|
| 2.6. New or improved clinical guidelines | Number of projects contributing to the development of new or improved clinical guidelines | 13 | 0 | 5 | 10 | 20 | |
| 2.7. Management of health data | Number of common standards, protocols and frameworks developed by the projects to enable better access to data, sharing and analysis of health-related data | No baseline available | 0 | 3 | 7 | 10 | |
| 2.8. Demonstration of data integration | Number of pilots developed by the projects demonstrating integration of data provided by the private and public sectors | No baseline available | 0 | 5 | 10 | 20 | |
| 2.9. Demonstration of AI in health care | Number of pilots developed by the projects demonstrating feasibility of use of artificial intelligence in health care | No baseline available | 0 | 1 | 2 | 3 | |
| **Impacts** | | | | | | | |
| 3.1. Creation of sustainable resources and infrastructures that facilitate translation of the knowledge to innovations | Number of established new research networks, new clinical networks, further public-private collaborations on health R&D&I, research infrastructures, biobanks, collaborative platforms etc. (that outlive the project and are accessible to broader scientific community) | 10 | 0 | 4 | 7 | 15 | |
| 3.2. Development of preventive or therapeutic strategies in different therapeutic areas to | Share of projects that aim to develop new or improved existing methodologies also across disciplines addressing public health needs[61] included in the list of the WHO Europe Health 2020 priority areas[62] | No baseline available | 90% | 90% | 90% | 90% | 100% |

- National and regional public procurement organisations
- National payer and reimbursement organisations (incl. health insurance companies)
- National healthcare authorities: examples are: Dutch NZA; http://www.euregha.net/ (membership list of regional and local health authorities); https://eurohealthnet.eu/list-of-members/ (first part of the membership, not the research members)

[61] SBA definition (article 125.1) "For the purpose of this Regulation, an unmet public health need shall be defined as a need currently not addressed by the health care systems for availability or accessibility reasons, for example where there is no satisfactory method of diagnosis, prevention or treatment for a given health condition or if people access to health care is limited because of cost, distance to health facilities or waiting times".

[62] https://www.euro.who.int/__data/assets/pdf_file/0011/199532/Health2020-Long.pdf; www.ihi.europa.eu/sites/default/files/uploads/Documents/About/IHI_KPIs_WHO2020PriorityAreas.pdf

| KPI name | Unit of measurement | Baseline[56] | Target[57] 2023 | Target 2025 | Target 2027 | Ambition >2027 | Status |
|---|---|---|---|---|---|---|---|
| address unmet public health needs | | | | | | | |
| 3.3. Cross-sector activities established by the partnership that will help contribute to a globally competitive EU health care industry | Number of activities in which cross-sector collaboration drives health innovation, such as:<br>• Spin-off companies, entities or activities created based on outputs of the project (e.g., new commercial or non-profit entities)<br>• Collaboration agreements between large companies[63] & SMEs[64] established for purposes that go beyond the scope of the project during and/or after project lifetime.<br>• Other activities where the joint contribution of different al partners has generated cross-sectoral health innovation.<br>Examples of collaboration activities across health industry sectors that contributed to the transition to a green and digital economy (as outlined in the new Industrial Strategy for Europe[65]) | No baseline available | 0 | 5 | 10 | 20 | |

[63] For-profit legal entities with an annual turnover of EUR 500 million or more (Single Basic Act, Art. 123.5)

[64] Small and medium-sized enterprises (SMEs) are defined in the "EU recommendation 2003/361" (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003H0361&from=EN) as of page 4 and in the European Commission "User guide to SME definition" (https://ec.europa.eu/docsroom/documents/42921) especially in page 13.

[65] "European industrial strategy 2019-2024" (https://ec.europa.eu/info/strategy/priorities-2019-2024/europe-fit-digital-age/european-industrial-strategy_en) and "Updating the 2020 New Industrial Strategy: Building a stronger Single Market for Europe's recovery" (https://ec.europa.eu/info/sites/default/files/communication-industrial-strategy-update-2020_en.pdf)

## Annex 10 – In-kind contributions to additional activities (IKAA) report

The additional activities undertaken during the year 2022 (i.e. from 1 January until 31 December 2022) and reported by IHI private members to the Programme Office by 31 May 2023 are under assessment by the Programme Office. The value of these additional activities will be validated in 2023 and included in the CAAR 2023.

## Annex 11 – Annual accounts

The annual accounts are provided in a separate document, which is officially handed over to the budgetary authorities, the European Court of Auditors, and the external auditors.

They are also published on the IHI website.

# Annex 12 – Materiality criteria

The ‘materiality’ concept provides the Executive Director with a basis for assessing the significance of any weaknesses or risks identified and thus whether those weaknesses should be subject to a formal reservation in the annual declaration of assurance. This annex provides an explanation of the materiality threshold that was applied as a basis for this assessment.

The JU control objective is to ensure that the residual error rate of payments made to beneficiaries, i.e. the level of errors that remain undetected and uncorrected, does not exceed 2% by the end of the research programmes. The guidance of the European Court of Auditors as well as lessons learnt from previous audits were taken in account for defining the 2% threshold. Progress towards this objective is to be (re)assessed annually, in view of the results of the implementation of the ex-post audit strategy. As long as the residual error rate is not (yet) below 2% at the end of a reporting year within the programme’s life cycle, a reservation would (still) be made. Nevertheless, apart from the residual error rate, the Executive Director may also take into account other management information at his disposal to identify the overall impact of a weakness and determine whether or not it leads to a reservation.

When deciding whether or not something is material, qualitative and quantitative terms have to be considered.

In qualitative terms, the following factors are considered as part of the materiality criteria:

- the nature and scope of the weakness;
- the duration of the weakness;
- the existence of mitigating controls which reduce the impact of the weakness;
- the existence of effective corrective actions to correct the weaknesses (action plans and financial corrections) which have had a measurable impact.

In quantitative terms, in order to make a judgement on the significance of a weakness, the potential financial impact is taken into account.

The assessment of weaknesses was made by identifying their potential impact and judging whether any weakness was material enough that its non-disclosure could influence the decisions or conclusions of the users of the declaration of assurance.

Accordingly, the following considerations were taken into account:

JU programmes are multi-annual in nature thus the control strategy is designed for the whole programme duration. The holistic measure of control effectiveness must reflect the entirety of programme implementation at the time of reporting. The error rates are therefore calculated cumulatively for the entire programme period to date. This enables to continuously monitor the final control objective that is set to be achieved at the end of the programme. As the programme advances, the reliability of the control measure continues to improve.

Furthermore, the analysis must also include an assessment of whether (1) the results of the audits carried out until the end of the reporting year were sufficient and adequate to meet the multi-annual control strategy goals; and (2) whether the preventive and remedial measures in place are deemed to be adequately effective in order lead to the expected reduction in the error rate by the end of the programme.

**Effectiveness of controls**

The main legality and regularity indicators for payments made to beneficiaries, are the representative and residual error rates detected by ex-post audits, measured with respect to the amounts accepted after ex-ante controls.

The ***representative error rate*** **(RepER)** is the error rate resulting from the representative audits. It provides a reasonable estimate of the level of error in the population relating to the accepted JU contributions on completion of the audits but does not take into account the corrections and follow-up undertaken by the JU.

The calculation of the residual error rate subsequently uses the representative error rate as the starting point.

The representative error rate for a population from which one or more samples have been drawn is calculated according to the following formula[66]:

$$\frac{\sum_{i=1}^{n} \mathrm{err}_i * \mathrm{SI}_i}{\mathrm{P}}$$

- n = total sample size;
- $\mathrm{err}_i$ = error rate (in %) in accepted JU contributions detected on individual transactions from the sample (in range [0, 100%]; i.e. only errors relating to overpayments are counted);
- $\mathrm{SI}_i$ = sampling interval used for selecting transactions from the sample;
- P = total accepted JU contribution (EUR) in the auditable population (i.e. all paid financial statements).

The ***residual error rate*** (**ResER**) is the level of error remaining in the population after deducting corrections and recoveries made by the JU. This includes the extension of audit results to non-audited financial statements of the audited beneficiaries to correct systematic errors. The formula for the residual error rate is[67]:

$$\mathbf{ResER\% = \frac{(RepER\% * (P\text{-}A) - (RepERsys\% * E)}{P}}$$

Where:

- **ResER%** = residual error rate, expressed as a percentage;
- **RepER%** = representative error rate, or error rate detected in the representative JU sample, calculated as described above;
- **RepERsys%** = systematic portion of the RepER% (the RepER% is composed of complementary portions reflecting the proportion of systematic and non-systematic errors detected) expressed as a percentage;
- **P** = total amount of the auditable population relating to accepted JU contributions, expressed in euros;

66 Based on the Horizon 2020 Ex-post Audit Strategy (2016 – 2025).

67 Idem.

- **A** = total value of audited accepted JU contributions, expressed in euros;
- **E** = total non-audited amounts of accepted JU contributions of all audited beneficiaries. This will consist of the total JU's share, expressed in euros, of all non-audited cost statements received for all audited beneficiaries.

The calculation of the error rates is performed on a point-in-time basis, i.e. all the figures are cumulative and provided up to the date of the last sample of which audit results are available for the error rate calculation.

# Annex 13 – List of projects

Factsheets on all IMI1 and IMI2 projects can be found on the IHI website.

# Annex 14 – List of acronyms

| Acronym | Meaning |
|---|---|
| AA | Additional activities |
| AAR | Annual Activity Report |
| ABAC | Accrual Based Accounting System |
| ACE | Angiotensin converting enzyme |
| AD | Alzheimer's disease |
| ADME | API uptake, distribution, metabolism and excretion |
| AI | Artificial intelligence |
| ALS | Amyotrophic lateral sclerosis |
| AMD | Age-related macular degeneration |
| AMR | Antimicrobial resistance |
| AMRI | Alliance of Medical Research Infrastructures |
| ANRT | Association nationale de recherche et de technologie |
| API | Active pharmaceutical ingredient |
| ARES | Advanced Records System |
| ASD | Autism spectrum disorder |
| ATM-AVI | Aztreonam-avibactam |
| ATMP | Advanced therapy medicinal product |
| BBB | Blood-brain barrier |
| BCEC | Brain capillary endothelial-like cells |
| BMGF | Bill and Melinda Gates Foundation |
| BMJ | British Medical Journal |
| BMR | Biannual Monitoring Report |
| BOA | Back office arrangements |
| CCA | Commitment appropriations |
| CA | Contract agent |
| CAAR | Consolidated Annual Activity Report |
| CA-ARTI | Community-acquired acute respiratory tract infection |
| CACHE | Critical Assessment of Computational Hit-finding Experiments |
| CAFS | Commission Anti-Fraud Strategy |
| CAJU | Clean Aviation JU |
| CAR | Chimeric antigen receptor |
| CAS | Common Audit Service |
| CBE JU | Circular Bio-based Europe JU |
| CC | Confidential Counsellor |
| CCHFV | Crimean Congo Haemorrhagic Fever Virus |
| CDI | *Clostridioides difficile* infection |
| CDISC | Clinical Data Interchange Standards Consortium |
| CDM | Common data model |
| CDTI | Centre for the Development of Industrial Technology |

| | |
|---|---|
| CE | Conformité Européenne |
| CEF | Connecting Europe Facility |
| CERT-EU | Computer Emergency Response Team |
| CH JU | Clean Hydrogen JU |
| CIOMS | Council for International Organisations of Medical Science |
| CMS | Content management system |
| CNS | Central nervous system |
| CO | Cardiac output |
| COCIR | European Coordination Committee of the Radiological, Electromedical and Healthcare Information Technology (IT) Industry |
| COMPASS | H2020 workflow tool providing harmonisation between business processes & validation workflows |
| COPD | Chronic obstructive pulmonary disease |
| CORDA | Common Research Data Warehouse |
| COS | Clinical observational study |
| COVID-19 | Coronavirus disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) |
| C-Path | Critical Path Institute |
| CPIM | Critical Path Innovation Meeting |
| CRS | Common representative sample |
| CSIRO | Commonwealth Scientific and Industrial Research Organisation |
| CTIS | Clinical trials information system |
| CV | Curriculum vitae |
| CVS | Clinical validation study |
| CVS CTR | Cardiovascular systems contractility |
| DA | Dopaminergic |
| DARWIN | Data Analysis and Real World Interrogation Network |
| DEP | Digital Europe Programme |
| DG | Directorate-General |
| DG BUDGET | European Commission Directorate-General for Budget |
| DG RTD | European Commission Directorate-General for Research and Innovation |
| DICOM | Digital imaging and communications in medicine |
| DIKI | Drug-induced kidney injury |
| DOI | Digital object identifiers |
| DRC | Democratic Republic of the Congo |
| DREADD | Designer receptors exclusively activated by designer drugs |
| DTAP | Diphtheria, tetanus and acellular pertussis |
| Dx | Diagnostic |
| EATRIS | European Advanced Translational Research Infrastructure in Medicine |
| EAU | European Association of Urology |
| EC | European Commission |
| ECA | European Court of Auditors |
| ECG | Electrocardiogram |
| ECRAID | European Clinical Research Alliance on Infectious Diseases |

| | |
|---|---|
| eCRF | Electronic case report form |
| ED | Executive Director |
| EDCTP3 | European & Developing Countries Clinical Trials Partnership 3 |
| EDPS | European Data Protection Supervisor |
| EEG | Electroencephalogram |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EFTA | European Free Trade Association |
| EHDS | European Health Data Space |
| EHR | Electronic health record |
| EIT | European Institute of Innovation and Technology |
| ELF | European Lead Factory |
| ELLA | Enzyme-linked lectin assay |
| EMA | European Medicines Agency |
| ePI | Electronic product information |
| ePiE | European pharmaceuticals in the environment |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQA | External quality assessment |
| ERDF | European Regional Development Fund |
| ERIC | European Research Infrastructure Consortium |
| ERM | Enterprise risk management |
| ESC | European Society of Cardiology |
| EU | European Union |
| EUFEPS | European Federation for Pharmaceutical Sciences |
| EUPATI | European Patients' Academy on Therapeutic Innovation |
| EU-Rail | Europe's Rail JU |
| EuroHPC JU | European High Performance Computing JU |
| EuropaBio | European Association for Bioindustries |
| EVD | Ebola virus disease |
| EXO | Exchange online |
| ExPEC | Extraintestinal pathogenic *E. coli* |
| F&T | Funding and Tenders (Portal) |
| FAIR | Fraud and irregularity in research |
| FAIR | Findable, accessible, interoperable, reusable |
| FC | Financial contribution |
| FDA | US Food and Drug Administration |
| FG | Function group |
| FIGON | Federation for Innovative Drug Research Netherlands |
| FIH | First in human |
| FNIH | Foundation for the National Institutes of Health |
| FOP | Fibrodysplasia ossificans progressiva |
| FP | Full proposal |
| FP7 | Seventh Framework Programme |

| | |
|---|---|
| FR | Financial rules |
| FTE | Full time equivalent |
| FWC | Framework contract |
| GA | Grant Agreement |
| GABA | γ-aminobutyric acid |
| GAP | Grant Agreement preparation |
| GB | Governing Board |
| GCGH | Grand Challenges in Global Health |
| GCP | Good clinical practice |
| GDP | Gross Domestic Product |
| GDPR | General Data Protection Regulation |
| GP | General practitioner |
| H2020 | Horizon 2020 |
| HAI | Haemagglutination inhibition |
| HAP | Hospital acquired pneumonia |
| HBP | Human Brain Project |
| HDR UK | Health Data Research United Kingdom |
| HE | Horizon Europe |
| HERA | Health Emergency Preparedness and Response Authority |
| HES | Higher or secondary education establishment |
| HPLC | High Performance Liquid Chromatography |
| hiPSC | Human induced pluripotent stem cell |
| hPSCreg | Human pluripotent stem cell registry |
| HR | Human resources |
| HTA | Health technology assessment |
| iAMD | Intermediate age-related macular degeneration |
| IAS | Internal Audit Service of the European Commission |
| iASD | Idiopathic autism spectrum disorder |
| IC | Internal control |
| ICHOM | International Consortium of Health Outcomes Measurement |
| ICF | Internal control framework |
| ICMR | Indian Council of Medical Research |
| ICT | Information and communication technology |
| ICU | Intensive care unit |
| IHI JU | Innovative Health Initiative Joint Undertakings |
| IKAA | In-kind contributions to additional activities |
| IKC | In-kind contribution |
| IKOP | In-kind contributions to operational activities |
| IMI1 JU | Innovative Medicines Initiative 1 Joint Undertaking |
| IMI2 JU | Innovative Medicines Initiative 2 Joint Undertaking |
| IPCEI | Important Project of Common European |
| IPR | Intellectual property rights |

| | |
|---|---|
| iPSC | Induced pluripotent stem cell |
| IR | Implementing rule |
| irAE | Immune related adverse event |
| irAOP | Immune related adverse outcome pathway |
| IT | Information technology |
| ITF | Innovation Task Force |
| IVD | *In vitro* diagnostic |
| IVE | Influenza vaccine effectiveness |
| iVZW | internationale vereniging zonder winstoogmerk / international non-profit association |
| JAMA | Journal of the American Medical Association |
| JDRF | Juvenile Diabetes Research Funding and Advocacy |
| JIF | Journal impact factor |
| JSIS | Joint sickness insurance scheme |
| JTI | Joint Technology Initiative |
| JUs | Joint Undertakings |
| KDT JU | Key Digital Technologies Joint Undertaking |
| KB | Knowledge base |
| k.o. | Knock-out |
| KIP | Key impact pathway |
| KPI | Key performance indicator |
| LC-MS/MS | Liquid chromatography with tandem mass spectrometry |
| LEAP | Longitudinal European Autism Project |
| LHS | Learning Healthcare System |
| LIPUS | Low-intensity pulsed ultrasound stimulation |
| LRP1 | lipoprotein receptor-related protein 1 |
| LT | Long-term contract |
| mAb | Monoclonal antibody |
| MAT | Monocyte activation test |
| MDCG | Medical Device Coordination Group |
| MDD | Major depressive disorder |
| MDR | Multi-drug resistant |
| mHSPC | Metastatic hormone-sensitive prostate cancer |
| MIM | Microsoft identity manager |
| MRC | Medical Research Council |
| mRNA | Messenger ribonucleic acid |
| MS | Multiple sclerosis |
| NA | Neuraminidase |
| NAFLD | Non-alcoholic fatty liver disease |
| NASH | Non-alcoholic steatohepatitis |
| NB | Notified bodies |
| NCA | National Competent Authorities |
| NCP | National Contact Point |

| | |
|---|---|
| NET | Nerve excitability testing |
| NF | Neurofibromatosis |
| NGN2 | Neurogenin 2 |
| NGO | Non-governmental organisation |
| NI | Neuraminidase inhibition |
| NTM | Non-tuberculous mycobacteria |
| OAR | Organs at risk |
| OECD | Organisation for Economic Cooperation and Development |
| OI | Optical imaging |
| OLAF | European Anti-Fraud Office |
| OMOP | Observational Medical Outcomes Partnership |
| PA | Payment appropriations |
| PA | *Pseudomonas aeruginosa* |
| PEOF | Patient Engagement Open Forum |
| PBK | Physiologically-based pharmacokinetic |
| PCR | Polymerase chain reaction |
| PD | Parkinson's disease |
| PDX | Patient derived xenografts |
| PET | Positron emission tomography |
| PFF | Proximal femur fracture |
| PK/PD | Pharmacokinetic/pharmacodynamic |
| PloS | Public Library of Science |
| PMS | Phelan-McDermid Syndrome |
| POS-VAP | Perpetual Observational Study into Ventilator Associated Pneumonia |
| PoV | Proof of viability |
| PPI | Public and patient involvement |
| PPP | Public-private partnership |
| PPP | Public procurement planning |
| PPS | Patient preference study |
| PPSC | Pivot Park Screening Centre |
| PRO | Patient reported outcome |
| PROM | Patient reported outcome measure |
| pSS | primary Sjögren's Syndrome |
| PUB | Public body |
| QA | Quality assurance |
| QALY | Quality-adjusted life year |
| QS | Quality system |
| QST | Quantitative systems toxicology |
| QWBA | Quantitative whole-body autoradiography |
| 3Rs | Replace, reduce and refine (the use of animals in research) |
| R&D | Research and development |
| R&I | Research and innovation |

| | |
|---|---|
| RA | Rheumatoid arthritis |
| RAFS | Common Research Family Anti-Fraud Strategy |
| REC | Research organisation |
| RepER | Representative error rate |
| ResER | Residual error rate |
| RIA | Research and Innovation Action |
| RMT | Remote monitoring technology |
| RRF | Recovery and Resilience Facility |
| RSV | Respiratory syncytial virus |
| RTO | Research and Technology Organisation |
| RWE | Real world evidence |
| SA-PJI | *Staphylococcus aureus* prosthesis joint infection |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SBA | Single Basic Act |
| SCIC | (European Commission) Directorate-General for Interpretation |
| SCD | Subjective cognitive decline |
| SDG | Sustainable Development Goal |
| SEE | South-eastern Europe |
| SEP | Staff establishment plan |
| SEP | Selection and evaluation phase |
| SEP | H2020 IT tool for submission and evaluation of proposals |
| SEP DS | SEP Data Store |
| SESAR 3 JU | Single European Sky ATM [air traffic management] Research 3 JU |
| SGG | Strategic Governing Group |
| SHANK | SH3 and multiple ankyrin repeat domains |
| SIP | Science and Innovation Panel |
| SIR | Staff implementing rules |
| SLA | Service level agreement |
| SLC | Solute carrier |
| SLE | Systemic lupus erythematosus |
| SME | Small and medium-sized enterprise |
| SNS JU | Smart Networks and Services JU |
| SNE | Seconded national expert |
| SO | Specific objective |
| SOFIA | Submission of Information Application |
| SOP | Standard operating procedure |
| SP | Short proposal |
| SPOC | Single Point of Contact |
| SRA | Strategic Research Agenda |
| SRG | States Representatives Group |
| SRIA | Strategic Research and Innovation Agenda |
| SS | Single stage |

| | |
|---|---|
| SSO | Single sign-on |
| ST | Short-term contract |
| STAR | Sjögren's Tool for Assessing Response |
| SyGMa | H2020 IT tool for grant management |
| T1D | Type 1 diabetes |
| T2D | Type 2 diabetes |
| TA | Temporary agent |
| TB | Tuberculosis |
| TBEV | Tick-borne encephalitis virus |
| TeNT | Tetanus neurotoxin |
| TRL | Technology readiness level |
| TSC | Tuberous sclerosis complex |
| TTG | Time to grant |
| TTI | Time to inform |
| TTP | Time to pay |
| TTS | Time to sign |
| UK | United Kingdom |
| UMC | Uppsala Monitoring Centre |
| US | United States |
| VAP | Ventilator-associated pneumonia |
| VAP-PA | *Pseudomonas aeruginosa* ventilator-associated pneumonia |
| VBB | Virtual biobank |
| VE | Vaccines Europe |
| VF | Visual function |
| VN | Virus neutralisation |
| WHO | World Health Organisation |
| WSI | Whole slide images |
| WT | Wellcome Trust |

# Annex 15 – Governing Board analysis and assessment of the CAAR

### Analysis and Assessment of the Consolidated Annual Activity Report 2022 (CAAR 2022) by the IHI JU Governing Board

Key objectives for 2022 were set out in the Work Programme (WP 2022) and its amendments and included: 1) establishing the **IHI JU governance structure** and the necessary operational and administrative processes and standards, in accordance with the SBA; 2) execution of **Strategic Research Agenda** priorities; 3) ensuring continuity with and management of the **legacy from IMI2** JU; 4) ensuring **sound budget implementation**; 5) developing and deploying an assertive **communication strategy** to promote IHI JU, its objectives and new rules for participation; 6) exploring **synergies** with relevant programmes at Union, national, and regional level; 7) improving and broadening access to project outcomes by embedding **dissemination** and **exploitation** activities in all stages of the project lifecycle.

The Governing Board recognises **the progress made by the JU** towards achieving these objectives and notes that during the course of 2022, **IHI completed its first full year of operations**, dedicating efforts to set up the governance structures, processes, tools and documentation to allow IHI to launch its first calls for proposals. The diverse sectors of the pharmaceutical, medical technology, biotechnology, digital health and vaccines industries were **successfully integrated** into the IHI programme.

In 2022, IHI achieved the following:

- Setting up of two advisory governance bodies - the **States Representatives Group** and the **Science and Innovation Panel** (further to the Governing Board set up already at the end of 2021).
- Putting in place modern, **collaborative platforms** to facilitate the work and activities of all new IHI governance bodies.
- Adoption of the **Strategic Research and Innovation Agenda.**
- Further development of the **IHI website** and visual identification tools, newsletter and social media channels.
- Organisation of several stakeholder **events** to explain IHI, its rules and procedures, and call
- topics.
- Launch of the **first 3 IHI calls for proposals** with 11 topics.
- The **evaluation** of proposals from IHI's first calls for proposals.
- Launch of– a **platform** to submit ideas for an IHI call topic; 20 ideas were collected by the end of 2022 whereby more than half were submitted in a personal capacity.
- Setting up of an **internal task force on synergies** to ensure close collaboration and consistency with other European partnerships and initiatives.
- Implementation of the portfolio of **legacy projects** launched under **IMI and IMI2 programmes**
- and promotion of their successes.

IHI launched **Call 1** (single-stage with four topics) and **Call 2** (two-stage with two topics) on 28 June, and **Call 3** (single-stage with five topics) on 13 December. The **evaluation** of Call 1 was fully completed in 2022 and **grant preparation** started in December. The evaluation for IHI call 2, stage 1 was also completed in December 2022.

**Communication activities** focused on promotion of IMI project results and the new IHI partnership:

- News articles, brochures, videos and **success stories** were published.
- **Social media** and the **newsletter** were used to promote editorial content.

- Press coverage showed reference to **IMI** in 4,182 articles worldwide.
- An online **IHI launch event** took place on 26 January to promote the transition from IMI to IHI, gathering an audience of more than 2,500 participants.
- A hybrid **event to promote calls 1 and 2** on 14 June (1,450 participants) and the creation of a **matchmaking platform** to facilitate consortium formation.
- An online event to **promote call 3** in December.
- Development of a **new IHI communication policy** to guide activities in the years to come.
- In 2022, the **IHI website** received 189.7 thousand visits.

In 2022, **IMI projects** continued to deliver **impactful results,** including improving and accelerating the drug development process, developing diagnostic and treatment biomarkers for disease, and developing new therapies for diseases where there is high unmet need. A number of IMI projects set up **legacy organisations** to ensure that work started during the funding period continues.

The analysis of projects' deliverables indicates outstanding scientific performance, with uptake of results in research processes, regulatory and clinical practice. **Success stories** of IMI projects[68] range from the development and validation of examinations capable of accurately detecting changes over time as regards age-related macular degeneration ("MACUSTAR") to the development of a tool to improve the assessment of drug efficacy on an **autoimmune disease** called *primary Sjögren's Syndrome* ("NECESSITY").

Other **key achievements** include the creation of a federated data network of standardised real world health data from 100 million EU citizens and making it available at scale to researchers ("EHDEN") and regulators' endorsement of a research framework for **patient preference studies** ("PREFER") with a qualification opinion from the European Medicines Agency (EMA).

Since the start of the IMI2 programme, projects have been **patenting developed technologies**. From the beginning of IMI2 until 31 December 2022, 7 patent/trademark/registered design applications were submitted and 12 patents/trademarks were awarded.

Furthermore, the following was carried out in 2022:

- As per Council Regulation 2021/2085 establishing Joint Undertakings, IHI JU participated extensively and actively in the process to explore and enhance collaboration and synergies via the establishment of **back-office arrangements** (BOA). **BOA accounting services** were the first to be implemented, in December 2022.
- In 2022, the **Internal Audit Service** (IAS) performed an **extensive risk assessment** covering all IHI JU auditable entities.
- In its report on the financial year 2022, the **European Court of Auditors** (ECA) issued an unqualified ('clean') opinion on the reliability of the accounts as well as on the legality and regularity of revenue and payments underlying the annual accounts. A final report on the audit opinion on 2022 accounts is due in November 2023.
- The CAAR 2022 provides information on the effectiveness of the **internal controls** implemented and on the main results of monitoring and supervision controls. The JU internal control system is considered effective.
- Based on the information provided in the CAAR 2022, key objectives set up for 2022 have been met in compliance with legality, regularity and **sound financial management**.

[68] IHI website: https://www.ihi.europa.eu/projects-results

**The Governing Board recognises the setting up of IHI and notes in particular that:**

- The launch of IHI means that **three programmes** are now running in parallel, with different sets of rules, as an important number of projects launched under IMI and IMI2 are still ongoing. Setting up a new programme from scratch (while still running projects from past programmes) was a challenge albeit a successful one.
- IHI implements **several EU policies** and adequately implements the different tasks as required by the SBA.
- In 2022, the **total budget for IHI** was **EUR 272,383,841** in commitment appropriations and **EUR 174,845,991** in payment appropriations.
- The 7-year mandate of the **Executive Director** ended in September, followed by the appointment of an Executive Director ad interim. The recruitment of the new Executive Director was ongoing in 2022.
- The IHI JU has an important role to play in contributing to the **digital transformation and resilience of healthcare systems**. Addressing these challenges demands the establishment of collaboration with other European partnerships and **synergies** with other relevant programmes.
- In relation to the use of **human resources**, activities carried out by JU staff in 2022 were in line with the assigned objectives.
- The IHI Programme Office formally switched to a **'hybrid' way of working**, significantly reducing its **office space** and, by extension, its **carbon footprint**. The office space IHI freed up is now subleased to another Joint Undertaking, thereby facilitating the continued creation of **synergies** and implementation of back office arrangements in a range of areas.
- As per the **Strategic Internal Audit Plan 2023-2025**, future audit topics are: 1) Governance and relations with stakeholders (2023); and 2) Back-office arrangements (possible cross-cutting audit in several JUs).
- The full **list of GB decisions** adopted in 2022 can be found on the IHI website as well as the GB platform. In the spirit of **transparency**, other documents are made public on the IHI website such as the agendas of the Science and Innovation Panel and States Representatives Group meetings, annual IHI activity reports and work programmes, and budgetary and financial management reports.
- Given that IHI launched its first calls for proposals in 2022, it is not possible at this stage to report on progress against IHI **key performance indicators** (KPIs).

### Assessment

The declaration of the *interim* Executive Director and the Consolidated AAR 2022 give a **good assessment** (clear, unambiguous, congruous) of operational and financial management in relation to the achievement of objectives, and the legality and regularity of the **financial operations** of the JU in the year 2022.

The Governing Board notes that the management of the JU has reasonable **assurance** that, overall, **suitable controls** are in place and working as intended, **risks** are being properly monitored and mitigated, and necessary improvements and reinforcements recommended by the auditors are being implemented.

The Governing Board notes the **smooth transition of IMI2 JU to IHI JU** and successful first year of operations.

The Governing Board notes the implementation of the IHI programme in alignment with **Strategic Research Agenda** priorities, bringing together the different stakeholders involved in health research, fostering cross-project collaboration while focusing on **high unmet medical and societal needs**.

Therefore, the IHI JU Governing Board hereby adopts this analysis and assessment of the Consolidated AAR 2022 of the authorising officer. This analysis and assessment will be included in the Consolidated AAR 2022.

Done at Brussels, on 23 June 2023.

For the Innovative Health Initiative Joint Undertaking,

*Signed*

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Salah-Dine Chibout
Chairperson of the Governing Board

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