Consolidated Annual Activity Report 2021

Contents

Factsheet – IMI and IHI at a glance

From 1 January to 29 November 2021, the organisation operated as the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU). On 30 November 2021, the legislation creating the Innovative Health Initiative Joint Undertaking (IHI JU) entered into force. The IHI legislation repeals the legislation creating IMI, and therefore the organisation operated as IHI JU from 30 November onwards.

Name	Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU)	Innovative Health Initiative Joint Undertaking (IHI JU)
Objectives	The Council Regulation establishing IMI2 JU sets out the following objectives: a) to support, in accordance with Article 25 of Regulation (EU) No 1291/2013, the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership or to address specific societal challenges in particular as described in parts II and III of Annex I to Decision 2013/743/EU, and in particular the challenge to improve European citizens' health and well-being; b) to contribute to the objectives of the Joint Technology Initiative on Innovative Medicines, in particular to: i. increase the success rate in clinical trials of priority medicines identified by the World Health Organisation; ii. where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases; iii. develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance; iv. develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators; v. reduce the failure rate of vaccine candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks; vi. improve the current drug development process by providing support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products.	The Council Regulation establishing IHI JU sets out the following objectives: General objectives a) contribute towards the creation of a Union-wide health research and innovation ecosystem that facilitates translation of scientific knowledge into innovations, in particular by launching at least 30 large-scale cross-sectoral projects, focusing on health innovations; b) foster the development of safe, effective, people-centred and cost-effective innovations that respond to strategic unmet public health needs, by exhibiting, in at least five examples, the feasibility of integrating health care products or services, with demonstrated suitability for uptake by health care systems. The related projects should address the prevention, diagnosis, treatment or management of diseases affecting the Union population, including contribution to Europe's Beating Cancer Plan; c) drive cross-sectoral health innovation for a globally competitive European health industry, and contribute to reaching the objectives of the new Industrial Strategy for Europe and the Pharmaceutical Strategy for Europe. Specific objectives a) contribute towards a better understanding of the determinants of health and priority disease areas; b) integrate fragmented health research and innovation efforts bringing together health industry sectors and other stakeholders, focusing on unmet public health needs, to enable the development of tools, data, platforms, technologies and processes for improved prediction, prevention, interception, diagnosis, treatment and management of diseases, meeting the needs of end-users; c) demonstrate the feasibility of people-centred integrated health care solutions; d) exploit the full potential of digitalisation and data exchange in health care; e) enable the development of new and improved methodologies and models for a comprehensive assessment of the added value of innovative and integrated health care solutions.

Name	Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU)	Innovative Health Initiative Joint Undertaking (IHI JU)
Founding legal act	Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking	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	Pierre Meulien	
Governing Board	Chair: Irene Norstedt Vice-chair: Olivier Laureau	Chair: Irene Norstedt Vice-chair: Salah-Dine Chibout
Other bodies	States Representatives Group (SRG): 27 European Union (EU) Member States and 16 countries associated to the Horizon 2020 Framework Programme Scientific Committee: 12 members including ad hoc members Strategic Governing Groups (SGGs): 7 groups	States Representatives Group (SRG): nominations were ongoing Science and Innovation Panel (SIP): Not established by 31 December 2021. Selection of 10 panellists subject to an open selection process.
Staff	Total posts: 56 (39 Temporary Agents, 15 Contract Agents, 2 Seconded National Experts) Posts filled: 50 (36 Temporary Agents, 13 Contract Agents, 1 Seconded National Expert)	
2021 budget	Commitment appropriations: EUR 10 972 070 Payment appropriations: EUR 210 351 818	
2021 budget implementation	Commitment appropriations: EUR 8 329 203 Payment appropriations: EUR 200 661 207	
Grants	15 grants signed in 2021 for a total value of EUR 413 million	
Strategic Research and Innovation Agenda	The focus of the IMI2 JU Strategic Research Agenda (SRA) is on delivering 'the right prevention and treatment for the right patient at the right time'.	Draft version available. Not adopted by the IHI Governing Board by 31 December 2021.
Call implementation in 2021	Calls launched: 0 Proposals submitted under two-stage Calls: • Short proposals submitted: n/a • Eligible proposals submitted: n/a • Full proposals submitted: 6 • Proposals selected for funding: 12 Proposals submitted under single-stage Calls: • Proposals submitted: n/a • Eligible proposals submitted: n/a • Proposals selected for funding: n/a Global project portfolio in 2021: 115 projects running during 2021 (8 under IMI1, of which 3 ended by 31 December 2021; and 107 under IMI2, of which 9 ended by 31 December 2021)	Calls launched: 0
Participation, including SMEs	For the IMI2 programme, SMEs account for 16 % of beneficiaries receiving funding (by participations).	

Unless stated otherwise, all data in this factsheet reflects the situation as of 31 December 2021.

Foreword

As I enter into my final months as Executive Director, I would like to take the opportunity to reflect on the activities, results and impacts of 14 years of an extraordinary public private partnership (PPP) - the Innovative Medicines Initiative (IMI) which now, due to its success, is itself being transformed into a brand-new partnership, the Innovative Health Initiative (IHI).

Following an investment of around EUR 5 billion from the public and private sectors, one can well ask what IMI has achieved, given that it was the world's largest PPP in biomedical research and innovation. Let's start with a few numbers.

182 large scale projects have been funded, involving thousands of researchers and hundreds of partners from the public and private spheres. IMI has acted as a magnet for collaboration, attracting over 30 Associated Partners bringing over EUR 200 million in contributions to the programme. In addition, over 30 companies joined IMI as EFPIA Partners in Research, bringing not only EUR 40 million in funding, but new expertise in fields like medical imaging, diagnostics, digital technologies and so on to the IMI ecosystem.

Through this dynamic use of resources coming from many disciplines, it is not surprising that several areas of biomedical R&D have been transformed.

For example, on antimicrobial resistance (AMR), IMI has developed a pan European clinical trial and laboratory network (through the COMBACTE projects) allowing the fast tracking of potential new anti-microbials. AMR fits well with the PPP model as it represents a true market failure.

IMI also has a considerable portfolio of projects addressing neurodegeneration and autism. We know how complex brain research is, and understanding neurological conditions like Alzheimer's disease and autism are perfect topics for precompetitive collaboration across the public/private space. The first transatlantic coalition in autism has been created, and the first clinical assessments for pharmacological interventions are in progress (via the AIMS-2-TRIALS project).

Vaccines are also a good topic for PPPs as it is relatively easy to define precompetitive areas, like immunological correlates of protection, which advance the field for everyone, or other targets like Ebola, where innovative platforms can be brought into action quickly and then reused for other diseases. This actually happened with the EBOVAC family of projects, which paved the way for a successful COVID-19 vaccine developed by Janssen (J&J).

Big data and digital technologies have played a big part in IMI's portfolio of projects and many of these have given rise to sustainable platforms that will play a major role in digital health well beyond the catalytic funding through IMI. For example, EHDEN (European Health Data and Evidence Network) has played a major role during the COVID-19 pandemic by collaborating with the European Medicines Agency (EMA) on monitoring treatments in real world settings. Another example is the creation of the European Institute for Innovation through Health Data (i-HD), which came directly from the EHR4CR project and has greatly accelerated the process for recruitment for clinical trials, one of the major bottlenecks in medicines R&D. Both projects have created vehicles (institutes or foundations) which will ensure their sustainability.

IMI has also established infrastructures in areas where they were lacking, such as paediatric clinical trials, and the use of medicines in pregnancy. IMI projects have also delivered world class high-throughput screening platforms like the European Lead Factory, which continues to produce new leads for ground-breaking therapies across many disease areas.

In summary, IMI's legacy is already impressive, and with over 100 IMI projects still ongoing, it is set to grow further in the coming years.

No wonder then that other industry sectors in the healthcare domain wanted to explore the possibility of developing a brand-new partnership with a significantly enlarged scope, to be able to tackle current big challenges that need to be overcome in order for European citizens to access the latest innovations at the scale required to make a difference.

This is how the Innovative Health Initiative was conceived, and on 30 November 2021, the legislation establishing IHI JU entered into force, marking the official start of the new cross-sector partnership.

This meant that for the Programme Office, 2021 was a pivotal transition year, and the entire team has been very busy both launching the new programme and looking after the IMI legacy in order to optimise the impact of this very significant long-term investment.

IHI has the potential to translate ground-breaking science and technology into innovations that will be integrated into health systems across Europe. The maturity of the sector (driven by IMI and many other European, national and regional actions over the past decade) now allows us to be ambitious in our collective objectives, whether they be taking advantage of the technology convergence across different actors of the health innovation space; increasing our understanding of disease so as to be able to prevent, intervene early, or treat in a more targeted manner; and finally design new pathways of innovation that will allow cost efficient uptake into European health systems.

I am looking forward to working with the IHI partners and the new governance bodies, as well as the wider health and research communities, to make this exciting new partnership a success.

As always, I would like to close this foreword by thanking the many people whose hard work and dedication make IMI/IHI a PPP success story. Firstly, our project participants - the researchers, patients, regulators, and other experts who deliver high-quality, sound results that are making a difference in so many fields.

Secondly, to all involved in the governing bodies of IMI. We have had amazing support from the States Representatives Group and the IMI Scientific Committee over the years, and both have contributed significantly to the quality of the programme and the monitoring of its results and impacts. The IMI Governing Board has been a steady support to us all, ensuring that we have implemented the IMI programme in complete alignment with the Strategic Research Agenda and with the appropriate financial oversight.

Finally, I would like to thank my colleagues in the IMI/IHI Programme Office. Every year, they work hard to make the partnership a success, and in 2021 they rose magnificently to the challenges of working from home and running IMI/IHI remotely, while also handling the increased workload of both managing the IMI programme and performing all of the intricate activities necessary to ensure the seamless transition to IHI.

Pierre Meulien

IHI Executive Director

Brussels, June 2022

Executive summary

From IMI to IHI…

The most significant event in 2021 was the transition from the Innovative Medicines Initiative 2 (IMI2) programme to the Innovative Health Initiative (IHI) programme. The process kicked off officially on 23 February, when the European Commission published a proposal for a Single Basic Act (SBA) establishing a number of joint undertakings under Horizon Europe, including IHI. The Council adopted the regulation on 19 November 2021, and it came into force on 30 November. The IHI Governing Board held its first meeting on 16 December, where they approved key decisions that allow the new joint undertaking to function.

IHI is designed to build on what worked well in IMI, address the lessons learnt, and leverage the benefits of cross-sectoral collaboration in research and innovation to better respond to current and emerging health needs.

In practice, this means that while some elements are staying the same as the organisation moves from IMI to IHI, other things are changing significantly.

Members and funding

As was the case in IMI, the 'public' member in the partnership is the European Union, represented by the European Commission.

The industry members are COCIR, EFPIA, EuropaBio, MedTech Europe, and Vaccines Europe, taking IHI beyond the pharmaceutical industry and bringing on board the medical technology, biotechnology, digital health and vaccine industries.

In addition, organisations that want to support specific areas of research without becoming full members of IHI can apply to become 'contributing partners' (similar to the Associated Partners in IMI2). In fact, the success of the IMI2 Associated Partners scheme resulted in the expansion of the new contributing partners scheme to all joint undertakings.

As in IMI, the EU will provide 50 % of the funding for IHI, and the industry members (and contributing partners) will contribute the other 50%, primarily through 'in-kind' contributions.

Subject areas

IMI started with a strong focus on the pharmaceutical sector. However, in recent years, we have launched growing numbers of projects in fields such as digital health, big data, diagnostics, and imaging. Under IHI, we plan to support truly cross-sectoral projects involving the biopharmaceutical, biotechnology, and medical technology sectors, including companies active in the digital area. By adopting an integrated, cross-sector approach, IHI will be well placed to have an impact on health research and healthcare, both of which are increasingly interdisciplinary in nature. We will also work more on disease prevention and early diagnosis, and gain a better understanding of the determinants of health and priority disease areas.

Governance

Like IMI, IHI has a Governing Board made up of equal numbers of representatives from the European Commission and the industry partners, plus a States Representatives Group (SRG) comprising representatives of the EU Member States plus countries associated to Horizon Europe.

New under IHI is the Science and Innovation Panel, an advisory body that will bring together representatives of the scientific community and the wider health sector, such as regulatory bodies, patients, and end users. The panel will also include representatives of the European Commission and the industry partners of IHI as well as SRG members. The panel may also invite additional ad-hoc experts to join in discussions of specific subjects.

This revised governance structure will help IHI to better incorporate in priority setting the views of various stakeholders involved in healthcare, and ensure that IHI projects adequately address public health issues and the needs of end users.

Calls for proposals and projects

Like IMI, IHI will work by running open, competitive Calls for proposals, and we will continue to publish draft topic texts before the Call launch to give applicants additional time to work on their proposals.

As in IMI, IHI will bring together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. However, as mentioned above, in IHI we expect to launch a larger proportion of truly cross-sectoral projects involving new stakeholders representing the other industry sectors.

Managing the transition

The Programme Office along with the IHI partners worked hard throughout the year to ensure a smooth transition from IMI to IHI. Perhaps the most visible expression of this was the launch of the IHI logo, visual identity and website at the end of the year. Behind the scenes, work also progressed on the preparation of the new IHI governance bodies, the finalisation of the Strategic Research and Innovation Agenda, the rules and procedures around Calls for proposals, and the transfer of our IT systems from IMI to IHI.

Launch of the last IMI2 projects

Another highlight in 2021 was the completion of the IMI2 project portfolio with the signature of the last 15 IMI2 project grant agreements. The 15 newly created projects have a total budget of EUR 413 million, with around half of this coming from the EU's Horizon 2020 programme, and the rest coming from EFPIA contributions and IMI2 Associated Partners as well as other sources.

There are new projects on cancer, a key priority for the EU as evidenced by the cancer mission created under Horizon Europe. PERSIST-SEQ aims to shed new light on the mechanisms that allow some cancers to become resistant to treatments. PROTECT-trial is comparing the merits of standard radiotherapy and proton therapy in people with cancer of the oesophagus whose treatment also includes chemotherapy and surgery. OPTIMA aims to harness the power of artificial intelligence to advance treatments and facilitate decision-making for physicians and patients with prostate, breast and lung cancer.

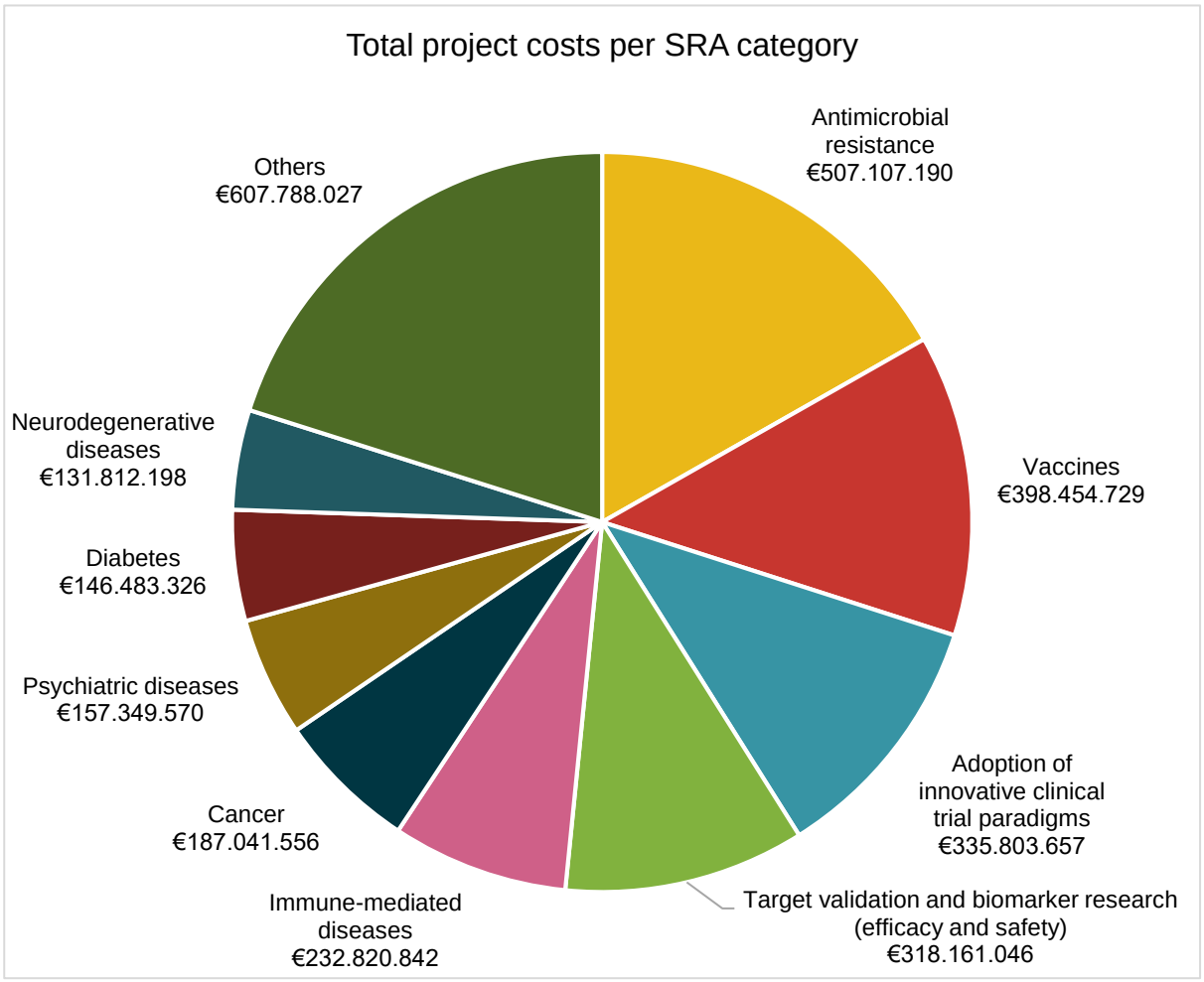
Infectious diseases have been a priority for IMI since the beginning, and the final batches of projects include four in this area. UNITE4TB aims to accelerate and improve clinical trials of combinations of existing and new drugs, with the goal of developing new and highly active treatment regimens for TB, including drug-resistant TB. PRIMAVERA will explore how vaccines and monoclonal antibodies can be deployed more effectively in the fight against antimicrobial resistance (AMR). UNITE4TB and PRIMAVERA are both part of IMI's AMR Accelerator Programme. 2021 also saw the launch of the Inno4Vac project on vaccine development, and PROMISE, which focuses on respiratory syncytial virus (RSV), a common infection which can cause severe illness in young children and the elderly, for example.

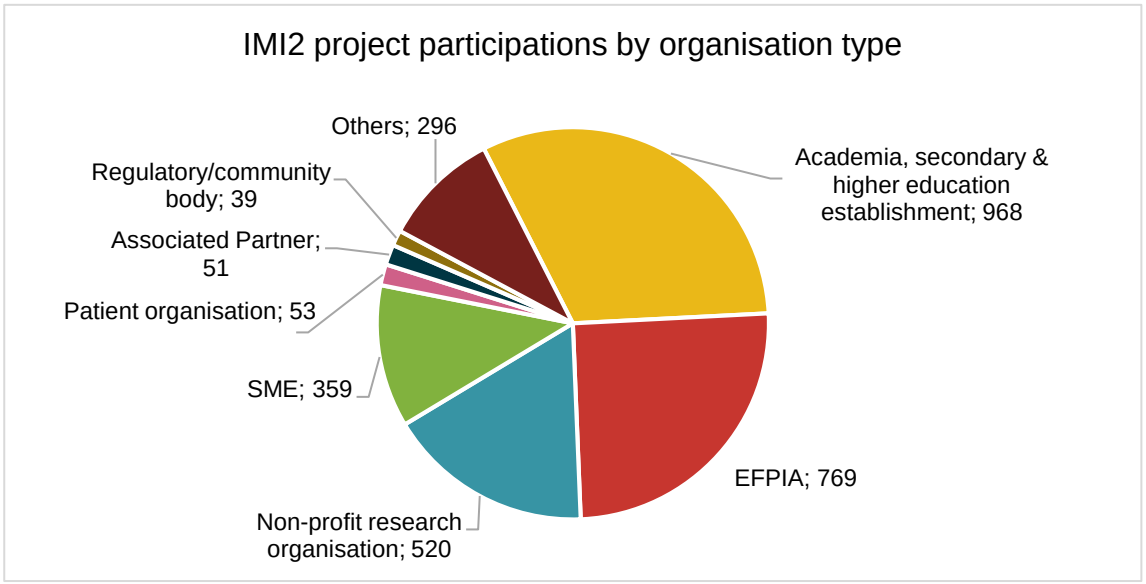
Other priority disease areas which are also represented in the final batches of projects are neurodegenerative diseases (EPND, PRISM2); autoimmune diseases (HIPPOCRATES), and rare diseases (SCREEN4CARE).

The rest of the new projects address cross-cutting issues in medical research and drug development, namely the real-world handling of protein drugs (RealHOPE); the role of transport proteins in disease (REsolution); the factors that drive patient adherence to treatment (BEAMER); and the issue of returning clinical trial data to participants (FACILITATE).

With the launch of these projects, the 123-strong IMI2 project portfolio is now complete. The charts below show the breakdown of the IMI2 funding by Strategy Research Agenda (SRA) category, and the breakdown of project participations by organisation type.

From a legal point of view, the legislation creating IHI replaces the legislation in place for IMI. This means that the IHI Programme Office will continue to manage the IMI projects, many of which still have years to run.


Total project costs per SRA category
Antimicrobial resistance €507.107.190
Vaccines €398.454.729
Adoption of innovative clinical trial paradigms €335.803.657
Target validation and biomarker research (efficacy and safety) €318.161.046
Immune-mediated diseases €232.820.842
Cancer €187.041.556
Psychiatric diseases €157.349.570
Diabetes €146.483.326
Neurodegenerative diseases €131.812.198
Others €607.788.027


IMI2 project participations by organisation type
Academia, secondary & higher education establishment; 968
EFPIA; 769
Non-profit research organisation; 520
SME; 359
Patient organisation; 53
Associated Partner; 51
Regulatory/community body; 39
Others; 296

IMI projects deliver results and have an impact

Meanwhile, throughout 2021, IMI's projects continued to deliver exciting, impactful results in a range of fields. Many of these are captured in our key performance indicators (KPIs), which offer a snapshot of IMI project results as of the end of 2021.

IMI2 projects have generated 275 assets that completed a significant milestone during the project lifecycle (the target was 50), and if we look at the IMI1 and IMI2 programmes together, the figure is 425. Assets include tools, methodologies, processes, services, training materials, etc.; and examples of significant milestones are key clinical trial phases, animal models, prototypes, commercialisation, patents, publications, etc.

In the tightly regulated world of medicine development, having an impact on the regulatory framework is a major achievement. Here, the IMI2 projects have registered 20 completed regulatory procedures (against a target of 10). The total for IMI1 and IMI2 projects together is 43.

Industry participants in many IMI2 projects are making use of new tools and processes generated by IMI2 projects, such as animal models, standards, biomarkers, standard operating procedures (SOPs), use of screening platforms, clinical trial networks, etc. The data shows 350 implementation results in IMI2 (versus a target of 50) and 669 implementation results if we consider both IMI1 and IMI2 programmes together.

The impacts of IMI projects in key areas (diabetes, dementia, health data, patient engagement and paediatric medicines) formed the focus of a series of online events that attracted 775 registrations.

Combating COVID

IMI has 8 projects working on treatments and rapid tests for COVID-19. A highlight was the discovery by scientists from IMI's CARE project of a highly potent monoclonal antibody against SARS-CoV-2. The new antibody, which is described in the journal Cell Reports, could protect patients for 4–6 months. That makes it an interesting preventive treatment option for unvaccinated, at-risk individuals or for vaccinated individuals who are unable to produce an immune response. Elsewhere, CARE research found: a genetic link to the likelihood of someone developing severe disease; new findings on how the virus indirectly damages the endothelial cells that line the blood vessels, lymph nodes and heart; and a new assay (a test used for analysis) for understanding antibody response in natural infection versus vaccination.

Other IMI2 coronavirus projects explored which existing medicines could be repurposed for use as COVID-19 treatments. MAD-CoV 2 published a paper identifying 200 approved drugs that could be used to treat COVID-19, and classified them into 9 distinct pathways within two overarching mechanisms of action: viral replication, and immune response. The Impentri project's trial of the cancer drug imatinib found that the drug did not meet its primary outcomes of reducing the time to stopping ventilation and supplemental oxygen. However, mortality (a secondary outcome) was lower in the imatinib group than the placebo group.

Projects working in other areas have also contributed to COVID work. Most notably, the Johnson & Johnson COVID-19 vaccine uses the company's AdVac technology. IMI's Ebola vaccine projects generated significant data on the safety of the AdVac vaccine platform, and this gave the company confidence to use the same platform for their COVID-19 vaccine.

The EHDEN project continued to deliver insights on vaccine safety. When studying vaccine safety, you need to know the normal, background levels of any 'adverse event of special interest' (AESI). Writing in the British Medical Journal, the team explains that the rates of AESI vary hugely by age and sex, for example, and this should be taken into account before using background rates for vaccine safety surveillance.

IMI projects are also turning to wearable devices to see if they can pick up signals of COVID-19 infection before the user starts to feel unwell. Indeed, this is the focus of the COVID-RED project, and in 2021 the project ran an extensive study to test if a smart 'Ava' bracelet could do this. The results of the study are still being analysed. On a smaller scale, the RADAR-CNS project developed a machine learning method to recognise people with COVID-19 based on heart rate data from a standard wearable fitness monitor such as a Fitbit.

Finally, 2021 marked the end of IMI's ZAPI project, which focused on a delivering tools and resources to allow a rapid response to outbreaks of zoonoses (i.e. diseases transmitted to humans from animals, like COVID-19). Many project outputs are now being used by industry partners, including an antibody against the

SARS-CoV-2 virus and platforms for the large-scale manufacture of vaccine candidates and antibodies. Crucially, the project also had an impact on regulatory processes.

Projects make their mark on regulatory processes

Impacts on regulatory processes are a key performance indicator for IMI, and in 2021 our projects continued to engage with regulators and ensure their results will have widespread applicability and use.

Over the course of two IMI projects (GetReal and the GetReal Initiative), researchers developed a suite of tools and resources to facilitate the use of real-world evidence in healthcare decision making. In 2021, the team launched the GetReal Institute to further develop the resources created by the projects and to bring together key stakeholders. In addition, the project's ADDIS tool will be used by regulators as an educational tool.

IMI's PREFER project passed a major regulatory milestone when it became the subject of the first EMA-EUNETHA (i.e. regulatory and health technology assessment) joint procedure. PREFER is investigating and testing the best ways to include patients' voices in medicine development and decision-making. A positive draft opinion from the EMA on the consortium's proposed framework for patient preference studies, as well as a document outlining points to consider when selecting methods for structured patient input to medical product decision-making, went through a public consultation in late 2021.

TransBioLine is developing biological markers that will reliably indicate whether a potential drug could be harmful to certain vital organs. The project has now had biomarkers for damage to the vascular system, central nervous system, kidney and liver accepted into the FDA's Biomarker Qualification Program.

How to successfully integrate patients into research projects

According to the IMI KPIs, over half of IMI projects include patients in some way or another, but how can projects ensure that patient engagement works well and brings value to both patients and other partners in the project? IMI projects that have succeeded in this field regularly share their advice and lessons learned in the scientific literature.

For example, osteoarthritis project APPROACH published a paper explaining how their Patient Council worked, and addressing both the formal and informal elements of patient involvement. Meanwhile PIONEER has developed a core outcome set for prostate cancer that is relevant for all stakeholders, including patients. A paper explains how the project achieved this and offers recommendations for other research projects where patient co-creation is key to success.

Finally, the challenges of communication between patients and scientists are highlighted in a paper by the AMYPAD project. The paper outlines the differences in the way 'Alzheimer's disease' is understood by lay audiences compared to the research context.

An ongoing commitment to excellence in administration and sound financial management

Throughout 2021, the entire IMI/IHI team maintained a rigorous approach to the administration of our calls and projects and our operational and administrative budget.

On Call and grant management, we hit all official targets, namely:

- Time to inform (TTI): **75** days out of a target of 153 days
- Time to grant (TTG): **223** days out of a target of 245 days
- Time to pay (TTP) pre-financing: **10** days out of a target of 30 days
- TTP interim payments: **61** days out of a target of 90 days
- TTP final payment: **70** days out of a target of 90 days.

For the operational payment appropriations, we maintained a high execution rate of 96 %.

This was achieved thanks to the continued use of the Horizon 2020 IT management tools and regular monitoring. IMI also maintained a low error rate for ex post audits (below the 2 % materiality threshold), demonstrating the effectiveness of IMI's control procedures.

On the administrative side, budget execution was good, with commitment and payment appropriations reaching 90.85 % and 81.88 % respectively.

Despite the ongoing challenges posed by COVID-19 and its dramatic impact on the way we work, the Programme Office remained focused and ensured adherence to sound financial management principles and effective internal control in all its activities. This is recognised by the European Court of Auditors (ECA), which again gave an unqualified ('clean') opinion on the reliability of IMI's 2020 accounts as well as on the legality and regularity of the revenue and payments underlying the annual accounts.

The joint undertaking also has good gender balance in a number of areas. For example, in the Programme Office, 66 % of the staff is female. Looking at the IMI programme, the proportion of women on the governance bodies when the programme finished was as follows:

- Governing Board: 5 out of 10 members (50 %)
- SRG: 24 out of 39 appointed nominees (61.5%)
- Scientific Committee: 5 out of 12 full members (41.7 %)

There was also a good gender balance in the use of experts for the evaluation of proposals (22 out of 40 experts - 55%) and for interim reviews (38 out of 86 experts - 43%)

Turning to the IHI programme, the 5 out of 8 members (62.5%) of the new Governing Board are women.

1 Achievements of the year

1.1 Key objectives for 2021

The key objectives for 2021 were set out in the Annual Work Plan (AWP) 2021 and were based on the overall objectives of IMI2 JU as set out in Article 2 of Council Regulation (EU) No 557/2014. The AWP was initially adopted by the IMI Governing Board and was re-adopted by the IHI Governing Board following the entry into force of the legislation creating IHI.

A summary of the progress made against the objectives for 2021 is given below. More information on all points can be found throughout the report.

Objective 1: Ensure a smooth transition to the new proposed cross-sectorial partnership in health under Horizon Europe by providing lessons learned at operational level and involving key members of IMI2 JU staff in discussions where appropriate.

Throughout 2021, the Programme Office worked hard to ensure a smooth transition to the new partnership. Following careful planning and coordination activities, the transition of all the IT tools, including the record management tool ARES, was carried out successfully. Technically this took place in one day from 30 November to 1 December, ensuring full business continuity. The visual identity for the new programme was also prepared for the transition. This included publishing the new IHI website and first batch of communication materials.

Specific working groups comprising staff members with relevant expertise were set up. The working groups covered areas like governance, grant management, administration, and finance to mention a few examples. This ensured that the lessons learned were shared and considered in the planning and preparations. The transition took place successfully 30 November 2021 when the legislation creating the Innovative Health Initiative Joint Undertaking (IHI JU) entered into force.

This transition was validated by the first IHI Governing Board (GB) which took place on 16 December 2021, where all of the legal and financial legacies of IMI were transferred to IHI, the Executive Director of IHI was given their authorisation powers, and the IHI GB rules of procedure were adopted.

Objective 2: Complete the execution of the Strategic Research Agenda priorities, bringing together the different stakeholders involved in health research (including SMEs, regulators and patient organisations) through the continued monitoring of project implementation and by fostering cross-project collaboration.

The following IMI2 calls launched in 2020 were completed in 2021:

- IMI2 – Call 20 (two stages, 6 topics, launched 21 January 2020): 6 grant agreements were signed, covering the AWP priorities of infection control including vaccines, oncology, immunology, and other enablers of research topics.
- IMI2 – Call 22 (one stage, launched 23 June 2020): 3 grant agreements were signed resulting from this restricted Call to maximise the impact of IMI2 JU objectives and specific priorities.
- IMI2 – Call 23 (two stages, 6 topics, launched 23 June 2020): 6 grant agreements were signed covering the AWP priorities of neurodegeneration and other neuroscience priorities, infection control including vaccines, big data, digital health, clinical trials and regulatory research, oncology, facilitating rare disease therapies (including advanced therapy medical products) reaching patients in Europe, and other enablers of research.

Given that the regulation for IMI2 required that all commitments be made before the end of 2020, and the IHI regulation only came into force at the end of the year, no Calls were launched in 2021.

In December 2021, IMI/IHI organised a follow-up meeting with the representatives from the projects tackling COVID-19 funded under IMI2 - Call 21, who shared their projects' updates/results/news. The project representatives also shared their experience on how the projects adapted as the pandemic evolved and discussed the steps taken towards the sustainability of the results.

IMI continued throughout 2021 the systematic involvement of patients and carers at all levels of its activities. Members of the pool of patients / carers participated in the second stage evaluation of proposals submitted for IMI Calls for three topics under IMI2 - Call 23, and joined the expert panels for the interim review of two projects. In addition, in 2021, 26 members of the patient pool attended IMI project close-out meetings. IMI organised a webinar with the European Medicines Agency on the European Regulatory Process that was attended by 84 patients and carers.

Objective 3: Ensure sound budget implementation through the effective and efficient management of grant award process, close monitoring of projects and error rate.

For the operational payment appropriations, the JU maintained a high execution rate of 96 %. On Call and grant management, IMI achieved the regulatory targets for:

- Time to inform (TTI): **75** days out of a target of 153 days
- Time to grant (TTG): **223** days out of a target of 245 days
- Time to pay (TTP) pre-financing: **10** days out of a target of 30 days
- TTP interim payments: **61** days out of a target of 90 days
- TTP final payment: **70** days out of a target of 90 days.

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

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

During 2021, IMI held 36 interim review meetings of its ongoing projects. During these meetings, 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 IMI office.

Objective 4: Demonstrate the EU added value of IMI2 JU through assertive communication to target audiences with emphasis on the openness, transparency, relevance, and coherence of IMI2 JU activities.

Continued to disseminate IMI project results and success stories by boosting the diversity of our output to include over 100 written articles in different styles as well as short, accessible videos for promotion via social media. All IMI project factsheets were added to the newly created IHI website, to facilitate their promotion in the future.

Organised the 'IMI Impact Series', a series of short virtual events focusing on IMI's impact on diabetes, data, dementia, patient engagement and paediatrics research. The events attracted an audience of 775 participants. The Programme Office also published dedicated impact pages on these areas on the IMI and IHI websites.

Continued to promote IMI project successes via all channels, namely social media (Twitter and LinkedIn, where engagement remains high), the IMI/IHI newsletter, media multipliers and other events.

Objective 5: Involve industry from related sectors other than the pharmaceutical industry (diagnostics, medical technologies industry, imaging, digital industry, food and nutrition, etc.) in IMI2 JU through proactive outreach strategies.

A number of companies opted to contribute to the IMI2 programme as EFPIA Partners in Research (PiR) by joining projects during 2021, including Aridis Pharmaceuticals, BASF SE, BioLizard, Charles River, Europharma and Evotec.

The launch of IHI at the end of 2021 marked the start of a new public-private partnership where other sectors are involved as full partners, contributing their resources to the programme, and guiding the work of the new partnership via seats on the Governing Board.

Given that no calls were launched in 2021, no new companies joined the programme during the year as Associated Partners.

Objective 6: Ensure IMI2 JU internationalisation and build productive linkages to major international efforts to address Global Challenges (AMR, Alzheimer and other dementias, autism, cancer, diabetes, emerging infectious diseases, etc.).

Over the course of its lifetime, the IMI platform has become a magnet for partners wanting to leverage their own investments through more open collaboration models.

Through its Associated Partners, IMI is forging new links and strengthening existing ones with initiatives elsewhere in the world. In 2021, Cohen Veterans Bioscience joined the PRISM 2 project. Cohen Veterans Bioscience is a US-based non-profit biomedical research and technology organisation dedicated to advancing brain health by fast-tracking precision diagnostics and tailored therapeutics.

In addition, many IMI projects actively seek to collaborate with other international initiatives, building productive links and accelerating the international outreach of the programme. Some recent examples are highlighted below.

RESOLUTE's knowledgebase (compilation of publicly available data on solute carriers) gained visibility and findability due to the project's interaction with the Illuminating the Druggable Genome (IDG) initiative (NIH programme) whose resource, Pharos database, is now interlinked with the RESOLUTE knowledgebase.

TransBioLine has formalised the Critical Path Institute (C-Path) joining the project. C-Path is a non-profit PPP with the US Food and Drug Administration (FDA) that aims to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies.

AIMS-2-TRIALS is the first neuropsychiatric consortium in Europe to incorporate candidate biomarkers in clinical trials of autism spectrum disorders (ASD). In 2021 the consortium started coordinating activities with the c4c project to ensure synergy and complementarity across paediatric trial efforts in the EU. Synergies with other international efforts, including the Province of Ontario Neurodevelopmental Network (POND, Canada), Simons Foundation Autism Research Initiative (SFARI), Clinical Research Associates; (CRA, US), the Autism Learning Health Network (ALHN, US), Autism Biomarkers Consortium for Clinical Trials ABC-CT (US), and the Cooperative Research Centre for Living with Autism (Autism CRC, Australia), have been established and/or further reinforced to better align trial and training activities of the project's clinical trials network on a global scale.

The AIMS-2-TRIALS consortium in 2021 also continued working to achieve the sustainable integration of AIMS-2-TRIALS data in a global context through the Autism Sharing Initiative, a collaboration to build a federated, global network for sharing anonymised genomics and clinical data according to FAIR principles to accelerate scientific discoveries and the development of precision therapeutics in autism. This initiative is a partnership between Autism Speaks and AIMS-2-TRIALS, as well as DNAstack (Canada-based SME) that brings together one of the largest collections of genomic and clinical autism data world-wide.

The Hypo-RESOLVE consortium signed a CDA (confidential disclosure agreement) with SWEET, a growing global network of certified diabetes centres aiming to improve the quality of, and reduce inequalities in, paediatric and adolescent diabetes care, enabling improved outcomes in children and young people with diabetes. One of the goals of the collaboration is to extend the project's findings and conclusions with respect to hypoglycaemia in diabetes to the paediatric population, and examine quality of life aspects of hypoglycaemia in children.

Several members of the NECESSITY consortium are chairs or members of the OMERACT Sjögren's disease working group. The OMERACT project aims to improve the development of outcome measures by involving relevant stakeholder groups and integrating their input to reach a consensus.

The RTCure project has developed synergies with the ongoing MEDALLION (CRUK/JGWP funded) and Bio-FLARE (MRC-funded) initiatives, which are clinical studies focusing on identifying potential mechanisms driving arthritis-associated autoimmunity. Data, samples and candidate therapies for mechanistic hypothesis testing and the identification of clinical candidates for the testing of tolerising therapies are made available to the RTCure consortium.

Objective 7: Improve and broaden access to IMI project outcomes by embedding dissemination in all stages of the project lifecycle.

During 2021, IMI held close-out meetings on 10 projects that had finished. The results and impacts were summarised on the IMI website and promoted. The number of close out meetings was again less than originally expected in 2021 due to consortia continuing to request no-cost extensions as work plans were disrupted by the COVID-19 pandemic.

IMI organised an online session based on the field manual Scaling Innovations Emerging from Public-Private Partnerships, which collected the experience of several IMI digital health projects.

To align with the reinforced requirements for projects working on COVID-19 (IMI2 - Call 21) on open access to research data, the Programme Office updated its open access guidelines for projects. Further information on specific IMI project assets to facilitate the FAIRification of data and specific resources for projects working on COVID-19 and SARS-CoV-2 was added.

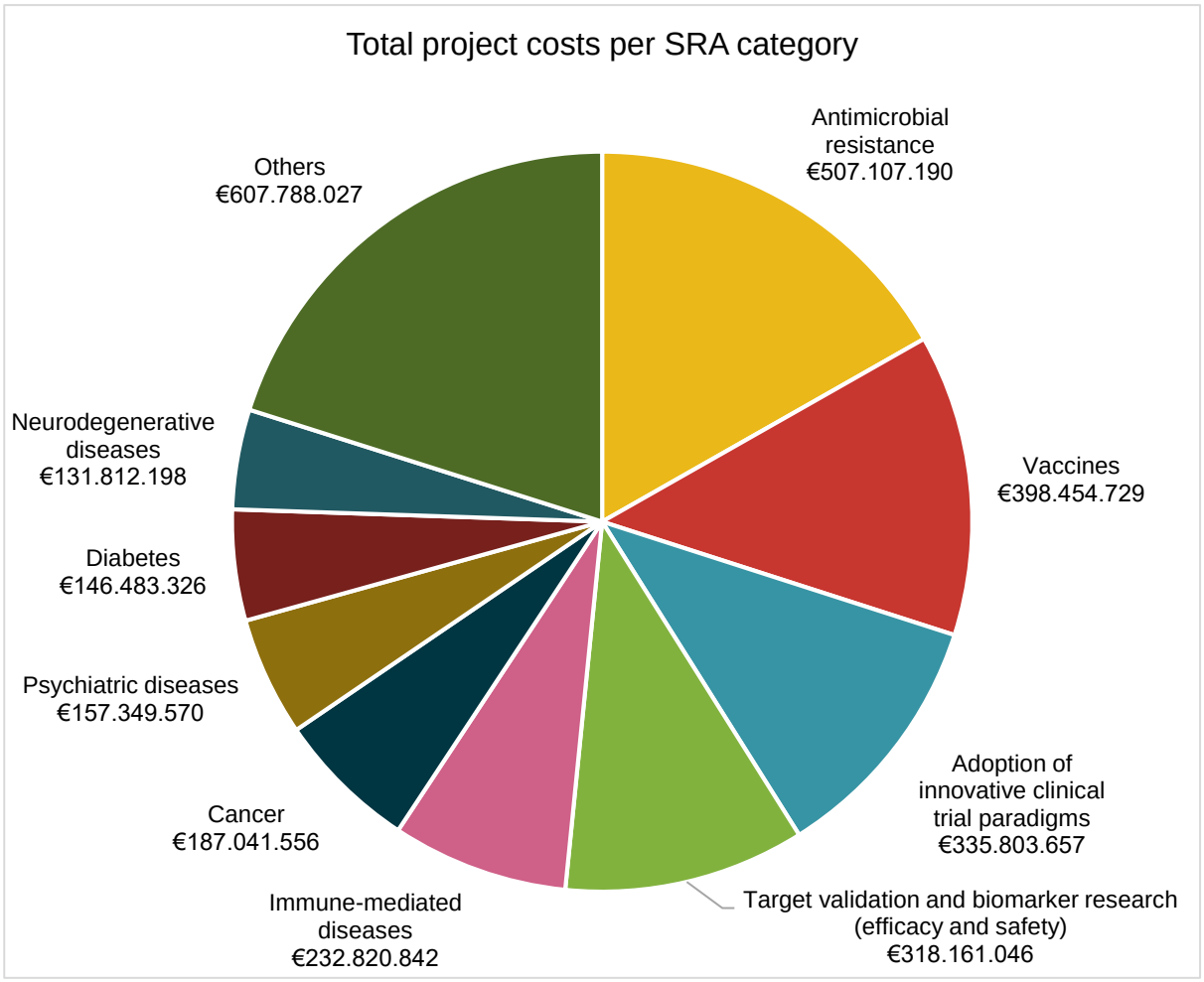
Regarding feedback to policy, the IMI office extended the exercise of mapping IMI projects against EU policies to two further areas: IMI's digital and paediatric portfolios. It also contributed to the DG RTD feedback to policy pilot based on the ERAvsCorona Action Plan.

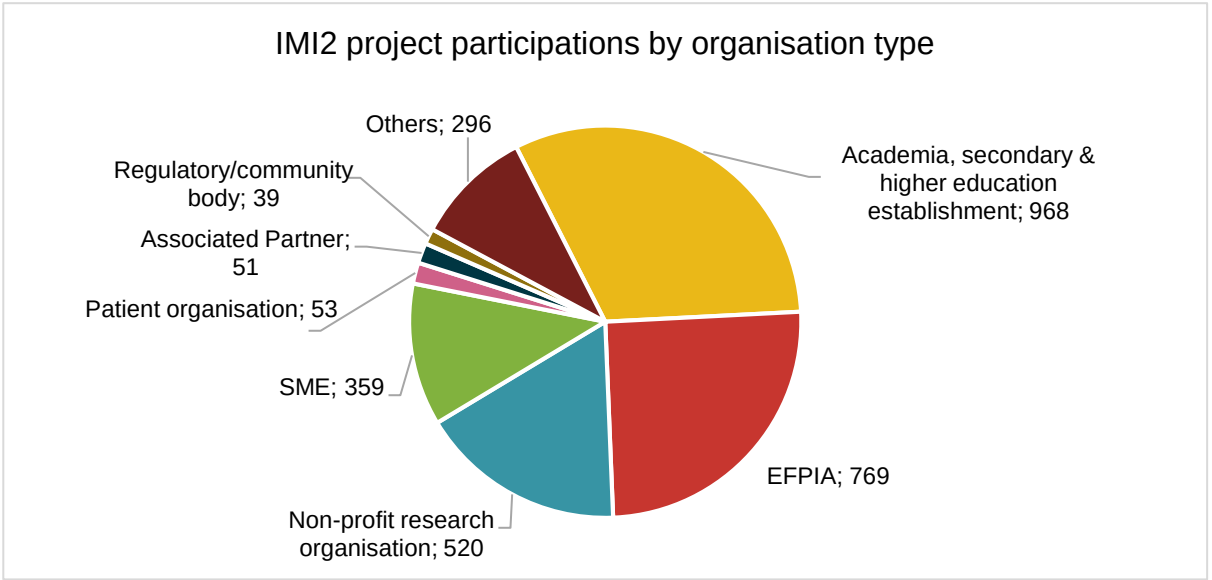
IMI representatives took part in the DG RTD Horizon Europe Feedback to Policy Group and the Horizon Europe Dissemination and Exploitation Group meetings.

1.2 Research and innovation results

The IMI2 project portfolio is complete!

In 2021, the final IMI2 projects were launched, completing the 123-strong IMI2 portfolio. The charts below show the breakdown of the IMI2 funding by Strategy Research Agenda (SRA) category, and the breakdown of project participations by organisation type.





The 15 newly created projects have a total budget of EUR 413 million, with around half of this coming from the EU's Horizon 2020 programme, and the rest coming from EFPIA contributions and IMI2 Associated Partners as well as other sources. They include projects on cancer (a key priority for the EU as evidenced by the cancer mission created under Horizon Europe), infectious diseases, neurodegenerative diseases, autoimmune diseases, and rare diseases, as well as projects addressing cross-cutting issues in health research.

Cancer

Some 90 % of cancer deaths occur in people who initially responded well to treatment, but whose cancer subsequently became resistant to treatment. PERSIST-SEQ aims to shed new light on the mechanisms behind this resistance to treatments.

Advances in research mean that for many cancers, there are more treatment options than ever. The aim of OPTIMA is to harness the power of artificial intelligence (AI) to advance treatments and facilitate decision-making for physicians and patients with prostate, breast and lung cancer.

PROTECT-trial is comparing the merits of standard radiotherapy and proton therapy (an innovative form of radiotherapy) in people with cancer of the oesophagus whose treatment also includes chemotherapy and surgery.

Infectious diseases

Identifying new treatments and treatment combinations that could shorten the treatment time for tuberculosis (TB) and tackle drug resistance is difficult and time-consuming. The aim of UNITE4TB is to accelerate and improve clinical trials of combinations of existing and new drugs, with the goal of developing new and highly active treatment regimens for TB, including drug-resistant TB.

Vaccines and monoclonal antibodies (mAbs, laboratory-made antibodies similar to those your body makes in response to an infection) could play a key role in the fight against AMR. The aim of PRIMAVERA is to develop mathematical models and an epidemiological repository that will facilitate the assessment of different vaccines and mAbs in terms of their likely impact on AMR.

Recent advances in fields such as immunology, big data and artificial intelligence could potentially speed up the development of new vaccines and make the whole process more efficient. The aim of Inno4Vac is to harness these advances and incorporate them into the vaccine industry.

Respiratory syncytial virus (RSV) is an infectious disease that can cause severe illness in young children, the elderly, and people with weakened immune systems. PROMISE builds on the work of the RESCEU project and aims to advance our understanding of RSV to aid in the design of public health strategies as well as the development and use of vaccines and therapeutics.

Autoimmune diseases

Psoriasis is an autoimmune disease that primarily affects the skin. However, 20-30 % of people with psoriasis develop psoriatic arthritis, symptoms of which include pain, joint stiffness and fatigue. HIPPOCRATES aims to deliver knowledge and tools that will make it easier to spot the psoriasis patients who are at greatest risk of developing psoriatic arthritis, and diagnose them faster.

Neurodegenerative diseases

Social withdrawal is a common early symptom of many neurological disorders. PRISM 2 aims to validate the findings of the PRISM project on social withdrawal in schizophrenia and Alzheimer's disease, and investigate whether they also apply to major depressive disorder.

Researchers worldwide have amassed a wealth of biological samples and data that could yield vital information on biomarkers relating to neurodegenerative diseases. However, finding samples, and then accessing and using them, is far from easy. The aim of EPND is to establish a collaborative platform that would link up existing European research infrastructures and so speed up the discovery of new biomarkers for neurodegenerative diseases.

Rare diseases

The goal of Screen4Care is to dramatically shorten the time it takes rare disease patients to get a diagnosis and treatment. It will do this through the genetic screening of newborn babies and by designing new artificial intelligence algorithms to identify rare disease patients early on in their disease via electronic health records.

Cross-cutting issues in health research

Many new medicines are based on proteins, but if stored or handled inappropriately, the proteins can break down, compromising the safety and efficacy of the product. RealHOPE's goal is to improve our understanding of how protein drugs are handled in the real world, and the effect this has on product quality.

Transport proteins act as our cells' gatekeepers, controlling the flow of nutrients and other molecules (including drugs) into and out of the cell. REsolution builds on the work of the RESOLUTE project by generating new knowledge on genetic variation in solute carriers, the largest group of transport proteins.

Around half of all patients do not take their treatment as prescribed, and this can have a dramatic impact on patients' health and quality of life. BEAMER aims to add to our understanding of the factors that influence patient adherence across disease areas, and deliver guidance that various stakeholders could use to address patients' needs and boost adherence.

Clinical trials and studies generate vast amounts of high-quality data, yet it is rarely returned to the people taking part in the trial. Furthermore, the data is typically siloed in separate repositories and cannot be used for other studies. The aim of FACILITATE is to develop a prototype of a patient-centred, data-driven process that would allow innovative data sharing and the re-use and return of clinical trial data to study participants.

Analysing IMI project results

The overarching goal of the IMI1 programme was to significantly improve 'the efficiency and effectiveness of the drug development process with the long-term aim that the pharmaceutical sector produce more effective and safer innovative medicines'.

For IMI2, the goals are more specific:

- improve the current drug development process by providing support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products;
- develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators;
- where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
- increase the success rate in clinical trials of priority medicines identified by the World Health Organisation;
- develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance;
- reduce the failure rate of vaccine candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks.

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 IMI's key performance indicators (KPIs). The categories were selected due to their alignment with the goals of IMI, and because they allow IMI 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 2 of this report. Figures on the KPIs can be found in Annex 1.

Here, a selection of success stories demonstrates how IMI projects are delivering results in disease areas with high unmet medical and social needs (such as diabetes, antimicrobial resistance, and brain disorders); and more broadly addressing ongoing challenges in medicines research and drug development.

What is notable is the number of projects whose outputs are recognised by regulators in various ways. Regulatory recognition shows that the tools, resources and protocols developed by IMI projects are good enough to be used widely in drug development. This in turn increases their impact.

1.2.1 IMI projects deliver results on COVID-19

In 2021, IMI's projects continued to deliver results that contribute to the fight against COVID-19. While many findings came from the portfolio of projects dedicated to coronavirus treatments and diagnostics, many came from projects working in other fields.

CARE scientists discover a highly potent antibody against SARS-CoV-2

Researchers involved in IMI's CARE project isolated a highly potent monoclonal antibody against SARS-CoV-2, one of the most powerful identified so far. Writing in the journal Cell Reports, the scientists explain that the monoclonal antibody targets the SARS-CoV-2 spike protein and is effective at neutralising all variants of concern identified at the time the research was carried out, including the delta variant.

In addition to its antiviral properties, the new antibody is designed to have a lasting effect in humans. A typical unaltered antibody provides protection for up to 3–4 weeks, but this new one can protect patients for 4–6 months. That makes it an interesting preventive-treatment option for unvaccinated, at-risk individuals or for vaccinated individuals who are unable to produce an immune response. Immunocompromised patients, organ transplant recipients and those suffering from certain kinds of cancer could be protected against SARS-CoV-2 by receiving antibody injections two or three times a year.

In a press release, the researchers explain that they plan to build on these promising results in association with a start-up company that will perform clinical development and production of the antibody-containing drug, through cooperation and intellectual property agreements. Clinical trials of the drug should begin in late 2022.

Other exciting results from the CARE project in 2021 include:

- A paper in Cell flags up a genetic link to the likelihood of someone developing severe disease.
- A paper in Circulation shows how SARS-CoV-2 indirectly damages the endothelial cells that line the blood vessels, lymph nodes and heart.
- A new assay (a test used for analysis) for understanding antibody response in natural infection versus vaccination, described in Science Translational Medicine.
- Insights into the durability of different antibodies against the spike protein, described in the Journal of Virology.

Repurposing: a promising source of COVID-19 treatments

Since the start of the COVID outbreak, a lot of research has focused on whether existing drugs could also prove effective as COVID treatments. The MAD-CoV 2 project used computational biology and machine learning approaches to identify existing, approved drugs that could be repurposed to treat COVID. They identified 200 drugs, 40 of which are already in clinical trials. The team classified the drugs according to the way they work and within two overarching mechanisms of action: viral replication (126 drugs) and immune response (74). Two drugs (proguanil and sulfasalazine) implicated in viral replication were shown to inhibit

viral replication in cell assays. This analysis opens up new avenues for the rapid repurposing of approved drugs into clinical trials, the team concludes in their paper in Science Advances.

Elsewhere, MAD-CoV 2 looked at combination treatments for COVID-19. The drug remdesivir has been shown to improve outcomes for COVID-19 but not decrease mortality. The project studied the effect of combining remdesivir with soluble angiotensin-converting enzyme 2 (ACE2, the protein that the virus uses to break into and infect our cells). In a lab-based study, they found that combining the two compounds has an additive effect. Writing in EMBO Molecular Medicine, they note that their data lays the groundwork for the study of combinatorial treatment regimens in future clinical trials.

Finally, Impentri published the results of its study on the efficacy and safety of cancer drug imatinib as a treatment for COVID patients in intensive care. The results suggest that although oral imatinib does not change the time to discontinuation of supplemental oxygen and ventilation compared to placebo, mortality was 49 % lower in the imatinib group than in the placebo group. The project subsequently launched a similar trial using intravenous imatinib.

Progress on diagnostics

The RAPID-COVID project has developed two CE-marked diagnostic panels which can identify not only SARS-CoV-2 (the virus that causes COVID-19), but several other respiratory infections such as flu and respiratory syncytial virus (RSV). If used widely, this device would help doctors to rapidly determine the most appropriate treatment for patients with respiratory symptoms.

Elsewhere, the DRAGON project is developing artificial intelligence (AI) models based on imaging (for example CT scans) to provide a diagnosis and prognosis of COVID-19. In 2021, the project set up a distributed learning network involving six clinical sites across Europe. Datasets uploaded by a partner to its local DRAGON machine will never be transferred over the network. During the training process, AI models to be trained are downloaded from a remote server at the beginning of a training pass, and reuploaded to that server when a training pass is finished. Therefore, privacy sensitive data never leaves the data stores while available to the learning application.

Finally, IMI projects are investigating if wearable devices and apps could help to detect COVID cases early. Here, over 12 000 people completed the COVID-RED study into the ability of the Ava wearable device and associated app to detect COVID cases early.

On a smaller scale, researchers from the RADAR-CNS project developed a machine learning method to recognise people with COVID-19 from heart rate data provided by wearable physical fitness monitors such as a Fitbit. By comparing 19 participants with COVID-19 symptoms to 19 participants without symptoms, researchers showed the method was able to correctly identify all patients with symptoms (100 % sensitivity) and performed very well on identifying people without symptoms (90.6 % specificity), suggesting it would provide a low rate of false alarms. RADAR-CNS's focus is on the use of devices to predict relapses in people with conditions such as multiple sclerosis, severe depression and epilepsy. The results, published in Pattern Recognition, show how IMI projects can have impacts beyond their core areas.

COVID-19 vaccine based on technology tested for safety & immunogenicity in IMI Ebola projects

In 2021, the Johnson & Johnson COVID-19 vaccine received conditional marketing authorisation from the European regulators. The vaccine uses the company's AdVac technology. Through the EBOVAC projects, IMI funded Phase 1, 2 and 3 clinical studies that generated data on the safety of the AdVac® vaccine platform, providing evidence upon which the European Medicines Agency based its decision.

According to a representative from Johnson & Johnson: 'Studies specifically supported by EBOVAC played an important role supporting our successful licensure application for the Ebola vaccine with the European Medicines Agency. Additionally, they gave the company confidence to use the AdVac® platform to initiate the development of COVID-19 vaccine.'

Harnessing the power of big data to assess vaccine safety

IMI's EHDEN project continued to use big data to assess COVID-19 vaccine safety. In a paper published in the British Medical Journal, the team describes how they carried out the largest, most extensive global network study on background rates for adverse events of special interest (AESIs) for COVID-19 vaccines. Knowing the background rates of these events, which include things like heart attack, stroke, and blood clotting, is crucial to assessing vaccine safety. However, the EHDEN team identified significant differences in the observed rates of AESIs based on the age groups and sex of more than 126 million people across four continents and 13 total databases used in the observational study. Furthermore, differences were observed across people in distinct databases. The team recommends that the same database be used to estimate post-COVID-19 vaccine and background rates for comparison in vaccine safety monitoring.

Lessons learnt during the pandemic could improve clinical trials in the long term

In a conventional clinical trial, patients have to make regular trips to the clinic for check-ups to monitor their condition. IMI's Trials@Home project was set up in 2019 to explore options for using digital technologies and wearables to assess clinical trial participants remotely, thereby reducing or even eliminating trips to the clinic. When the COVID-19 pandemic struck, many clinical trials were forced to shift from in-person assessments to remote assessments.

Trials@Home assessed when and how regulators provided guidance on how ongoing clinical trials could operate during the pandemic. Writing in Clinical Pharmacology and Therapeutics, they explain that 24 out of 27 EU national competent authorities published country-specific clinical trial guidance from 47 to 66 days after the first European COVID-19 case. Guidance was provided most frequently for regulatory management, safety management, documentation management, and CT monitoring.

The team concludes: 'The regulatory guidance observed during the pandemic has the potential to transform clinical trial conduct post–COVID-19, through revisiting regulatory requirements and investigation of the quality of remotely generated data.'

Probing the impact of the pandemic on people with major depressive disorder

Concerns about the impact of the pandemic and associated restrictions on people's mental health are common. But what about people who already have a diagnosis of major depressive disorder (MDD)? IMI's RADAR-CNS project used remote monitoring technology and self-reported questionnaires to track MDD symptoms and sleep patterns in people with MDD.

The study found no evidence that depressive symptoms or self-esteem changed between pre-, during- and post-lockdown periods. However, average sleep duration (in minutes) decreased significantly coming out of the lockdown period. The findings, published in BMC Psychiatry, also demonstrate the utility of remote measurement technology and wearables to evaluate the impact of COVID−19.

1.2.2 Regulatory impacts demonstrate strength of PPP approach

In the tightly regulated world of medicine development, having an impact on the regulatory framework is a major achievement. Impacts on regulatory frameworks are a key performance indicator for the IMI2 programme. By the end of 2021, IMI2 projects had registered 20 completed regulatory procedures (against a target of 10). The total for IMI1 and IMI2 projects together is 43.

Regulators tentatively endorse PREFER's patient preference approach

A major regulatory milestone was reached for researchers working on the PREFER project, which is investigating and testing the best ways to include patients' voices in medicine development and decision-making.

The project is finalising a set of recommendations that industry, regulatory authorities and health technology assessment (HTA) bodies will be able to use to develop guidelines on how and when to include patient perspectives on the benefits and risks of medicines.

In parallel, the consortium worked out a research framework for patient preference studies, as well as a document with points to consider when selecting the methods for carrying out a patient preference study.

The consortium submitted an application for a qualification opinion to the EMA and EUnetHTA (the first joint regulator and health technology assessment bodies joint procedure), and the EMA released a draft opinion that endorses both the framework and the points to consider document, 'as a comprehensive reference document for planning and conducting patient preference studies'.

The draft opinion underwent a one-month consultation period so that researchers, patients, pharmaceutical companies, regulators, HTA bodies or anyone else could contribute their comments before EMA releases its final opinion.

Experience with patient preferences studies is limited and there are still many research questions to be addressed. PREFER's work, endorsed by the EMA, will help to encourage collaborative research and sharing of experience in this field. More specifically, it will help scientists from academia and industry with input from patients to plan and design patient preference studies well, and allow regulators and HTA bodies to gain experience in reviewing data from these studies.

GetReal projects leave living legacy on real world evidence

The job of a HTA organisation is to assess the value of a new drug. To do this, they need real-world evidence (RWE), i.e. observational data obtained outside the context of randomised controlled trials, such as that generated during routine clinical practice. However, there is little guidance on how to generate RWE and integrate it into drug development. The IMI projects GetReal (2013-2017) and GetReal Initiative (2018-2021) broke ground in that they brought together all the relevant stakeholders to begin to work towards a consensus on best practices in the use of RWE in drug development, as well as regulatory and reimbursement decision-making.

In 2021, the team behind the projects launched the GetReal Institute as a Netherlands-based non-profit organisation to build on the results of the projects. The independent, member-led organisation will ensure access to, as well as the further development and adoption of, (new) tools, methods and best practices in the generation and use of real-world evidence for better healthcare decision-making.

Membership is open to organisations of key stakeholders including decision makers, public and private researchers, patients and clinicians, data custodians, and technology developers.

The project also released the open access GetReal Trial Tool that provides guidance on the options and implications of introducing real world elements in clinical trial design. They also upgraded the Aggregate Data Drug Information System (ADDIS) tool, which focuses on structured benefit-risk assessment, preference elicitation, and shared (clinical) decision-making. ADDIS will be used by regulators as an educational tool. Finally, another GetReal legacy, the GetReal Academy, continues to deliver courses on RWE.

Ultimately, by creating the conditions for trusted multi-stakeholder discussions and generating science-led knowledge and resources, the GetReal and GetReal Initiative have place Europe at the forefront of efforts to integrate RWE into drug development.

Markers of medicines safety make regulatory milestone

Predicting which potential medicines could be harmful to major organ systems is a major challenge during drug development. The TransBioLine project is developing biological markers (biomarkers) that will reliably indicate injury of the liver, kidneys, pancreas, blood vessels, and central nervous system (CNS). To ensure the biomarkers can be widely used, the project has been in close contact with regulatory authorities on both sides of the Atlantic. By the end of 2021, the project had had four 'letters of intent' accepted into the Biomarker Qualification Program of the US Food and Drug Administration. The letters cover biomarkers for drug-induced vascular injury (DIVI), drug-induced CNS injury (DINI), drug-induced kidney injury (DIKI), and drug-induced liver injury (DILI).

The Biomarker Qualification Program supports stakeholders working on new biomarkers and provides a framework for the review of biomarkers for use in regulatory decision-making. The acceptance of a letter of intent represents an important first step in the pathway towards qualification. If a biomarker ultimately

receives a qualification recommendation, it may be used in the context for which it is qualified in any CDER (Center for Drug Evaluation and Research) drug development programme to support the regulatory approval of a new drug.

1.2.3 Putting patients at the centre of research and innovation

According to the IMI KPIs, over half of IMI projects include patients in some way or another, but how can projects ensure that patient engagement works well and brings value to both patients and other partners in the project? IMI projects that have succeeded in this field regularly share their advice and lessons learned in the scientific literature.

A fresh APPROACH to patient engagement in osteoarthritis research

IMI project APPROACH was set up with the goal of paving the way for more personalised treatments for osteoarthritis, a common form of joint disease. The project set up a Patient Council comprising five people with osteoarthritis from across Europe. In 2021, the members of the council and other project partners published a paper in Research Involvement and Engagement where they describe how the council worked and the challenges and lessons learned.

In addition to looking at practical issues such as organisational structures, budgets and meetings, the article also explores more informal elements such as building relationships and changing researcher perceptions and attitudes. It also sets out in concrete terms how patient input helped to improve the project, for example by improving the experience and engagement of study participants by providing input on the clinical protocol and ensuring effective communication with participants.

'Overall, as the experience in APPROACH demonstrates, patient involvement may not always be easy and will need time to grow,' the authors of the paper conclude. 'But it is an enriching experience for patients and researchers involved, and has broad benefits that range beyond the scope of the research project.'

PIONEER puts patients at the heart of prostate cancer study

PIONEER is an IMI project using big data approaches to address key knowledge gaps related to the screening, diagnosis and treatment of prostate cancer patients. One focus of the project is on delivering core outcome sets (COS) for prostate cancer. COS are an agreed, minimum set of outcomes that should be measured and reported in all clinical trials, and if used widely, they make it easier to compare or combine results from different trials.

From the start, PIONEER wanted to include all relevant stakeholders in the development of its COS, including prostate cancer patients themselves. In a paper in European Urology Focus, the project sets out the following recommendations for patient engagement in COS development:

- Collaborate closely with patient organisations such as the European Cancer Patient Coalition in setting the research agenda.
- Actively involve patients throughout the different stages of COS development and always give patients an opportunity to provide feedback
- Understand the challenges that COS development can introduce, as the process is methodologically focused and quite removed from the actual patient experience (i.e. additional interviews with patients can enable researchers to bridge the gap between the abstract process and the patient perspective).
- Provide patients with additional support before, during, and after consensus meetings to ensure that additional concerns and questions can be addressed in lay language and that all patients can actively engage.
- Disseminate findings in lay language to increase the availability of the findings across all relevant stakeholders and maximise their impact.

1.2.4 IMI projects contribute to goals of Cancer Mission

Cancer is a top priority for the EU, as evidenced by the Beating Cancer Plan and the Cancer Mission under Horizon Europe. IMI projects are contributing to the fight against cancer in diverse ways. Moreover, as many IMI cancer projects are still relatively young, we can expect a growth in research outputs in this area in the coming years.

Projects team up on prostate cancer

In 2021, IMI big data projects PIONEER and EHDEN teamed up to run a 'study-a-thon' on prostate cancer. During the 5-day virtual event, over 240 data scientists, clinicians, epidemiologists, patients, and statisticians from 20 countries crunched data on prostate cancer patients drawn from 17 databases across 6 countries. Their aim was to assess what happens in the long term to people with prostate cancer whose disease is managed using the 'watchful waiting' approach. In watchful waiting, the patient's disease is 'watched' for developments until they require palliative treatment, with the aim being to maintain quality of life.

By working in the concentrated set-up of the study-a-thon, the team was able to achieve in days results that would have taken months otherwise. Using the results of the study-a-thon, the team drafted two papers for submission to scientific journals.

European Lead Factory delivers promising potential cancer drugs

In the early stages of drug discovery, scientists screen large numbers of chemical compounds in the hunt for potential new drugs or other interesting molecules that could be used in drug development.

The European Lead Factory (currently funded through the IMI project ESCulab project) is a screening service with a vast chemical library that can be trawled by researchers and drug developers on the hunt for compounds that will have an effect on a particular biological pathway in the body. If a compound is found that can inhibit a particular process involved in disease, it might then progress to early preclinical testing, and in the long run, to a new drug.

Two drug companies, Israeli SME Metabomed and German pharmaceutical company Merck KGaA, both identified compounds in ELF's high-quality compound collection that showed promise in inhibiting their target pathways, both of which are involved in the development of cancer. Both compounds have now advanced to phase 1 human clinical trials.

Europe's top childhood cancer experts lay ground rules for moving forward on drug testing

IMI project ITCCP4 joined forces with US experts in paediatric cancer to reach a much-needed consensus on the best way forward for the pre-clinical testing of childhood cancer drugs. The group published their recommendations in the journal Molecular Cancer Therapeutics.

Cancer is a leading cause of death in children, and while the drugs that are used to treat adult cancer might work in children, there are not many options for treatment if those fail. What is needed are innovative drugs that have been developed specifically for children. It is hard to test new drugs, however, because both data and tumour models relevant to children are scarce, making it hard to carry out experiments to understand how tumours that emerge in childhood evolve, and how they resist treatment.

The recommendations are intended to guide the use of cell-based and mouse models for paediatric malignant tumours, as well as the scope and content of preclinical proof-of-concept data packages to inform the clinical development of promising agents. What's needed, the authors say, is access to 'comprehensive, well-validated preclinical tools, notably relevant animal models that effectively capture the molecular heterogeneity of paediatric cancer from treatment naïve and relapsed patients.'

1.2.5 Action on antimicrobial resistance

Antimicrobial resistance (AMR) remains a major threat to human and animal health worldwide; a recent report estimates that in 2019, some 1.2 million people worldwide died as a direct result of antibiotic-resistant bacterial infections. AMR is a priority area for IMI, as evidenced by the number and scale of IMI projects in this area, as well as their impressive outputs.

COMBACTE projects' legacy assured

IMI's COMBACTE projects have built up a network of over 1 200 hospitals and 900 labs across Europe that are ready to participate in clinical trials and studies on AMR. The COMBACTE projects have used the networks themselves for a number of clinical trials, demonstrating that the set-up works well. In 2021, a new entity, dubbed ECRAID, was set up to support clinical trials of new antimicrobial drugs. ECRAID builds on and ensures the legacy of the COMBACTE projects as well as another EU-funded project, PREPARE.

Meanwhile the COMBACTE projects continued to deliver results from the many trials they are already running with their networks. For example, the ANTICIPATE study provided valuable insights on *Clostridioides difficile* infection (CDI), which is one of the most common healthcare-associated infections. These helped to inform the design of the MICROCARE trial, which got underway in 2021 and is evaluating the efficacy of DAV132 in people with blood cancer. DAV132 is designed to protect the gut microbiome in patients who are at risk of CDI.

The projects also published results from the phase 2 clinical trial SAATELLITE in the Lancet Infectious Diseases. The results support the potential role of monoclonal antibodies in preventing ventilator-associated pneumonia (VAP) caused by *Staphylococcus aureus*. The next step is a phase 3 trial of the same drug.

COMBACTE-CDI puts spotlight on C. diff infections

IMI's COMBACTE-CDI project, which finished in 2021, set out to shed new light on the extent and impact of *Clostridioides difficile* infection (CDI) across all healthcare sectors in Europe. This information is essential for the development of better methods to prevent and treat infections.

Their findings helped confirm some long-held suspicions about CDI, including the intuition that there are many cases in the community that aren't being counted, meaning people are being exposed to the bug out in the real world and getting sick but not getting diagnosed.

The project found that there are as many as three times more people with infections in the community as there are in hospitals, but that these are not found because of a lack of 'clinical suspicion'. Hospital cases also turned out to be missed by clinicians, but to a lesser extent. Other important findings relate to the types of *C. diff* that circulate: certain types are *only* found in hospital cases, but others were found at similar levels in both the community and hospital. This, the researchers concluded, suggests a common transmission source.

In terms of regional differences, the findings show that countries that test less have more outbreaks of infection (epidemics), and that in those countries, there are more cases of the particular types of *C. diff* that tend to lead to these epidemics. Interestingly, they found that even though antibiotic prescribing overall can be linked to outbreaks, the type of antibiotic matters. The project partners concluded that more testing, coupled with fewer antibiotic prescriptions, could do a lot to bring the number of cases down.

Many project findings are summarised in an infographic and a research paper that is currently a pre-print. Overall, the results have significant impact for guideline development in terms of testing and treatment, as well as focusing on the need for education and training to ensure compliance with guidelines and for aiding the design of clinical trials of CDI treatment or management options.

ENABLE shows how public-private approach can advance antibiotic development

The ENABLE project set up a highly successful platform that advances the development of promising new antibiotic compounds. It guides researchers, including those in universities and SMEs, through the challenging early stages of antibiotic development to the point that they are ready to enter clinical testing.

French SME Mutabilis joined ENABLE in 2017 with a promising novel antibiotic called EBL-1463 that kills bacteria by interfering with the synthesis of their cell walls. Through ENABLE, the compound was developed further, allowing it to become a clinical candidate. In 2021, Mutabilis announced that it had received funding from CARB-X to keep developing EBL-1463 once ENABLE has finished.

ENABLE, along with the IMI's European Lead Factory, also played a key role in the development of a potential antibiotic that could reverse antibiotic resistance in bacteria that cause conditions such as sepsis, pneumonia, and urinary tract infections. The potential drug was first identified during a screen of the European Lead Factory's compound collection. It was then further developed in the ENABLE project. The compound is described in detail in a 2021 paper in Nature Chemistry.

'The collaborative efforts of academics and industry scientists have discovered a brand-new class of drug that can shut down one of the ways bacteria fight back against antibiotics. This research is the culmination of years of work, from screening huge libraries of chemicals, through to testing the best drug candidates in pre-clinical studies in the lab,' said lead author Christopher Schofield from the University of Oxford. 'We are actively progressing this new drug type towards clinical trials in people, most importantly in lower- and middle-income countries where resistance to carbapenem antibiotics is widespread.'

1.2.6 Delivering results in diverse areas

As the graphs above demonstrate, IMI has projects covering diverse areas, including specific disease areas as well as cross-cutting challenges in medical research. Many projects focus on issues such as big data and medical technologies, subjects that are likely to become even more significant with the launch of IHI.

Results build trust: how to create a pan-EU health data space

Experts from IMI's Big Data for Better Outcomes (BD4BO) programme have issued some recommendations on how to make the European Health Data Space really work for patients, doctors and researchers.

The BD4BO programme was set up to explore new, improved and ethical ways for researchers to unleash the collective power of healthcare datasets, with the ultimate aim of improving real-life outcomes for patients.

In response to the European Commission's announcement of their intention to put in place a European Health Data Space (EHDS), experts from BD4BO offered up the following recommendations based on their extensive experience of working out the right tools and rules for harnessing and exploiting big data via a multi-themed portfolio of research projects.

- Showing results can build trust.
- Use what already exists.
- Getting everyone on board will require big investments.
- Ensure an interoperable and flexible architecture.
- Meaningful codes of conduct will strengthen citizens' rights.

RADAR-CNS highlights how tech can help patients and healthcare professionals alike

IMI's RADAR-CNS project is developing new ways of monitoring major depressive disorder, epilepsy, and multiple sclerosis using wearable devices and smartphone technology.

In 2021 the project was awarded the Harald Fey prize for their work on the use of wearables to gauge the likelihood of sudden unexpected death in epilepsy (SUDEP). Wearable sensors can be used to detect seizures in people with epilepsy. The RADAR-CNS team suspected that they could also be used to detect not only the seizure itself, but also to measure post-ictal immobility, or the absence of motion following a seizure, a warning sign that the person is at increased risk of a complication that can cause SUDEP.

The researchers fitted accelerometers, which measure sudden motion, on people presenting with convulsive seizures at a hospital epilepsy monitoring unit. Of 22 seizures, 20 were followed by post-ictal immobility while two were followed by agitation. The results from the wearable's algorithm matched that of experts who watched video recordings of the patients. The study, published in Epilepsia, showed that wearables could

offer hope as a continuous, non-invasive, long-term way to identify risk factors associated with seizures, with potentially great clinical importance.

Elsewhere, the project revealed that data detected by Bluetooth sensors can approximate behaviours and social indicators associated with depression. A study of over 300 people found that nearby Bluetooth device count data (NBDC) collected by mobile phones has the potential to reflect changes in people's behaviour and what is going on in their life, and this is concurrent with the changes in their depressive state. The NBDC data also have a significant value in predicting depressive symptom severity. Bluetooth data is a relatively easy form of monitoring to put in place and is more continuous and less intrusive than traditional approaches. As such the findings may provide the basis for more effective mental health monitoring practice in real-world settings. The research was published in JMIR mHealth and uHealth.

c4c makes pan-European trial network for paediatric clinical trials a reality

IMI's c4c project aims to enable hospitals and clinical sites across Europe to become 'trial ready' for paediatric clinical trials. The project's pan-European paediatric clinical trial network includes 19 national hubs across 21 European countries providing access to over 250 clinical sites. In 2021, three proof of viability studies, designed to test the functionalities of the network, got underway and started recruiting patients. In addition, industry-sponsored studies went through site identification and trial feasibility services, as a first step to further test the viability of the network.

The project also consolidated its network as follows:

- put in place a unique confidential disclosure agreement cascade process and related templates, allowing for the fast and efficient exchange of confidential information between the study sponsor and single point of contact (SPoC), national hubs and sites during site feasibility, study start-up and conduct;
- updated the standardised template for the clinical trials agreement (CTA) to promote timely completion of preparations for site opening;
- defined a core set of performance metrics for national hubs and sites.

A RESOLUTE approach to studying an important group of proteins

Transport proteins are the gatekeepers of our cells, effectively controlling the flow of nutrients and other molecules across the cell membrane. 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 detail.

IMI's RESOLUTE project is delivering a range of open access tools to help the research community study SLCs more easily and use them in drug development. For example, in 2021, the team added 447 DNA sequences of SLCs to the RESOLUTE plasmid collection. The sequences are publicly available via Addgene.

The project has also released a set of SLC-knockout cell lines to the open access ATCC (American Type Culture Collection) cell repository. This will ensure longevity and long-term impact of the generated resources of benefit to the wider scientific community. The cells will be made available after quality control by the ATCC.

Neuronet Knowledge Base showcases IMI's neurodegeneration projects

IMI's Neuronet project has launched a Knowledge Base which brings together in one place information on over 20 IMI neurodegeneration projects. The comprehensive resource is an integral part of Neuronet's endeavour to boost collaboration across the research portfolio by identifying gaps, multiplying the portfolio's impact, and enhancing its visibility.

As well as providing an overview of the IMI neurodegeneration research programme through its interactive dashboard, the Knowledge Base acts as a one-stop shop to explore the diverse projects and outputs of the programme. In addition to links to over 500 publications, the Knowledge Base includes an 'asset map' showing the different assets resulting from the projects, such as genetic datasets, clinical cohorts, and data platforms.

Furthermore, the Knowledge Base offers access to a regulatory, health technology assessment & payer engagement Decision Tool to help researchers identify the key processes and procedures for engagement with these stakeholders at key points in the development of an asset.

The Knowledge Base was launched in February 2021 – by the end of the year, it had received 16 000 views and over 2 000 users.

1.3 Project impacts and dissemination

Exploitation of project results

In 2021, IMI added a page on exploitation of project results to the 'resources for projects' section of the IMI website. IMI organised an online session based on the field manual Scaling Innovations Emerging from Public-Private Partnerships, which collected the experience of several IMI digital health projects. The masterclass offered practical advice and solutions to facilitate designing and implementing strategies for deployment and scale up of results delivered by IMI and, in the future, by IHI.

Open access

To align with the reinforced requirements for projects working on COVID-19 (IMI2 - Call 21) on open access to research data, the Programme Office updated the open access guidelines for projects. The update also included the addition of further information on specific IMI project assets to facilitate the FAIRification of data, and specific resources for projects working on COVID-19 and SARS-CoV-2.

Project impacts and dissemination

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 IMI. IMI consistently reminds its projects of the importance of dissemination, and in 2016 issued a practical guide on this that remains valid to date.

Feedback to policy

At their meeting of 19 June 2020, IMI Governing Board members requested the Programme Office to map IMI projects against EU policies. Following a pilot exercise on antimicrobial resistance presented at the end of 2020, in 2021 the Programme Office extended the mapping exercise to two further areas: IMI's digital and paediatric portfolios. It also contributed with the results of IMI projects to the DG RTD feedback to policy pilot based on the ERAvsCorona Action Plan.

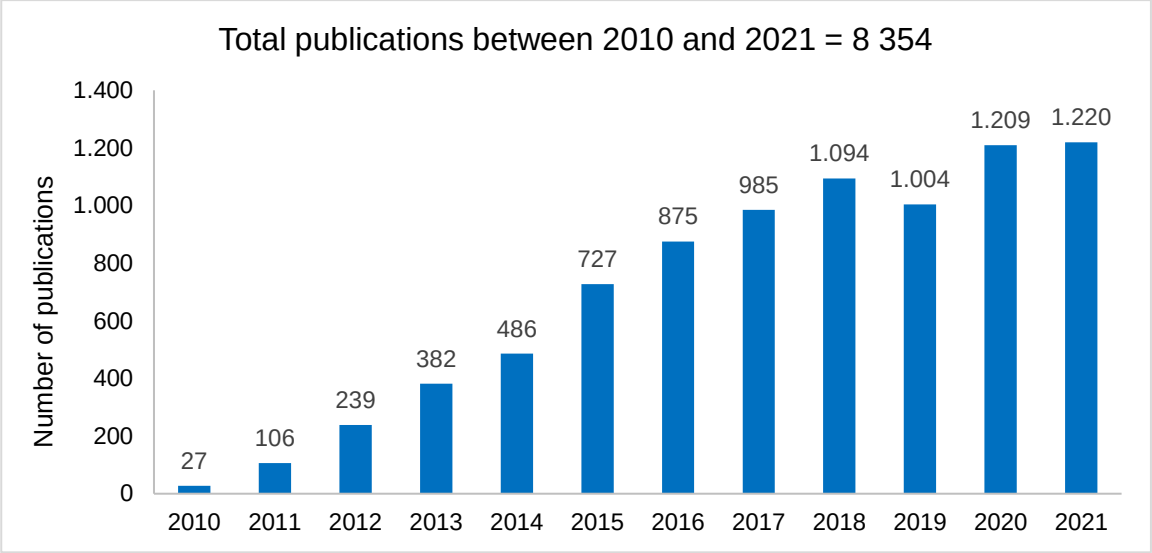
In addition, IMI representatives took part in the DG RTD Horizon Europe Feedback to Policy Group and the Horizon Europe Dissemination and Exploitation Group meetings.

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 (formerly Thomson Reuters), have consistently demonstrated both the sheer volume and high quality of research taking place in IMI projects.

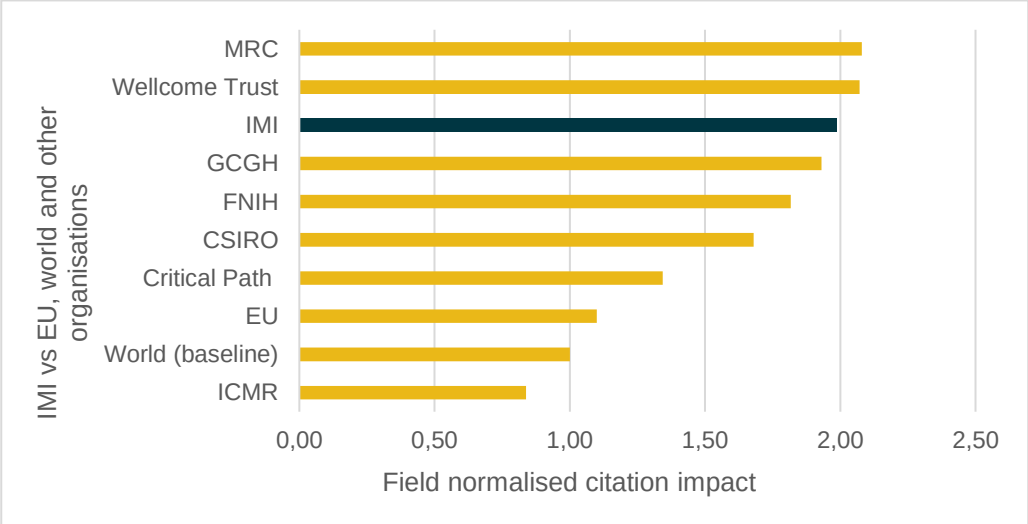
IMI projects are now producing an average of over 1 000 publications per year

In 2021, IMI projects produced 1 220 publications, bringing the total number of publications produced by IMI projects between 2010 and 2021 to 8 354. As the graph below shows, until 2018 the number of IMI research publications per year increased steadily and for the last 3 years (2019-2021) it has remained stable between 1 000 and 1 200 publications per year. This trend in publication output is to be expected as IMI is starting to mature and therefore its output begins to stabilise.



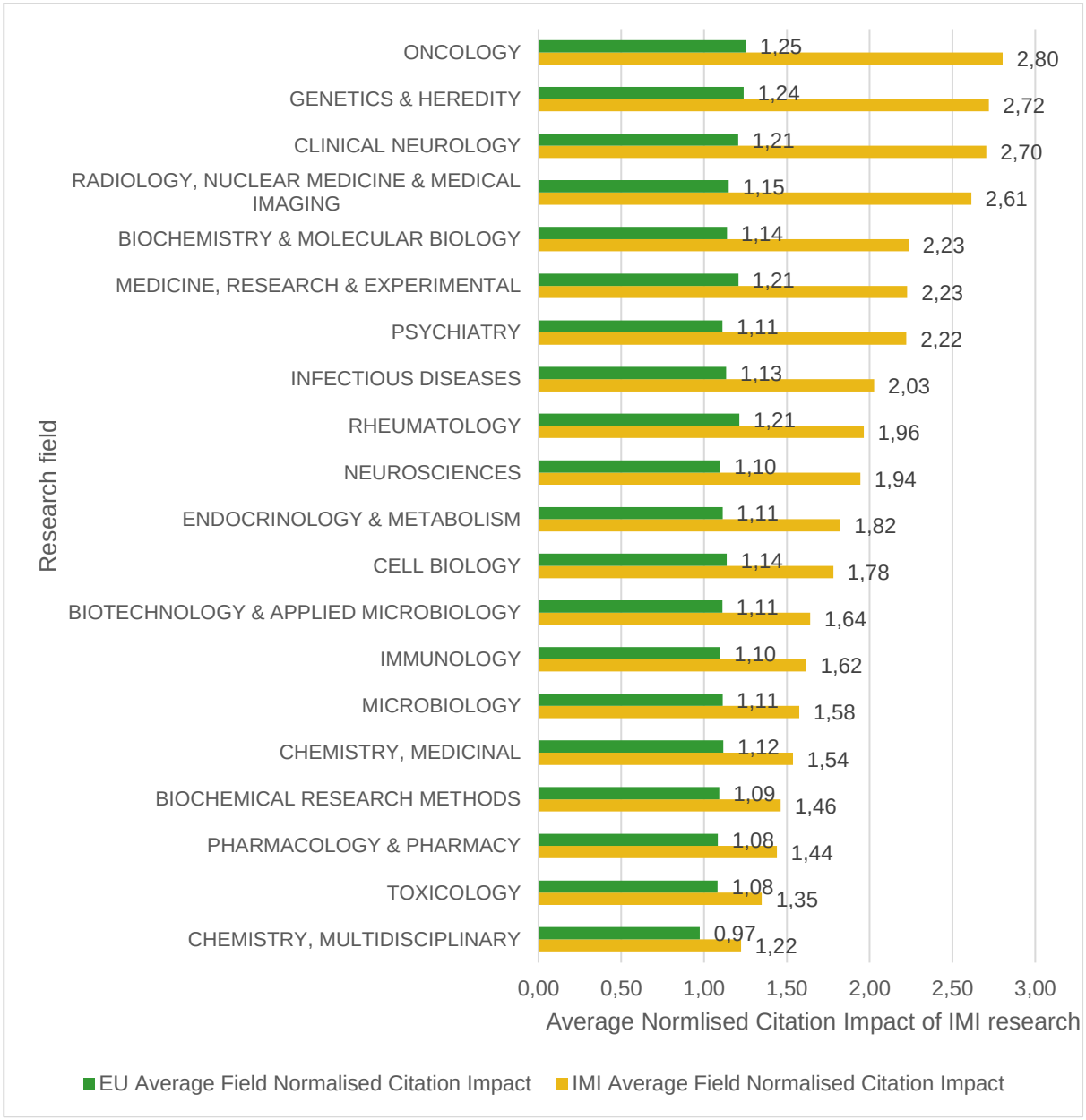
The citation impact of IMI research is higher than EU and world averages

The field-normalised citation impact for all IMI papers is 1.99 (compared to 1.10 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 notably the case in the fields of oncology, genetics and heredity, clinical neurology, radiology, nuclear medicine, and medical imaging where the IMI citation impact is between 2.6 and 3.



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

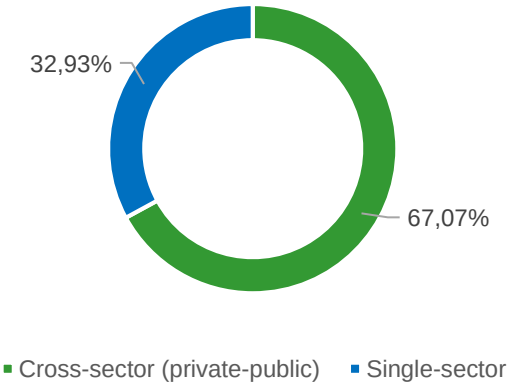
- 24.82 % of papers from IMI projects are ‘highly cited’, meaning they are in the top 10 % of papers by journal category and year of publication.
- IMI projects have published in 1 416 journals to date, and the average journal impact factor for IMI research is 8.22.
- Journals with a particularly high impact factor that have published IMI research include Nature (and other Nature journals e.g. Nature Drug Discovery, Nature Molecular Cell Biology, Nature Clinical Oncology, Nature Cancer, Nature Microbiology, Nature Biotechnology), Lancet, Chemical Reviews, and the Journal of the American Medical Association (JAMA).
- 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; IMI research produced higher number of papers compared to non-collaborative research.

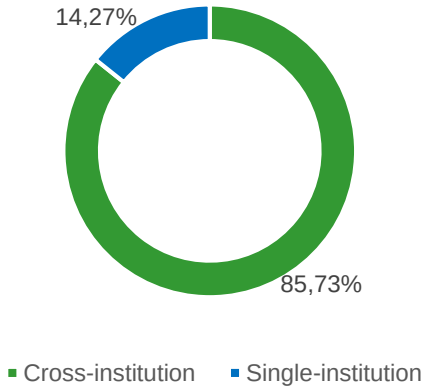
Cross-sector collaboration

Two-thirds of (67.07%) of all IMI project papers were published by co-authors working in different sectors.



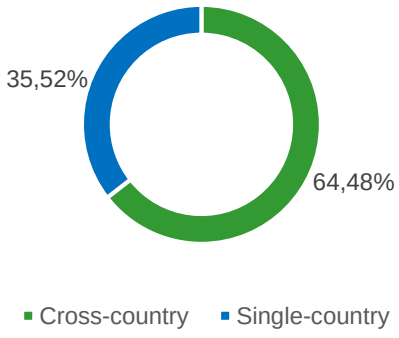
Cross-institutional collaboration

More than three-quarters (85.7%) of IMI project papers involved collaboration between different institutions.



International collaboration

More than half (64.48%) 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 1.60 and 3.22.

Top 10 IMI projects producing the highest number of publications

Project	Total publications	Mean field normalised citation impact
BTCure	709	1.79
EU-AIMS	559	2.05
ULTRA-DD	428	1.88
EMIF	323	2.39
NEWMEDS	218	2.12
CANCER-ID	206	3.22
AIMS-2-TRIALS	198	2.57
INNODIA	198	1.60
EUROPAIN	181	2.41
ORBITO	171	1.68

Between 2010 and 2021, IMI published papers in **1 416 different journals**.

Top 10 journals by number of IMI publications

Rank	Title	JIF	IMI papers
1	Scientific Reports	4.38	194
2	PLOS ONE	3.24	188
3	Annals of the Rheumatic Diseases	19.10	127
4	Nature Communications	14.92	116
5	Frontiers in Immunology	7.56	95
6	Diabetologia	10.12	79
7	Journal of Medicinal Chemistry	7.45	76
8	Arthritis Research & Therapy	5.16	69
9	Journal of Alzheimer’s Disease	4.47	66
10	Pain	6.96	55

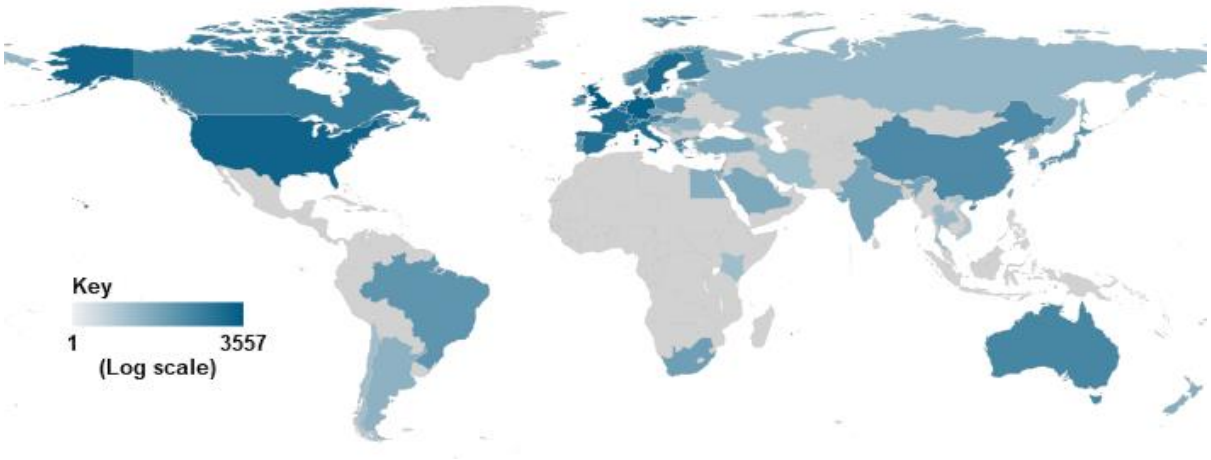
Top 10 journals by journal impact factor (JIF) in which IMI projects have published

Rank	Title	JIF	IMI papers
1	Nature Reviews Molecular Cell Biology	94.44	1
2	Nature Reviews Drug Discovery	84.69	8
3	Lancet	79.32	4
4	Nature Reviews Clinical Oncology	66.68	8
5	Nature Reviews Cancer	60.72	2
6	Nature Reviews Microbiology	60.63	2
7	Chemical Reviews	60.62	3

8	JAMA - Journal of the American Medical Association	56.27	7
9	Nature Biotechnology	54.91	1
10	Chemical Society Reviews	54.56	1

The analysis also reveals the global reach of IMI's research activities. In total, **128 countries** have at least one paper funded by IMI.

Countries with at least 1 paper funded by IMI



The scale shows countries having from 1 publication to 3 557 publications (UK being the top end with 3 557 publications).

1.4 Stakeholder engagement

1.4.1 SME engagement

Although no Calls were launched in 2021, several IMI projects have actively recruited and supported small and medium-sized enterprises (SMEs) outside of the project.

For instance, in 2021 the EHDEN project expanded the free online training available to SMEs through the EHDEN Academy, and 14 courses are now available. Using these courses, the project trained and certified an additional 19 SMEs in 2021, which means that 47 SMEs in 19 countries are now eligible to harmonise the data of the EHDEN data partners and are included in the EHDEN business directory. 25 of these SMEs are already actively working with EHDEN Data Partners on the harmonisation of data to the OMOP common data model.

In January 2021, FAIRplus ran their second Innovation and SME Forum which brought together nearly 100 researchers and data management experts from academia, SMEs and industry working with life science data. The forum focussed on how SMEs could maximise their FAIRification business offer to pharmaceutical companies.

The project has also launched a training fellowship which provides free FAIRification training with a particular focus on SMEs.

For the IMI2 programme, SMEs account for 16 % of EU funded beneficiaries (by participations), 25 % of EU funded beneficiaries (by participants), and receive 12 % of EU funding.

1.4.2 Patient engagement

IMI recognises that patients can make a vital contribution to shaping research, making it more effective and more oriented to patient needs. IMI-funded research is 'patient-centric', and IMI provided a valuable opportunity for patient groups to participate in various activities and subsequently improve the relevance, quality and validity of its projects from the patient perspective. The Programme Office continuously engages with patients and promotes patient involvement in its projects and activities at both strategic and operational levels. As of the end of 2021, close to 56 % 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 almost 60 % for IMI2 projects alone.

IMI continued throughout 2021 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. Following the activities of the patient expert pool which took place in 2020, the Programme Office continued to invite patients from the pool to perform a variety of roles and tasks. These include:

- Evaluation of proposals submitted for IMI Calls for proposals – three patient experts participated in expert panels that evaluated proposals for IMI2 - Call 23, stage 2: topic 1 (1 expert), topic 5 (1 expert) and topic 6 (1 expert).
- Monitoring of IMI projects – two patient experts participated in expert panels that carried out the monitoring of the IMI2 projects AIMS-2-TRIALS (1 expert) and RADAR-AD (1 expert).

To deploy the full potential of the IMI pool of patient experts, the 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 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 2021, 26 patients and carers attended the following IMI close-out meetings: EPAD (1), SPRINTT (3), COMPACTE-CDI (1), ULTRA-DD/CANCER-ID (4), ADAPTED (4), EFOEUPATI/PARADIGM (13).

Additionally, patients participated in different patient–centred activities organised by IMI projects. Some of these involved: a workshop on patient preferences organized by PREFER in collaboration with the Drug Information Association (DIA); an expert panel group to carry out a Delphi survey launched by GRAVITATE HEALTH; participation in the Patient Engagement Open Forum (PEOF) organised by EUPATI and EPF; and participation in the RADAR-AD Patient Advisory Board.

Within the context of interactive sessions with the IMI Pool of patient experts, in February 2021, IMI organised a webinar with the European Medicines Agency on the European regulatory process. The webinar attracted 84 patients and carers who had the opportunity to learn about the European regulatory pathway of a medicine, the role of patients in the regulatory process and the different aspects of IMI-EMA collaboration.

Furthermore, in October 2021, IMI organised an event dedicated to IMI's impact on patient engagement as part of the IMI impact event series to showcase the major impact of IMI in advancing patient involvement through projects like EUPATI, PARADIGM and PREFER, and explore the different challenges and benefits of collaborating with patients and carers by using concrete examples of IMI projects. The speakers, all carers and patients involved in IMI projects such as EUPATI, c4c, APPROACH, PIONEER, and RADAR-AD, shared their experiences and highlighted the strengths, challenges, and impact of engaging with patients to conceptualise, design, conduct research and disseminate findings. The event reached an audience of 198 participants representing academia, industry, research bodies, and patients. Patients and carers were also key speakers at the IMI impact events focusing on diabetes and dementia in June 2021.

Creating and developing communication channels with patients is instrumental in keeping them engaged and informed about the latest developments in IMI. Throughout 2021, IMI provided detailed updates on its activities to patients with IMI news and highlights from projects.

1.4.3 Regulatory engagement

As the scientific knowledge derived from IMI projects has the potential to support the evolution of the regulatory environment, IMI continued to maintain in 2021 a close collaboration with regulators, mainly the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). Regular teleconferences took place throughout the year with the EMA and FDA, providing an opportunity to exchange information on activities relevant for IMI. In addition, interaction with the EMA and other national regulatory agencies in the EU occurred also through the IMI Scientific Committee members.

IMI continued to encourage consortia to take advantage of possible ways to engage in early dialogue with regulators and raised awareness among consortia of existing services offered by the EMA and FDA. This year a number of projects benefited from these services, in particular through innovation task force (ITF) meetings at EMA for input on the project plan, and the EMA's qualification advice of novel methodologies for drug development, resulting in a number of letters of support issued. Furthermore, one project, PREFER, went through also the first parallel EMA-HTA (health technology assessment) qualification opinion of novel methodologies for drug development procedures.

Finally, the work carried out within the framework contract service awarded on 'supporting regulatory acceptance of IMI results' to the Critical Path Institute, Limited has progressed. The set-up phase of the contract, which aimed at identifying and prioritising the relevant project results that would be suitable for regulatory endorsement, was completed, and the preliminary analysis and identification of information/data gaps for selected projects has started.

1.5 Calls for proposals and new projects

1.5.1 Management of Calls in 2021

In 2021, there was one ongoing Call in Stage 2 (IMI2 - Call 23). The evaluation for stage 2 Call 23 was completed in 2021 and the Grant preparation and Grant Agreement signature were completed in the same year. Two Calls were at the stage of granting process (IMI2 - Calls 20 and 22). The evaluations for IMI2 - Calls 20 and 22 were completed in 2020 but Grant preparation and Grant Agreement signatures were completed in 2021.

Each single stage and stage 2 evaluation encompasses ethics screening of the full proposals performed by a separate ethics expert panel. In 2021, ethics screening was carried out for Call 23 (stage 2).

An overview of these activities is displayed in the chart on the next page.

The key points in the submission and evaluation process are highlighted as follows:

- Cx Topics Text GB DEC – Call x topics text Governing Board decision
- Cx – Call Launch
- SP SUBM – Short proposal submission deadline
- SP Evaluation – Short proposal evaluation
- SP GB DEC – Short proposal Governing Board decision
- FP SUBM – Full proposal submission deadline
- FP Evaluation – Full proposal evaluation
- FP GB DEC – Full proposal Governing Board decision
- GAP – Grant Agreement preparation
- GA – Grant Agreement

The chart also provides information on the consultation period of the IMI2 advisory bodies (the States Representatives Group – the SRG, and the Scientific Committee – the SC), as well as of the European Commission (EC).

Ethics evaluation process

In addition to the scientific evaluations, the IMI Programme Office organises ethics for stage 2 and single stage proposals recommended for funding. Within the H2020 ethics appraisal framework, the IMI Office independently operates the ethics screenings with external ethics experts. In 2021, IMI ran one ethics screening for the six proposals of IMI2 - Call 23, stage 2. All six proposals were conditionally cleared by the expert panels with 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.

Redress

In 2021, there were 4 redress complaints, all concerning the evaluation outcome. For 3 redress cases, no grounds were found to support any of the complaints. For 1 redress case concerning IMI2 – Call 23, the redress committee considered that the complaint was founded. Therefore, for the proposal in question a re-evaluation of the specific criterion affected was carried out. The results of this re-evaluation had no impact on the final ranking of the evaluation.

Chart showing overview of call processes in 2021

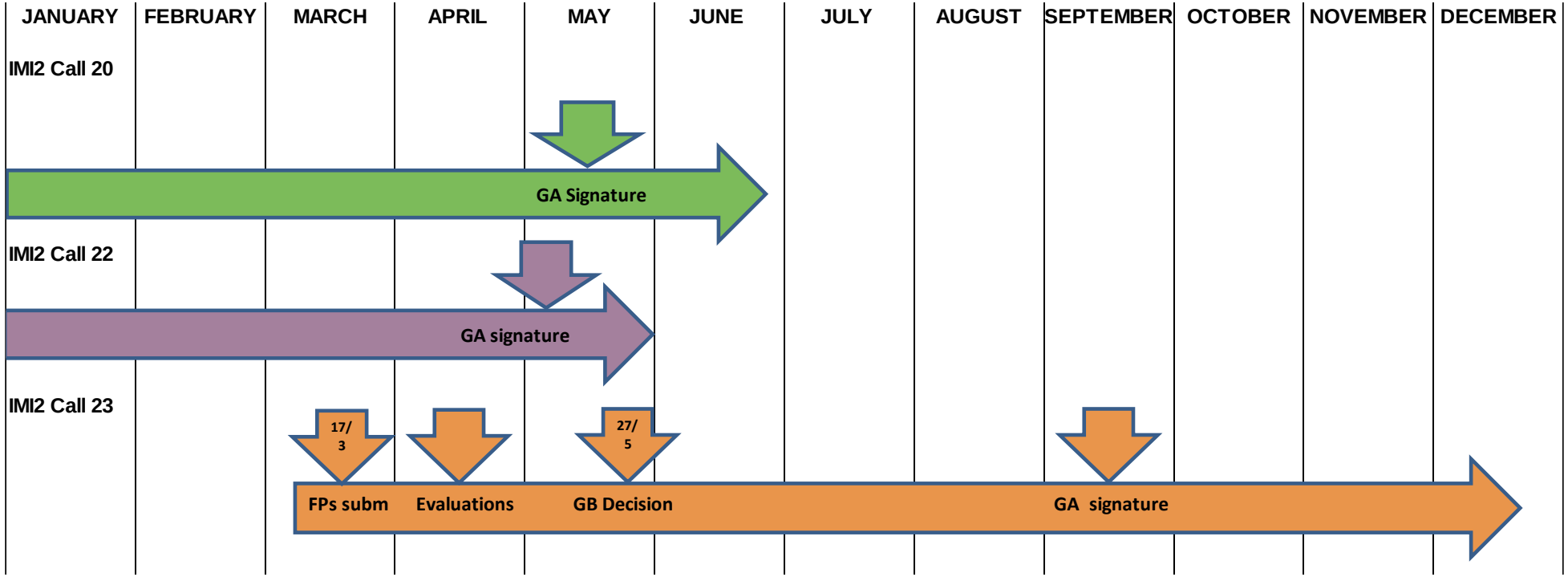


Table summarising key information related to IMI2 call launches, submission deadlines and Grant Agreements signed in 2021

IMI2 Call	Topics	Call process	Launch date	Deadline for submission of SPs	SPs received (FPs in single stage Calls)	Participants in eligible SPs, FPs	SPs selected to prepare a FP	FPs selected for funding	GAs signed in 2021
20	Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis Innovations to accelerate vaccine development and manufacture Academia and industry united innovation and treatment for tuberculosis (UNITE4TB) Tumour plasticity Proton versus photon therapy for oesophageal cancer – a trimodality strategy Handling of protein drug products and stability concerns	Two-stage	21/01/2020	12/05/2020	27	330	6	6	6
22	Restricted Call to maximise impact of IMI2 JU objectives and specific priorities	Single stage	23/06/2020	29/09/2020	8	153	N/A	3	3
23	Returning clinical trial data to study participants within a GDPR compliant and approved framework Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases Optimal treatment for patients with solid tumours in Europe through artificial intelligence Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies Behavioural model of factors affecting patient adherence	Two-stage	23/06/2020	29/09/2020	56	826	6	6	6

Evaluation experts

In 2021, IMI2 JU used 39 experts from 20 countries in the evaluation of IMI2 – Call 23 (second stage).

Most of the experts (92.31 %) came from the EU, UK, and Horizon 2020 associated countries. More than one third of the appointed experts came from academia (38.46 %), 23.8 % came from research organisations, 20.51 % came from private for-profit entities, 7.69 % came from public bodies and 10 % came from other types of organisations.

IMI2 Call	Total no. experts	Scientific evaluation	Rapporteurs in science evaluation	Ethics screening	Observers	Gender female	Gender male
Call 23 - stage 2	39	34	N/A	4	1	22	17

Progress / activities by call in 2021

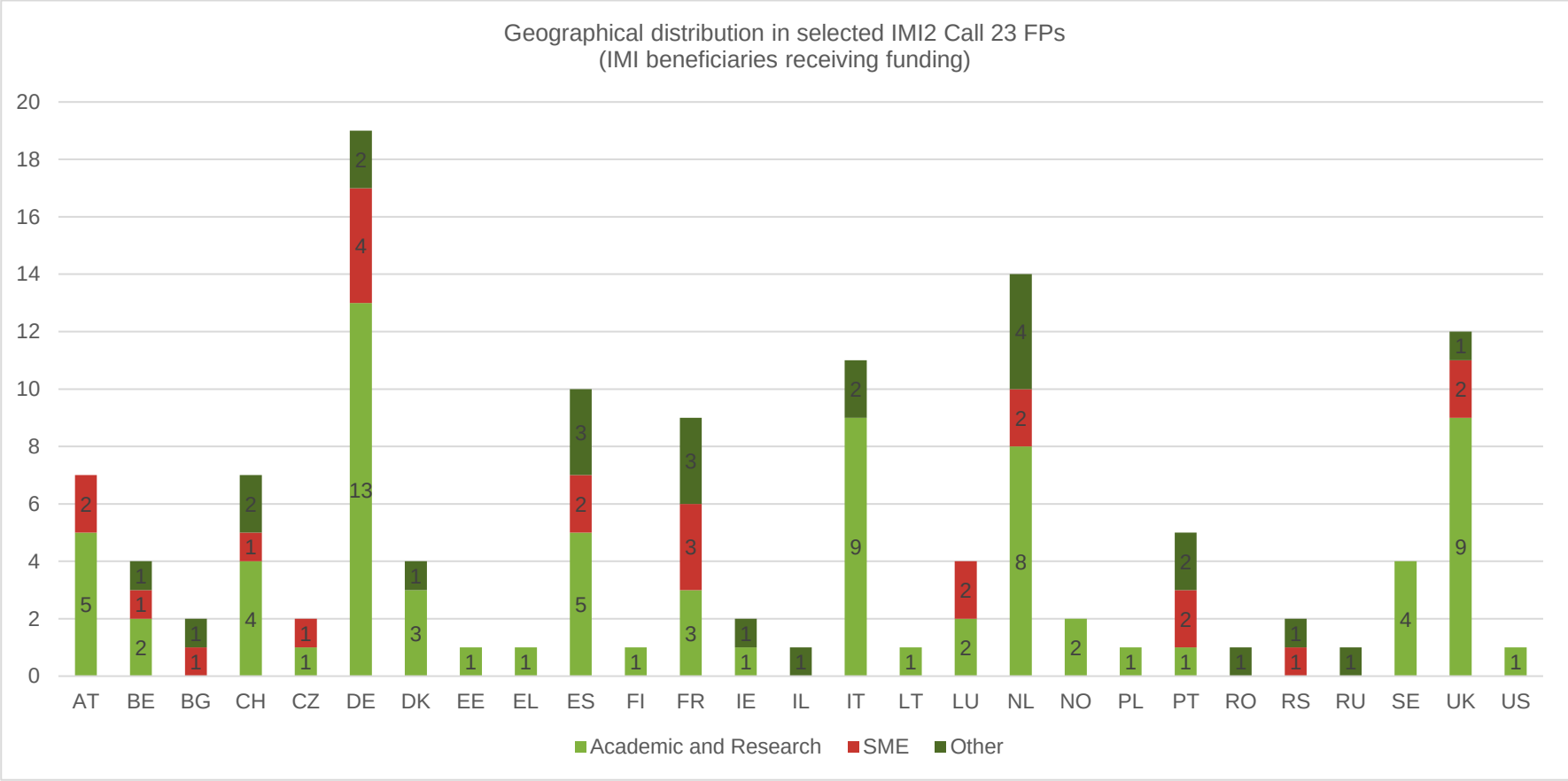
In 2021, IMI organised 1 evaluation session for the second stage of Call 23, which was launched in 2020. The evaluation session was completed successfully, according to the IMI rules and procedures. Call 20, which was launched in 2020, was at the GA stage in 2021.

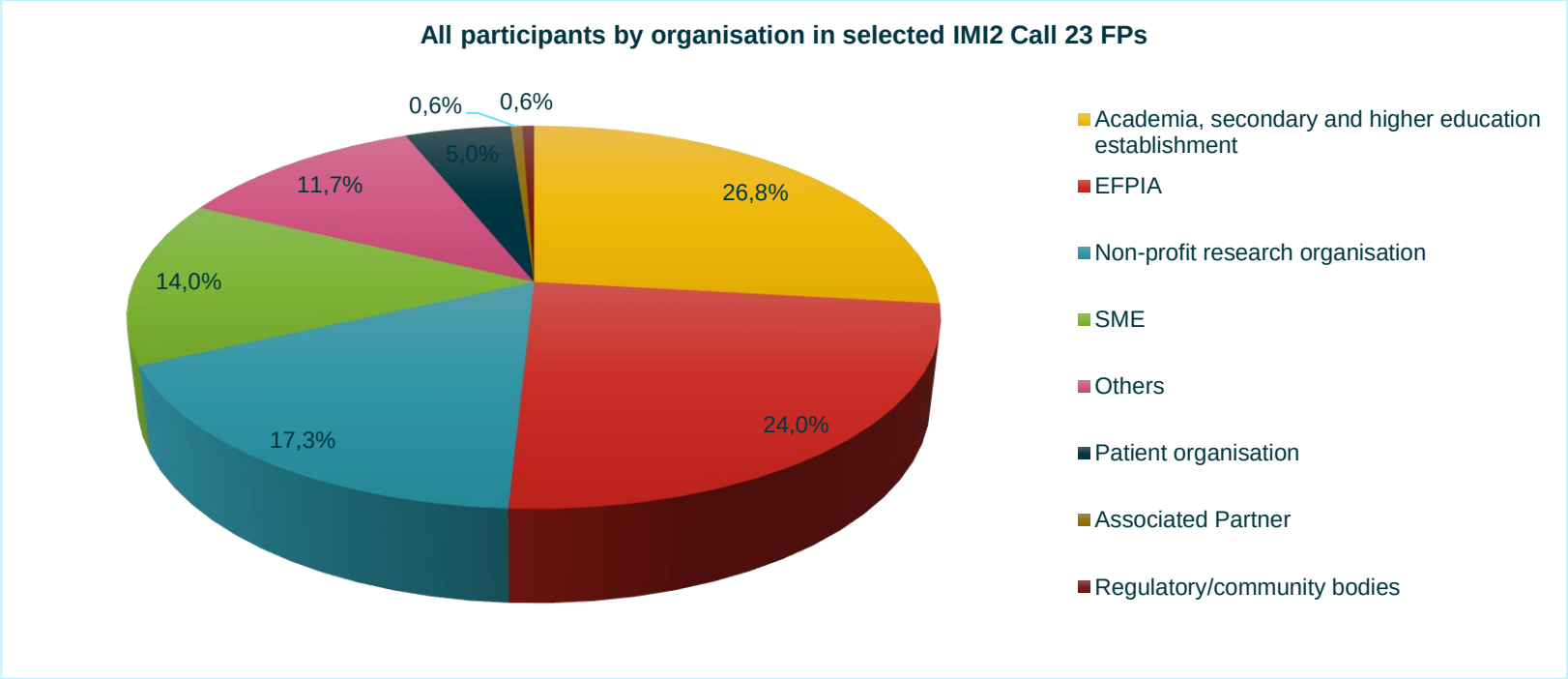
The table below presents Call 23 in different stages of the process in 2021, from the Call launch until sending the letters to start GAP, and Call 20, which was at the latter stage.

IMI2 Call	Call process	Number of topics	Launch date	Submission deadline S1 (or SS)	Approval of evaluation results in S1	Invitation to prepare FP in S2	Submission deadline S2	Approval of evaluation results in S2	Invitation to start GAP
Call 20	Two-stage	6	21/01/2020	12/05/2020	14/07/2020	16/07/2020	19/11/2020	27/01/2021	01/02/2021
Call 23	Two-stage	6	23/06/2020	29/09/2020	20/11/2020	30/11/2020	17/03/2021	26/05/2021	31/05/2021

Participant details

IMI2 – Call 23: Selected full proposal participant details





* *Note: One participant might be part of a consortium in more than one FP*

Table summarising the number of beneficiaries and budgets for projects with GAs signed in 2021

IMI2 call	Project acronym	No. IMI beneficiaries	No. EFPIA companies	No. Associated Partners	IMI funding to academic & research orgs. (EUR) (1)	IMI funding to SMEs (EUR) (2)	IMI funding to patient orgs. (EUR) (3)	IMI funding to other orgs. (EUR) (4)	Total IMI contribution to bene-ficiaries (EUR) (1+2+3+4)	EFPIA in-kind contribution (EUR)	Associated Partners' contribution (EUR)	Total budget (EUR)
20	HIPPOCRATES	23	4	0	8 450 867.50	1 660 125.00		100 000 .00	10 210 992.50	11 035 000.00		21 252 242.50
20	Inno4Vac	37	4	0	13 906 093.75	2 922 760.00		1 771 146.25	18 600 000.00	19 942 552.00		38 542 552.00
20	PERSIST-SEQ	11	5	0	1 497 441.25	3 029 128.75		2 531 410.00	7 057 980.00	6 973 400.00		15 781 255.00
20	PROTECT-trial	17	0	2	1 489 850.00			10 150.00	1 500 000.00		1 500 000.00	4 763 733.75
20	RealHOPE	16	9	0	2 787 528.75	145 847.50	12 500.00	194 107.50	3 139 983.75	3 959 000.00		7 132 733.75
20	UNITE4TB	26	4	2	83 149 888.00	5 277 628.75		4 072 483.25	92 500 000.00	92 150 000.00	350 000.00	214 825 256.00
22	PRISM 2	12	2	1	2 284 971.25	1 645 935.00		50 000.00	3 980 906.25	2 825 181.00	1 088 466.00	8 115 012.69
22	PROMISE	16	6	0	3 111 250.00	565 625.00		67 500.00	3 744 375.00	3 280 012.00		7 024 387.00
22	REsolution	7	2	0	182 777.50	175 000.00		642 222.50	1 000 000.00	1 000 000.00		2 162 500.00
23	BEAMER	22	7	1	3 098 747.50	1 682 500.00	726 093.75	441 562.00	5 948 903.25	5 590 008.00	356 000.00	12 069 286.75
23	EPND	19	10	0	7 927 210.00	1 352 845.00	354 152.00	399 945.00	9 680 000.00	9 325 500.00		19 005 502.25
23	FACILITATE	20	9	0	1 688 286.25	940 000.00	393 225.00	316 238.75	3 260 000.00	3 578 711.00		6 922 698.50
23	OPTIMA	32	5	0	6 409 405.00	2 470 267.00	202 312.00	1 378 013.00	10 459 997.00	10 579 800.00		21 317 779.50
23	PrIMAVeRa	16	3	0	5 982 175.00	243 550.00		274 275.00	6 500 000.00	2 750 000.00		9 250 000.00
23	SCREEN4CARE	26	9	0	8 719 803.75	2 368 398.75	736 895.00	113 471.25	11 938 568.75	13 100 000.00		25 038 568.75

Note: The total budgets indicated here do not include additional funds brought into projects from sources other than IMI, EFPIA or Associated Partners.

1.5.2 Interim reviews for IMI projects

In 2021, IMI conducted 36 reviews for projects from IMI2 – Calls 6, 7, 8, 9, 10,12, 13, 14, 15, 16 and 21.

IMI project acronym	IM2 Call #	Full project name	Interim review
RADAR-AD	Call 12	Remote assessment of disease and relapse – Alzheimer's disease	14-15/01/2021
EBOVAC 3	Call 8	Bringing a prophylactic Ebola vaccine to licensure	21/01/2021
PD-MitoQUANT	Call 13	A quantitative approach towards the characterisation of mitochondrial dysfunction in Parkinson's disease	21/01/2021
AIMS-2-TRIAL	Call 10	Autism Innovative Medicine Studies – 2 – Trials	21-22/01/2021
PD-MIND	Call 13	Parkinson disease with mild cognition impairment treated with nicotinic agonist drug	25/01/2021 06/12/2021
RTCure	Call 9	Rheuma Tolerance for Cure	01/02/2021
iConsensus	Call 10	Integrated control and sensing platform for biopharmaceutical cultivation process high-throughput development and production	12/02/2021
NeuroDeRisk	Call 13	Neurotoxicity de-risking in preclinical drug discovery	04/03/2021
ReSOLUTE	Call 10	Research empowerment on solute carriers	16-17/03/2021
MELLODDY	Call 14	Machine learning ledger orchestration for drug discovery	19/03/2021
PIONEER	Call 10	Prostate cancer diagnosis and treatment enhancement through the power of big data in Europe	06-07/05/2021
ESCulab	Call 12	European screening centre; unique library for attractive biology	01/06/2021
EBiSC2	Call 13	EBiSC2 – A sustainable European bank for induced pluripotent stem cells	16-17/06/2021
TransQST	Call 6	Translational quantitative systems toxicology to improve the understanding of the safety of medicines	22-23/06/2021
KRONO	Call 21	Evaluation of a production ready portable, point-of-need platform (instrument and reagents), direct from nasal swab test for the molecular diagnostic detection of COVID-19 infection	01/10/2021
IM2PACT	Call 12	Investigating mechanisms and models predictive of accessibility of therapeutics (IM2PACT) into the brain	04/10/2021
CARE	Call 21	Corona accelerated R&D in Europe	05-06/10/2021
ConcePTION	Call 13	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation	08/10/2021
TransBioLine	Call 13	Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease	12-13/10/2021
VALUE-Dx	Call 13	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use	13/10/2021
IMPENTRI	Call 21	Development of Impentri, an intravenous imatinib formulation for COVID-19 acute respiratory distress syndrome (ARDS)	14/10/2021
MACUSTAR	Call 7	Intermediate AMD: development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention	18/10/2021
DRAGON	Call 21	Rapid and secure AI imaging based diagnosis, stratification, follow-up, and preparedness for coronavirus pandemics	19/10/21

IMI project acronym	IM2 Call #	Full project name	Interim review
MAD-COV2	Call 21	MAD-COV2	22/10/2021
RAPID-COVID	Call 21	Robust automation and point of care identification of COVID	22/10/2021
COVID-RED	Call 21	COVID-19 infections - remote early detection	26/10/2021
c4c	Call 10	conect4children - Collaborative network for European clinical trials for children	28/10/2021
MOBILISE-D	Call 13	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement	04/11/2021
3TR	Call 14	Identification of the molecular mechanisms of non-response to treatments, relapses and remission in autoimmune, inflammatory, and allergic conditions	15-16/11/2021
PharmaLedger	Call 15	PharmaLedger	16/11/2021
BIOMAP	Call 13	Biomarkers in atopic dermatitis and psoriasis	18-19/11/2021
VHFMoDRAD	Call 8	Viral haemorrhagic fever: modern approaches for developing bedside rapid diagnostics	24/11/2021
GNA NOW	Call 16	Novel Gram-negative antibiotic now	24/11/2021
NECESSITY	Call 12	New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients	06/12/2021
EU-PEARL	Call 15	EU patient-centric clinical trial platform	16/12/2021
STOPFOP	Call 13	Saracatinib trial to prevent FOP	17/12/2021

Each expert reviewer panel consisted of at least three experts, including one from the IMI Scientific Committee and one from the full proposal evaluation panel.

RADAR-AD

The RADAR-AD project goal is the development and validation of technology-enabled, digital, quantitative, and sensitive measures of functional decline in people with early-stage Alzheimer's disease (AD).

The reviewers reported that the project has produced very relevant results in relation to the first part of the planned work and that when completed, the project will have a positive impact on the development of methods used to monitor progress of AD/mild cognitive impairment (MCI) and the effects of care by identifying specific functional domains and the most relevant remote technologies for their monitoring. The consortium accomplished several important research goals in a high-quality, scientific manner and has already achieved significant results which the participating institutions can take to the next level of implementation. The reviewers also acknowledged that unfortunately the clinical work of the project has been severely impacted by the COVID-19 pandemic.

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. In addition, the reviewers recommended to further develop the communication and dissemination activities, especially toward healthcare stakeholders.

EBOVAC 3

The EBOVAC3 project aims to assess, through clinical trials in children and adults in Africa, the safety and effectiveness of an Ebola vaccine regimen. As such it will help to improve the world's preparedness to deal with an Ebola outbreak.

The overall IMI EBOVAC programme, including EBOVAC3, has been highly successful as it has significantly contributed to the marketing authorisation in the European Union (July 2020) of an Ebola vaccine. For example, the reviewers recommended to improve and update the EBOVAC website on a regular basis with

achievements about the projects' activities, an introductory page with appropriate charts, guides, etc…; to reorganise its content so it is easier to see the connection between the different EBOVAC projects.

PD- MitoQUANT

Focusing on mitochondria dysfunction in Parkinson's disease (PD), the PD-MitoQUANT project aims to identify and validate molecular drivers and mechanisms of the condition and discover innovative therapeutic targets that can be further developed by the pharmaceutical companies.

According to the panel of experts, the consortium achieved very good and highly relevant scientific results within the reviewed period, despite some delays caused by the COVID-19 pandemic. Notably, the consortium demonstrated that p91 induces neuropathology in *in vitro* and *in vivo* PD models. The experts recommended putting a clear focus of the exploitation plans of the SMEs participating to the project.

AIMS-2-TRIALS

The AIMS-2-TRIALS project aims to enhance the understanding of autism spectrum disorders (ASD) and to impact the development of new treatment approaches via validation of novel biomarkers and endpoints for clinical trials and using a precision medicine approach.

The reviewers reported that although there have been rather severe impediments to progress due to COVID-19, the expansive and ambitious undertaking has yielded a wealth of information. Significant results have been achieved already in terms of biomarker discovery. The set-up of the European Clinical Trial Network (CTN), in tight collaboration with people with autism, has the potential to grow into a sustainable infrastructure.

The reviewers recommended to further fine-tune the strategy for biomarker validation and include learnings from the COVID-19 pandemic to develop strategies to accelerate the project once restrictions are eased. The reviewers endorsed that the project should proceed and fully implement the remaining part two project activities.

PD-MIND

The project aims to identify the potential of the drug AZD0328 in a randomised, placebo-controlled, parallel group, international multicentre study on cognitive function in people diagnosed with PD-MCI (Parkinson's disease with mild cognitive impairment).

Two interim reviews took place in 2021. In the first review, the expert panel reported that the project had achieved some of its objectives and milestones. Significant delays have been caused by COVID-19 and other factors. The panel made several recommendations, including accelerating the start-up of the study and lengthening the timelines of the study. The panel also recommended a follow-up review to assess the progress of the project, including the implementation of the panel's recommendations. In the second review, the panel identified significant concerns that require appropriate follow up.

RTCure

RTCure is a 5-year project designed to provide insight into the onset and development of rheumatoid arthritis (RA), leading to innovative treatments aiming at immune tolerance.

The project has achieved most of its objectives and milestones for the period with minor deviations. The panel of experts recommended updating aspects of the contract and the timeline of several deliverables and milestones. Scientific recommendations were also made regarding the algorithms that have been generated for predicting the development of RA, the approach to the identification of at-risk patients, the knowledge integration of cellular/autoimmune biological pathways, the best candidates for clinical development, the need for more detailed patient stratification and the priority to discuss with EMA the development of tolerance-inducing medicines.

iConsensus

The project aims to develop innovative analytical, hardware, software, and high-throughput tools for the development, monitoring and control of mammalian cell cultivation processes for producing biopharmaceuticals.

The panel of experts reported that the project achieved most of its objectives and milestones to date despite the complications caused by COVID-19. They also highlighted that several novel tools have been developed (e.g. a prototype microbioreactor for mammalian cells, prototypes of CO_2, glucose and lactate sensors, and a tool allowing the quantification of cell concentration based on holographic images). These tools are valuable resources and will help advance research on the manufacturing of biopharmaceuticals.

The panel recommended that the project increase its visibility to both lay and scientific audiences. The reviewers also recommended that the project's duration be extended to compensate for delays caused by COVID-19.

NeuroDeRisk

The adverse effects of pharmaceuticals on the central or peripheral nervous systems are poorly predicted by the current *in vitro* and *in vivo* preclinical studies performed during research and development (R&D) processes. NeuroDeRisk aims to provide novel validated integrated tools for improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system and thus help to de-risk drug candidates earlier in the R&D phases. The focus is on three major types of neurotoxicity: seizures, psychological/psychiatric changes, and peripheral neuropathies. Increasing the predictivity of the preclinical toolbox is a clear need and would benefit human volunteers/patients (safer drugs) and the pharmaceutical industry (reduced attrition).

The panel of reviewers concluded that the work accomplished so far by the consortium delivered results, despite the conditions faced over 2020. However, it has been pointed out that a few aspects would need further attention. Therefore, a set of recommendations was proposed including, dissemination, regulatory and risks monitoring considerations.

ReSOLUTE

The project aims to intensify research and advance our knowledge on solute carriers (SLCs) by delivering tools, protocols, databases, and platforms on SLCs.

The expert panel reported that the project has fully achieved its objectives and milestones to date and has already delivered significant results for the research community. The panel recommended that it is important to capitalise on the successful set-up of the project and maximise the number of SLC proteins submitted for binder generation during the lifetime of the project, since these reagents will make a significant impact on the SLC field. The reviewers also recommended that the project's duration be extended to compensate for delays caused by COVID-19.

Some of the project results highlighted by the experts are: (1) a large set of codon-optimised solute of SLC genes in entry-vectors have been generated, which are publicly available (and hence sustainable) through Addgene; (2) several cell-lines for overexpression of SLCs have been generated and will shortly be made available through the ATCC cell-line repository.

MELLODDY

The expert panel reported that the project has achieved most of its objectives and milestones to date and has already delivered significant results for the research community. The panel commended the performance of a fully operational machine learning run involving the better part of the accumulated drug discovery data of all 10 pharmaceutical companies.

They also highlighted the following innovations in particular:

- a data standardisation framework including robust procedures and software scripts to format the chemical and conventional bioactivity data from different sources;
- federated machine learning models for chemical compound data with sparse features;
- software for end-to-end privacy-preserving federated machine learning - this software has been audited by an independent party and meets relevant industry standards for IT-technical and data security.

The expert panel made some recommendations including increased focus on the broad usability of the final results of the project.

PIONEER

The aim of PIONEER is to use big data to address key knowledge gaps related to the screening, diagnosis and treatment of prostate cancer patients. To do this, the project will standardise and integrate existing 'big data' from sources such as clinical trials and electronic health records into a single, innovative data platform.

Following the midterm review of the PIONEER project, the reviewers reported that the project has made good progress and that efforts should be continued and consolidated to reach the project objectives in the time frame of the PIONEER project. For instance, the reviewers recommended that success factors identified on data such as the study-a-thons and the collaborations with the HARMONY and EHDEN projects should be continued and, in some cases, consolidated.

ESCulab

The aim of the ESCulab project is to build on the achievements of the European Lead Factory; it makes available a collection of over half a million compounds and a state-of-the-art high throughput screening centre to support drug discovery programmes. Researchers with drug targets can apply to have their target screened free of charge against the project's compound collection, and get help developing any resulting hits. The objective of the project is to become self-sustaining so that it can continue to provide these services after the project has finished.

The panel of experts reported that the project has achieved some of its objectives and milestones. Due to COVID-19, there have been significant delays in the recruitment of new projects. Nevertheless, the consortium has managed the COVID-19 situation well and is progressing towards reaching the objectives. Implementation of the new mass-spectrometry (MS) based readout is an important addition, which offers an orthogonal methodology to verify target binding in addition to the functional readout.

The panel recommended that the project prioritise the efforts towards sustainability and that the consortium should consider redirecting some efforts to items of most strategic importance to create a viable sustainability proposition. The reviewers also recommended that the project's duration be extended to compensate for delays caused by COVID-19.

EBISC2

The project will deploy a business strategy for a sustainable, not-for-profit bank providing access to disease-relevant and quality-controlled human induced pluripotent stem cells, along with comprehensive data and freedom to operate for academic and commercial use.

The panel of experts reported that the project has achieved most of its objectives and milestones for the period with relatively minor deviations. Several recommendations were made regarding the exploitation and sustainability activities, the project visibility, the patient and public involvement/engagement and on the need to improve the mitigation actions related to COVID-19 pandemic.

TransQST

TransQST aims at strengthening the competitiveness and industrial leadership by advancing safer drug candidates, thereby reducing attrition and accelerating development, and reducing research and development time. More specifically, TransQST is orientated towards the development of translational quantitative systems-based toxicological models for four organs (the liver, kidney, cardiovascular and gastro-intestinal systems). It builds on existing pharmacokinetic/pharmacodynamic (PK/PD) models that have a physiological basis aiming to define systemic, as well as specific organ/cell exposure to drugs and metabolites in a holistic fashion.

During the second review, the panel of reviewers concluded that the project achieved many of the objectives as initially set. Particular attention was paid by experts to the assessment of tangible outcomes/results, their public availability, interactions with regulatory authorities, the validation of models, the mapping of enhanced/developed tools, the sustainability of results, and ways to maximise expected impacts. As a result, the consortium has been provided a set of recommendations to be implemented during the remaining project lifecycle.

KRONO

KRONO is an ambitious project aiming at bringing to the market a novel point-of-need (PoN) COVID-19 diagnostic test that has been proposed in the frame of IMI2 - Call 21 focusing on development of fast-track SARS-CoV-2 diagnostic tests. It gathers five participants (three academics and two industry partners), representing three countries (France, UK and Italy). At the time of the project initiation, the PoN technology had already acquired some maturity, i.e. it was being tested by the industrial partner (BioGen Ltd. and its related entity BG Research Ltd) in other diseases related to infectious agents (e.g. Ebola, Zika, sepsis). Early intellectual property rights (IP) had already been filed. A key, differentiating element of the developed PCR test in comparison with most competitors is the lack of a need for laboratory or cold-chain requirements. The KRONO project is based on a strong interdisciplinary approach gathering high level expertise, spanning form basic molecular virology to reference research and clinical academic centres specialised in infectious diseases. Partners are well familiar with the organisation and conduct of clinical trials and access to intensive care units (ICUs) hosting COVID-19 patients.

The period covered by the mid-term review corresponds to achievements made over the first 10 months of the project. The panel of experts reported that the beneficiaries have proven they have the capacity to fulfil their project plan and have submitted most deliverables according to their workplan. Any delays in the project so far are mainly a result of global delivery chain breakdowns due to the pandemic.

The panel of experts recommended that the precise timing of novel IP filing should be better indicated; it would be good to know in order to appreciate that filing will be done prior to the of end of project. The quality of deliverables should be improved, whereby more data should be included in the deliverables section. In addition, a specific website should be launched and implemented for KRONO. Furthermore, regarding the requirement for open access data generated in the project by and for the different beneficiaries to the research community within and outside of the consortium, the panel of experts recommended that the consortium dedicate more effort in complying with this requirement.

IM2PACT

The project aims to advance our understanding of the blood-brain barrier (BBB) to facilitate the development of more effective treatments for a range of neurological and metabolic disorders. More specifically, the project’s goal is to develop improved BBB models, investigate the transport mechanisms across the BBB in both health and disease, and develop innovative drug delivering systems to the brain.

The expert panel reported that, despite the delays caused by COVID-19, the project has achieved most of its objectives and milestones to date. They also highlighted that several novel tools have been developed (e.g. antibodies, cell lines, single cell enrichment protocols), which will be valuable resources and help advance research in BBB drug delivery.

The experts recommended that project increase its visibility to both lay and scientific audiences. The reviewers also recommended that the project’s duration be extended to compensate for delays caused by COVID-19.

CARE

The goal of the CARE project is to deliver treatments for the current COVID-19 outbreak as well as future coronavirus outbreaks. Part of the project will focus on ‘repurposing’, in which drugs designed for other diseases are ‘repurposed’ for a new disease. Because a lot of work has already been carried out on these compounds, repurposing can deliver relatively rapid results. The project also aims to deliver new drugs designed specifically to treat COVID-19 and other coronaviruses. To identify potential drugs, the project will screen 600 000 compounds across different libraries. They will also investigate antibodies capable of neutralising the virus.

The reviewers considered that the project has achieved most of its objectives and milestones for the period and that the objectives of the project are relevant. The panel of experts recommended for instance that the communication & dissemination plan should be revised and that a schedule of publication on current results, be provided.

ConcePTION

ConcePTION aims to establish a new ecosystem for assessing the safety of medication use in pregnancy and during lactation.

Although the project is experiencing delays due notably to the COVID-19 pandemic, the panel valued the excellent work completed to date to set up the infrastructure and the commitment of the consortium to keep the critical work on track notably with the demonstration studies. The panel considered that the project is innovative and unique and offers great potential in promoting safe and efficient medication use among pregnant and breastfeeding women and altering both clinical and regulatory practice.

The panel made a number of recommendations to the consortium with the view to further maximising the impact of the project results, including having a clear strategy for communication of results as well as for sustainability (e.g. the knowledge bank).

TransBioLine

The aim of the project is to enable the development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease.

The panel of experts reported that the project has achieved some of its objectives and milestones. The achievements during the first half of the project are in sample collection and storage, analyte detection methods and interactions with the regulatory authorities (EMA and FDA). Letters of intent from WPs 1 (DIKI), 2 (DILI), 4 (DIVI) and 5 (DINI) have been accepted into the FDA Biomarker Qualification Program. These are key activities to ensure the success of the whole project and will aid sustainable impact.

The panel recommended to carefully manage the parallel progress in trials for all domains and redesign some of the analyses to accommodate smaller data sets if larger amounts of clinical data cannot be collected. It also advised the consortium to increase the number of publications in peer-reviewed scientific journals. In addition, the reviewers recommended that the project’s duration be extended to compensate for delays caused by COVID-19.

VALUE-Dx

The ambition of the Value-Dx project is to contribute to limiting the burden of antimicrobial resistance by determining the value of diagnostics to combat antimicrobial resistance by optimising antibiotic use and hence improving patient outcome. This project is thereby a prime example for a cross-sector and multidisciplinary consortium with the potential to make a difference in saving patients' lives by reducing AMR.

The panel of experts reported that the project has achieved most of its objectives and milestones for the period with relatively minor deviations.

The panel of experts recommended that the project should ensure that the value judgement and the proposed payment model for the diagnostic tool be validated for eastern European countries as well. Special recommendations will be needed on how to provide incentives to healthcare providers for using the diagnostic tool in those countries, which are less successful with enforcing clinical guidelines in treating patients. Moreover, clinical algorithms should be improved by adding COVID-19 diagnostics.

IMPENTRI

Impentri is a two-year project involving the repurposing and rapid development of an existing therapy, imatinib, as a new and improved therapeutic approach for acute respiratory distress syndrome (ARDS) resulting from SARS-CoV-2 infection. The panel or experts recognised that several work packages, deliverables and objectives have been reached and further insight in treating COVID-19 patients was gained (publication of the CounterCOVID results available in the Lancet Respiratory Medicine), but advised the consortium to reflect on strategies to enhance capacity for patient recruitment in order to complete the trial within the project timelines.

MACUSTAR

MACUSTAR aims to develop and validate appropriate and acceptable clinical endpoints in intermediate age-related macular degeneration (iAMD) to support the clinical development of novel treatments for this

condition, which is a leading cause of blindness in industrialised countries and for which there is currently no treatment available.

This was the second review of MACUSTAR, following an earlier review in February 2020. The expert panel of the second review reported that the recommendations from the earlier review have been mostly implemented, improving the implementation of the project, though some elements still needed to be reinforced. The expert panel of the second review reported that the project has achieved some of its objectives and milestones to date though the implementation has been impeded by several factors, including disruptions caused by COVID-19.

The expert panel recommended that the duration of the project be extended to mitigate against the delays experienced during project implementation so far. Several other recommendations were also proposed including continued enhancement of dissemination and communication activities and improvement in interactions with regulatory agencies with more input from project partners with industry/ regulatory expertise.

DRAGON

The project aims to develop a decision support system capable of more precisely diagnosing COVID-19 and providing more accurate predictions of patient outcomes. Drawing on new and existing data and samples, artificial intelligence (AI) and machine learning will be used to help clinicians identify the best treatments for patients.

The review took place at the end of the first year of the project. 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 remaining two years. The main output of the project highlighted so far by the expert panel was the establishment of the federated machine learning system that will be deployed for machine learning and may prove useful to pharmaceutical companies.

Several recommendations were made by the expert panel including the need to better plan the certification of tools developed in the project and to develop a clear exploitation plan with a focus on sustainability.

MAD-CoV2

The overall aim of the MAD-CoV 2 project is to develop and deliver a treatment for COVID-19 patients, which will significantly increase our capacity to handle the current outbreak of SARS-CoV-2. The project focuses on ACE2 (angiotensin converting enzyme 2), a protein used by the SARS-CoV-2 virus, to break into and infect cells.

The review took place after one year of activities, with another three years to go. The panel of experts were satisfied with the progress made to date but recommended a better consideration of the new variants into the future work as well as more effort towards exploitation and dissemination.

RAPID-COVID

RAPID-COVID aims at developing a novel PCR test able to detect not only SARS-CoV-2, but also several additional pathogens (viruses and bacteria), to support differential diagnosis of patients with symptoms. The innovative kit will be validated both as part of a high throughput device and in a point-of-care configuration.

The reviewers reported that the project has progressed adequately, despite challenges due to the COVID-19 pandemic, and has developed several promising results that have clear innovation potential. These need to be validated in the last part of the project.

The reviewers recommended to further enhance the project’s exploitation strategy and dissemination and communication activities.

COVID-RED

The COVID-RED project will evaluate the use and performance of a CE-marked device (wearable), which uses sensors to measure breathing rate, pulse rate, skin temperature, and heart rate variability for the purpose of early detection and monitoring of COVID-19 in general and high-risk populations.

The reviewers reported that while the project is making progress overall, it has faced a rapidly evolving COVID-19 situation and significant delays, already in the frame of a very ambitious project with very aggressive timelines.

The reviewers recommended an extension of the project timelines to allow the achievement of its objectives and impacts. The reviewers also made a number of recommendations to the consortium with a view to further maximising the impact of its results and ensuring their sustainability.

c4c

c4c aims to establish a sustainable pan-European paediatric clinical trial network that optimises the delivery of clinical trials in children. Although the project is experiencing delays notably with the running of the proof of viability trials to test the network due in particular to the COVID-19 pandemic, the panel was impressed by the excellent work the consortium has done so far and considered that the project could potentially be very impactful on the way paediatric medicines are developed. The panel appreciated particularly that the consortium took on board the expert recommendations made in the early review, and the thorough attention paid to the sustainability plans of the network and to the business model of the future organisation. The panel made a number of recommendations to the consortium with a view to further maximising the impact of the project results, including considerations for increased communication notably on competitive features offered by the network such as unique services to help with the sustainability of the successor organisation.

MOBILISE-D

The project aims to develop validated and accepted digital mobility outcomes (DMOs) to monitor the gait of people with varying mobility problems. Gait will be measured using digital technology, including body-worn sensors, focusing on several conditions that often affect mobility: chronic obstructive pulmonary disease (COPD), Parkinson's disease, multiple sclerosis, hip fracture recovery, and congestive heart failure.

This was the second review of MOBILISE-D, following an earlier review in October 2020. The expert panel of the second review reported that the recommendations from the earlier review have been mostly implemented, improving the implementation of the project, though with some elements still pending. The expert panel of the second review reported that the project has achieved most of its objectives and milestones to date. The main outputs of the project so far highlighted by the expert panel include the refinement of DMO definitions involving input from a group of diverse stakeholders, the development of novel clinical trial protocols and methodologies for the measurement of mobility in real-world environments, and fruitful engagement with regulatory agencies resulting in two letters of support from the European Medicines Agency.

A number of recommendations were made by the expert panel including the need to enhance dissemination and communication activities.

3TR

Autoimmune, inflammatory and allergic diseases are highly heterogeneous conditions in their clinical phenotype. However, despite their heterogeneity, it has been shown that they share genetic risk, share some disease pathways, and share specific clinical manifestations. Consequently, individuals with a disease may share an inflammatory molecular pattern with individuals with the other diseases. 3TR will integrate the analysis of seven autoimmune, allergic, and inflammatory conditions to identify the relationship between longitudinal molecular and microbiome profiles in blood cells and tissues, and disease trajectories to characterise and better predict why certain patient groups do not respond to certain treatments. Thereby, 3TR will challenge the conventional 'single disease'-based approach, in which diseases are classified according to their end-organ involvement rather than the molecular pathways underpinning them.

Given the magnitude of the 3TR scientific challenges, during the early project review particular attention was paid to the efficient launch of project activities especially in terms of clinical work aspects. The panel of reviewers concluded that the initial project implementation and overall progress of the project are in general in line with the work plan, even if there are some delays due to the COVID-19 pandemic. A set of recommendation has been proposed to optimise the achievement of project objectives and expected impacts (e.g. in terms of risks mitigation, engagement with regulatory authorities, dissemination of results, open access to data, etc.).

PharmaLedger

The expert panel reported that the project has achieved most of its objectives and milestones to date and has already developed several important use-case prototypes using their blockchain system. The panel highlighted the following in particular:

- Deployment of a cross-company decentralised blockchain network that supports reliable data sharing for the healthcare industry. Six nodes have already been recruited to test the platform.
- Development of open data sharing units (OpenDSU), an innovative off-chain storage and data exchange framework.
- Technical development of demonstrators for the eight use cases across three domains:
  - supply Chain: electronic product information (ePI or eLeaflet), clinical supply chain, finished goods traceability, and anti-counterfeiting (detecting falsified medicines packaging);
  - clinical Trials: clinical trial recruitment and eConsent (informed consent form);
  - health data: medical device IoT (internet of things) and personalised medicine.

The expert panel made some recommendations including exploiting the project's extensive network to ensure uptake of the use cases.

BIOMAP

Atopic dermatitis and psoriasis are serious skin diseases that affect over 300 million people globally. Atopic dermatitis causes itchy, inflamed skin that can become blistered, while psoriasis is characterised by red, scaly plaques on the skin. BIOMAP aims to shed new light on the underlying causes of both diseases, as well as the genetic and environmental factors that influence how a patient's disease will progress and how well they will respond to a given treatment. BIOMAP aims to identify new sub-types of the diseases that will allow clinicians and patients to make better, more personalised decisions on treatments.

The panel of reviewers concluded that BIOMAP has achieved several objectives in line with the project plan, such as the establishment of a collaborative network of clinicians, researchers, industry, and patient organisations; the establishment of pan-European BioSource; the set-up of the technical framework for developing a data warehousing and data analysis portal; and the development of the BIOMAP glossary. The panel provided the consortium with a set of recommendations to be implemented with the aim of maximising the project's impact (e.g. in terms of risks and delay mitigations, dissemination of results, integrative cross-cohort approach, patient engagement, sustainability, etc.).

VHFMoDRAD

The aim of VHFMoDRAD is to develop rapid point-of-care (POC) diagnostic tools capable of identifying a number of viral haemorrhagic fevers. The project builds on the work of IMI's EbolaMoDRAD project, which advanced the development of rapid diagnostics for Ebola. The new tools and methods developed by VHFMoDRAD will be validated in the field.

The panel of experts reported that the project has achieved most of its objectives and milestones for the period with relatively minor deviations.

The panel of experts deemed that the work presented by the consortium has provided encouraging results for the development of diagnostic tools for severe fever with thrombocytopenia syndrome virus, Yellow Fever virus, Rift Valley fever virus, and Zika virus. However, the submitted data needs to be integrated with new experiments aimed at extending this analysis against additional viral haemorrhagic fever viruses and arboviruses as well as at validating it in preclinical and clinical studies.

GNA NOW

GNA NOW is a 6-year project with the aim of managing a portfolio of novel mode of action drugs against Gram-negative bacteria to progress one compound through completion of Phase I studies plus one compound reaching Investigational New Drug stage and/or up to two compounds reaching clinical development candidate stage.

Although 2 work packages (WPs) have been discontinued due to technical issues with the leads, the panel of experts recognised that the project achieved some of its objectives and milestones. Several recommendations were made regarding the recruitment and triage of new leads to replace discontinued

WPs (e.g. using social media and other relevant platforms for the open calls), on the need to update the mitigation plan for the new identified risks and on the management of the IP issues concerning the new leads. The experts also recommended that the consortium should regularly update IHI on the advancement of the project and its scientific results.

NECESSITY

NECESSITY is a 4-year project aiming to identify discriminative biomarkers for stratifying primary Sjögren's Syndrome (pSS) patients, and deliver sensitive clinical endpoints to evaluate response to drug treatments in pSS patients for use in future clinical trials. The panel of experts reported that the project has achieved most of its objectives and milestones for the period with relatively minor deviations. Several recommendations were made by the expert panel regarding the use of social media to better promote the project and its results, the revision and update of some deliverables and risk mitigation plan, the immediate start of the clinical study to avoid further delay and a possible budget reallocation to those tasks needing supplementary resources and considering the future potential no-cost project extension (as already indicated by the consortium).

EU-PEARL

The project aims to create a framework for patient-centric integrated research platform (IRP) trials and develop a comprehensive set of tools and methods for the planning, implementation and analysis of such trials. Trial ready IRP networks will be developed for four disease areas with significant unmet medical needs: major depressive disorder (MDD), tuberculosis (TB), non-alcoholic steatohepatitis (NASH) and neurofibromatosis (NF).

The expert panel reported that the project has achieved most of its objectives and milestones to date. The provisional version of the Generic Master Protocol Template and its appendices for IRPs was highlighted by the panel as the most important output so far. The panel also acknowledged that the preliminary work performed to establish the IRP framework (both legal and operational) was in general delivered on time despite the disruptions caused by COVID-19.

A number of recommendations were made by the panel including the need to further develop plans for the sustainability of the project and to further enhance interactions with regulatory agencies.

STOPFOP

The project aims to investigate the efficacy and safety of the drug AZD0530 (saracatinib) for treating patients with fibrodysplasia ossificans progressiva (FOP).

The expert panel reported that the project has achieved some of its objectives and milestones to date. The project has experienced significant delays mainly due to the COVID-19 pandemic. In spite of these challenges, the consortium has made some significant progress including the opening of one study centre and support of patients from various locations to travel to this institution. A number of patients have already been enrolled in the clinical study.

The panel highlighted the importance of the timely study opening in the final country (the UK) and completing enrolment of the patients identified. The reviewers also recommended that the project's duration be extended to compensate for delays caused by COVID-19.

1.6 Key performance indicators and statistics

IHI KPIs

During 2021, significant progress was made in the development of key performance indicators (KPIs) designed specifically to monitor the progress of IHI. In fact, IHI was used as a pilot project for the development of programme-specific KPIs for joint undertakings. By the end of 2021, the draft IHI specific KPIs were at an advanced stage. They are scheduled to be formally adopted by the IHI Governing Board in 2022. The Programme Office will report on the IHI KPIs, as well as the relevant Horizon Europe KPIs and the cross-cutting KPIs for partnerships, in future reports.

IMI KPIs

The IMI2 objectives are far-reaching and ambitious. In order to track IMI's progress towards these objectives, IMI uses 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 programs 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 patients groups or healthcare professional association;
- the level of collaboration and SME participation so far.

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 2021 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 275 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 425 assets that completed a significant milestone so far. The definitions of 'projects' asset 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 impact the regulatory framework and received acceptance by regulatory authorities: in IMI2 there are 20 completed procedures (versus a target of 10) and if we look at both IMI1 and IMI2 programmes together there are 43 complete 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, SOPs, use of screening platforms, clinical trial networks, etc.). The data shows 350 implementation results in IMI2 (versus a target of 50) and 669 implementation results if we consider both IMI1 and IMI2 programmes together.

Additionally, more than half of the projects (60.40 %) involve patient organisations and healthcare professionals' 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 are reaching the end of IMI2 programme's 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 H2020 key performance indicators, 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 - the Framework Programme for Research and Innovation.

2 Management

2.1 Governance under IMI

The IMI governance bodies ran throughout 2021 until 30 November, when the legislation creating IHI came into force.

2.1.1 IMI Governing Board

The Governing Board was the main decision-making body of IMI2 JU. It carried the overall responsibility for the operations and oversaw the implementation of its activities, guaranteeing the fulfilment of the objectives set by the organisation. In 2021, the Governing Board held two formal meetings (26 March; 25 June). The list of decisions taken by the Governing Board in 2021 is available on the Governing Board page of the IMI website. The role of Chair of the Governing Board in 2021 was assumed as follows:

Dates	Chair
1 January – 6 July	Olivier Laureau (EFPIA)
7 July – 30 November	Irene Norstedt (European Commission)

2.1.2 IMI Executive Director

Dr Pierre Meulien was Executive Director of IMI (and subsequently IHI) throughout 2021.

2.1.3 IMI States Representatives Group

The IMI SRG was composed of one official delegate from each EU Member State and each country associated to the EU's research programmes. Each official delegate could be accompanied by a deputy and/or national expert(s) where needed. In 2021 the chair was Marta Gómez Quintanilla (Spain), and the vice chair was Jan Skriwanek (Germany). The SRG supported IMI as an advisory body and acted as an interface between IMI and relevant stakeholders within their respective countries. It could also provide opinions to the Governing Board, especially on programme orientation, progress and achievements. Information on SRG membership, including CVs and links to national websites can be found on the SRG page of the IMI website.

In 2021, the SRG met in February and July via teleconference (due to the COVID-19 pandemic). At the meetings, the Programme Office provided detailed updates on its activities, including on SMEs and patient engagement as well as on closed and ongoing projects, budget execution and forecasts and bibliometric report. During 2021, the SRG was consulted and/or duly informed on amendments (including technical ones) to the Annual Work Plan.

Finally, the IMI Programme Office ensured the regular interactions between the SRG and the SC through the respective chairs on matters of joint interest for the two advisory bodies.

2.1.4 IMI Scientific Committee

The Scientific Committee provided strategic, science-based recommendations to IMI and advised on the continued relevance of the Strategic Research Agenda and the scientific priorities, which are the basis of the Call topics. In 2021 the Scientific Committee, chaired by Professor Isabelle Bekeredjian-Ding, met in May and September remotely due to the COVID-19 pandemic. The agendas of the meetings are available on the Scientific Committee page of the IMI website. During the year, the work of the Scientific Committee focused mainly on providing advice on the scientific achievements, notably by providing input to the IMI dissemination activities of IMI project results and their impact. In this regard, the IMI Committee members contributed to the impact series events organised (see section 2.4). The Scientific Committee members also reported on the

IMI project reviews they participated in (see section 1.5.2), as well as on close-out meetings on IMI projects that had ended. As part of their role, the committee was consulted and/or duly informed on amendments (including technical ones) to the Annual Work Plan.

Finally, a virtual meeting was also organised together with the States Representatives Group, during which the first outcomes of a review study led by EFPIA Members capturing the value of the IMI digital portfolio projects were presented as well as the proposed actionable guidance developed to help other IMI projects. The Scientific Committee provided input to these recommendations that are included in the Field Manual on scaling innovations emerging from public-private partnerships.

2.1.5 IMI Stakeholder Forum

In 2021, the ongoing COVID-19 pandemic meant that holding a traditional live, one-day Stakeholder Forum was simply not feasible. Instead, IMI held a series of events focusing on IMI's impact in key areas, namely diabetes, dementia, health data, patient engagement, and paediatric medicines development. These events are described in more detail in the 'Communication and events' section.

2.1.6 IMI Strategic Governing Groups

Given that no calls were launched under IMI2 and preparations were underway for the launch of the new IHI programme, the majority of the Strategic Governing Groups (SGGs) were not active. However, the Translation Safety SGG met once and the Digital Health and Patient Centric Evidence Generation SGG met three times. All meetings were held remotely and focused on updates from ongoing projects and other relevant programmes.

2.1.7 IMI2 Associated Partners

To help IMI2 achieve its ambitious goals, IMI2 JU sought to involve a broad range of partners from different industrial sectors, charitable foundations and philanthropic organisations. Therefore, IMI2 membership was open to any legal entities interesting in supporting the IMI2 objectives in their specific areas of research through the possibility of becoming an Associated Partner.

By the end of 2021, 37 organisations had signed up as IMI2 Associated Partners, contributing EUR 203 million to IMI2 projects, with many Associated Partners contributing to multiple projects. The full list of Associated Partners can be found on the IMI website. An application from a further organisation is under review.

The success of the IMI2 Associated Partners scheme prompted the creation of the contributing partner status for IHI and its expansion to other newly-created joint undertakings under Horizon Europe.

2.2 Governance under IHI

2.2.1 IHI Governing Board

The Governing Board of IHI JU held its constitutive meeting on 16 December 2021, during which Irene Norstedt (European Commission) was appointed as its chairperson.

During its constitutive meeting, the Governing Board of the IHI JU adopted all decisions necessary to allow the Joint Undertaking to begin its operational activities. The full list of decisions adopted is available on the IHI website.

2.2.2 IHI Executive Director

The IHI Executive Director is Dr Pierre Meulien.

2.2.3 IHI States Representatives Group

In 2021, the European Commission contacted the Permanent Representations of the EU Member States and the Missions to the European Union of the countries associated to Horizon Europe programme, requesting them to nominate representatives for the SRG of the IHI JU.

2.2.4 IHI Science and Innovation Panel

The Science and Innovation Panel is the scientific advisory body of the IHI JU and is composed of permanent panellists, among which some shall be appointed by the Governing Board following an open selection process. It shall notably advise on the scientific priorities to be addressed in the work programme (including on scope of calls for proposals), on the scientific achievements and on creation of synergies with other Horizon Europe activities.

Together with the founding members of IHI JU, the Programme Office worked on the preparation of the necessary documents for the setting-up of the Science and Innovation Panel, including the open selection process and selection criteria to be adopted by the Governing Board.

2.3 Major developments

30 November 2021 marked the entry into force of 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

This regulation created the Innovative Health Initiative Joint Undertaking (IHI JU), along with eight other research partnerships, namely: Circular Bio-based Europe Joint Undertaking, Clean Aviation Joint Undertaking, Clean Hydrogen Joint Undertaking, Europe's Rail Joint Undertaking, Global Health EDCTP3 Joint Undertaking, Key Digital Technologies Joint Undertaking, Single European Sky ATM Research 3 Joint Undertaking, and Smart Networks and Services Joint Undertaking.

The new regulation also effectively repealed and replaced the legislation creating the existing joint undertakings, including Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

IHI is designed to build on what worked well in IMI, address the lessons learnt, and leverage the benefits of cross-sectoral collaboration in research and innovation to better respond to current and emerging health needs. In practice, while some elements are staying the same in the transition from IMI to IHI, other things are changing significantly and IHI should be considered as a new organisation, and not a simple continuation of IMI.

Members and funding

As was the case in IMI, the 'public' member in the partnership is the European Union, represented by the European Commission.

The industry members are COCIR, EFPIA, EuropaBio MedTech Europe, and Vaccines Europe, taking IHI beyond the pharmaceutical industry and bringing on board the medical technology, biotechnology, digital health, and vaccine industries.

In addition, organisations that want to support specific areas of research without becoming full members of IHI can apply to become 'contributing partners' (similar to the Associated Partners in IMI2).

As in IMI, the EU will provide 50 % of the funding for IHI, and the industry members will contribute the other 50%, primarily through 'in-kind' contributions.

Subject areas

IMI started with a strong focus on the pharmaceutical sector. However, in recent years, we have launched growing numbers of projects in fields such as digital health, big data and imaging. Under IHI, we plan to support truly cross-sectoral projects involving the biopharmaceutical, biotechnology, and medical technology sectors, including companies active in the digital area. By adopting an integrated, cross-sector approach, IHI will be well placed to have an impact on health research and healthcare, both of which are increasingly interdisciplinary in nature. We will also work more on disease prevention and gain a better understanding of the determinants of health and priority disease areas.

Governance

Like IMI, IHI has a Governing Board made up of equal numbers of representatives from the European Commission and the industry partners, plus a States Representatives Group (SRG) comprising representatives of the EU Member States plus countries associated to Horizon Europe.

New under IHI is the Science and Innovation Panel, an advisory body that will bring together representatives of the scientific community and the wider health sector, such as regulatory bodies, patients, and end users. The panel will also include representatives of the European Commission and the industry partners of IHI as well as SRG members. The panel may also invite additional ad-hoc experts to join in discussions of specific subjects.

This revised governance structure will help IHI to better incorporate in priority setting the views of various stakeholders involved in health care, and ensure that IHI projects adequately address public health issues and the needs of end users.

Calls for proposals and projects

Like IMI, IHI will work by running open, competitive Calls for proposals, and we will continue to publish draft topic texts before the Call launch to give applicants additional time to work on their proposals.

As in IMI, IHI will bring together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. However, as mentioned above, in IHI we expect to launch a larger proportion of truly cross-sectoral projects involving new stakeholders representing the other industry sectors.

Management of IMI projects

At the end of 2021, there were still 103 IMI projects ongoing, including 5 from IMI1. From a legal point of view, the legislation creating IHI repeals the legislation creating IMI, and IHI is the legal and universal successor in respect of all contracts, including employment contracts and grant agreements, liabilities and acquired property of the Innovative Medicines Initiative 2 Joint Undertaking established by Regulation (EU) No 557/2014, which it replaces and succeeds.

In practice, this means that the IHI Programme Office will continue to manage the many remaining IMI projects.

2.4 Communication and events

Two developments heavily influenced the work of the communications team in 2021: (i) IMI did not publish any new Calls for proposals; and (ii) the transition to the new partnership, which necessitated the development of a brand-new corporate identity. 2021 saw the launch of the last 15 IMI projects and the Programme Office continued to manage ongoing projects.

2.4.1 Keeping the focus on results and impact

The communications strategy for this last phase of the programme was focused on developing political support for and raising awareness of IMI among all target groups, by emphasising project results and impact.

News

News articles

For most of 2021, the IMI editorial strategy remained unchanged from 2020, meaning that every month we published one thematic editorial, together with three thematic articles/interviews with project partners, based on a set of pre-defined themes. However, in September, after having published thematic monthly content that ranged from paediatrics to infrastructure and vaccines, we took it in a new direction.

To capitalise on a wider variety of successes coming from the projects that do not fit into pre-set themes, we decided to produce articles based on individual project successes. All news articles are reproduced in the newsroom section of the IMI website, promoted on social media, and featured in the newsletter.

The communications team worked in close cooperation with its founding partners to further amplify the reach of project success stories.

Two IMI project stories were published in *Horizon Magazine*: Recovering drugs from sewers could reduce harm to wildlife and Five things to know about: Mixing and matching coronavirus vaccines. Both articles reached a readership figure well beyond the average Horizon Magazine readership per article and both were featured in thenakedscientists.com

IMI's Executive Director participated in a conversation with Michel Goldman, former IMI Executive Director on What value do Public Private Partnerships bring for society?, which is part of the podcast series *The EFPIA view*.

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. In total, these resulted in the following:

- Home page views while our article was promoted: 38 522
- Social media impressions: 40 021
- Newsletter impressions (opened): 48 582
- Clicks on article in newsletter: 630

Videos

Thematic videos were produced monthly until the implementation of the new strategy, meaning there were seven videos with thematic content produced in total. In addition, for the launch of the new partnership in December 2021, we produced an additional seven videos: one video introducing the leaders of the new partners and one video announcing the arrival of the new partnership. The video presenting the logos of the new partners counted almost 4k impressions.

Events

Given the exceptional circumstances imposed by the ongoing pandemic, we turned our traditional Stakeholder Forum into a series of short virtual events called the *IMI Impact Series*. The five Impact Series events held in 2021 focussed on diabetes, data, dementia, patient engagement and paediatrics research, and they reached an audience of 775 participants. The event panels featured a significant number of female speakers, with 20 women out of a total 33 speakers.

The #ImpactSeriesIMI can be accessed in the event section of both IMI and IHI webpages.

IMI also participated in external high-profile events to raise awareness of our goals and achievements while expanding our community. Pierre Meulien participated as a speaker, or was invited to contribute to, the following discussions and debates:

- 07/01: European Parliament - CONT Committee, hearing IMI on Discharge 2019
- 12-13/01: EJP RD Policy Meeting online –at session 'Research & Innovation for the benefit of rare diseases - Why public-private partnerships in health are key to success'
- 14/01: Online Workshop Science Business, 'The future HERA: What is at stake?'
- 27/01: Virtual debate, European Parliament - The Kangaroo Group, on 'The European Pharmaceutical Strategy - enabling patient access to gene therapy innovation?'
- 18/02: SPF21 meeting - 51st Meeting of the Portuguese Society of Pharmacology, the 39th Meeting of Clinical Pharmacology and the 20th Meeting of Toxicology. Keynote 'The impact of the Innovative Medicines Initiative (IMI) on the COVID-19 vaccines development'
- 09/03: World Dementia Council, Research Workshop II, open discussion –
- 16/03: European Brain Council and partners: the European Federation of Neurological Associations (EFNA) and GAMIAN-Europe: The Brain Awareness Week - Patient Engagement in EU-Funded Brain Research Projects
- 19/03: Marie Skłodowska-Curie Actions (MSCA) Research cluster: policy round table and funding opportunities
- 20/04: Online MedTech Forum - Innovative Health Initiative: the next horizon for MedTech companies
- 11/05: Innovation Under Pressure, innovation partnering focused on solutions targeting the SARS-COV-II crisis and infectious diseases
- 28/05: European Parliament - S&D ITRE Working Group
- 31/05: Online 8th edition of CEPS Flagship Event Ideas Lab: 'Seeking ImmUnity: Europe in a post-Covid World' - The Race to vaccine is (almost) over: How to make the EU's health sector more resilient the role of public-private partnerships?'
- 23/06: Canadian Institutes of Health Research conference: Dialogue on Public-Private Partnerships
- 28/09: European Parliament Workshop: The Innovative Health Initiative: Building on the success of the Innovative Medicines Initiative
- 29/09: Biotech Atelier 2021– Big Atelier - The future of Health - Innovations for a better Healthcare
- 03/11: IAVI 25-year anniversary funders meeting
- 05/11: ASAP European Alliance virtual Summit
- 09/11: Rare Conversations Conference 'European Rare Disease Ecosystem: A Collaborative Path Forward' in cooperation with EURORDIS, the European Joint Programme on Rare Diseases, EUCOPE and EuropaBio
- 06/12: World Dementia Council (WDC) Summit 2021 - Looking to the future: The dementia landscape
- 07/12: Organisation for Economic Cooperation and Development (OECD) online Conference 'Technology in and for society: Innovating well to meet global challenges'
- 14/12: EFGCP Annual conference: Clinical Research Value and Transparency - How to capitalise on the post-pandemic opportunities

2.4.2 Preparing for the transition to a new PPP

Following the Council adoption of the Single Basic Act, IMI became IHI in November 2021, impacting the partnership's core business, outreach and image. To prepare for this change, the communications team led the creation of a new logotype and a new corporate identity to ensure all new IHI communications products have a consistent look and feel. The communications team worked closely with the contractor and the IHI partners to design infographics, exhibition, and promotional materials. The Programme Office also worked with the designers and web developers plus the IHI partners to create the IHI website (ihi.europa.eu), which

uses the IHI visual identity and presents the new PPP to the world. The website was launched successfully on 15 December 2021.

In addition, the communications team supported the Executive Director in different meetings requested by Members of the European Parliament (ITRE Committee). The aim of these meetings was to share with the SBA negotiating team lessons learned in IMI that could be useful for the new partnership.

2.4.3 IMI communication channels and performance indicators

Website

IMI's website is the programme's main information hub, and all communication channels link back to its content. Three sections concentrated most of the new content produced in 2021: the newsroom, the project factsheets, and the thematic pages.

1. In total, the IMI communications team drafted more than 100 news articles from January to December, not including event communications or articles from third parties reproduced on our website.
2. The collection of IMI project factsheets was completed with the addition of the webpages for the last 15 IMI projects launched in 2021. Also, nine factsheets have been updated with the principal findings of the projects based on the project close-out presentations and follow-up interviews with the coordinators.
    - PARADIGM factsheet
    - EFOEUPATI factsheet
    - ADAPTED factsheet
    - SPRINTT factsheet
    - EPAD factsheet
    - COMBACTE-CDI factsheet
    - GETREAL INITIATIVE factsheet
    - CANCER-ID factsheet
    - ULTRA-DD factsheet
3. As part of the #ImpactSeriesIMI events, it was decided to create thematic landing pages that would act as a focal point for IMI research in the different areas. The content of these pages covers: an overview of the research challenges, what IMI is doing to overcome them, specific projects and activities that tackle specific problems, any related events, videos and news articles related to the theme. This new content is yet another step in our quest to make IMI research communication more user-friendly, particularly for non-stakeholders such as patients and non-experts. The pages have been transferred to the new IHI website, and will expand in number and content as research efforts advance.

Website traffic

Given the nature of IMI as a funding programme, the lack of calls for proposals is expected to have a direct impact on website traffic. This exceptional circumstance happened in 2021 and resulted in in a lower that usual number of website visits. In 2021 the website received 189.7k visits (in contrast with the 330.8k visits in 2020) with, on average, around 11k unique visitors per month. This last figure remained stable throughout the year since we did not experience the stark peaks we usually observe around the publication of our annual calls for proposals. The 'apply for funding' section of the website saw a drop from 150k page views in 2020 to 25k page views in 2021.

The share of visitors that came from jobs site EPSO dropped to 18 % (compared to 43 % in 2019 and 24 % in 2020) and the number of referrals from LinkedIn grew to 17 % (compared to 7 % in 2020 and 5 % in 2019).

'Project factsheets' and 'news and events' remained among the most visited sections. The most popular news story was about the vaccine project ZAPI. Visits to the newsroom rose from 471 total entries in 2020 to 742 in 2021. The project factsheets that received the most visitors were those of the projects H2O and MELLODDY.

On 15 December the new IHI website went live and received 3 446 visits resulting in 10 006 page views. The IMI website will be archived in 2022 but will remain accessible to the public.

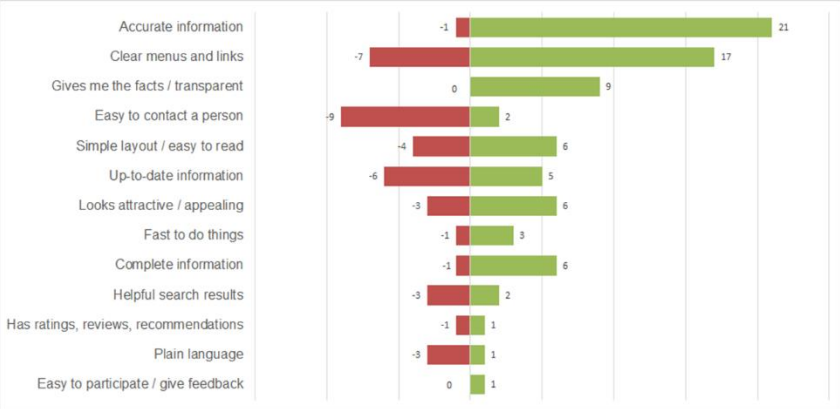
With regards to the geographic locations of website visitors, most came from the US, followed by Belgium, the UK, Germany, and France.

User experience study to aid new website design

In 2021 the communications team commissioned a study to provide evidence-based insights into our stakeholders' user needs. Although the analysis was based on 2020 indicators, it revealed some relevant trends that helped to design the new IHI website. The main findings were as follows:

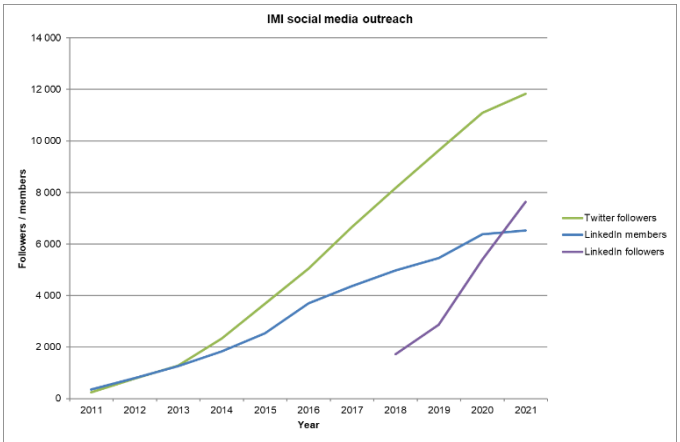
- Around 50 % of visitors arrive on the website via direct entry, which is a very high percentage when compared with similar websites. In comparison, the website europa.eu figures are around 22 %. This might suggest that a higher-than-average number of visitors know IMI and visit via a saved bookmark or by typing the URL. Only around 30 % of visitors arrived at the site via search engines, which is very low percentage compared to the 73 % in the case of europa.eu. Around 15 % of IMI's website visitors arrive via referrals, mainly through links on the europa.eu website, but also through LinkedIn and Facebook.
- 76 % access the site from a computer and 21 % from a smartphone
- Behaviour statistics show that visitors are slightly more engaged than the comparative sample from europra.eu, experiencing slightly more return visitors, slightly longer visits and more pages visited per session.

The results of the statistical analysis were complemented with a Customer Centric Index satisfaction questionnaire (CCI). The goal of the survey was to gather information about the website visitors general level of satisfaction and their user experience. Showing an overall level of satisfaction of 67.23 %, and particularly positive results for transparency and accurate information, the CCI yielded the following results:



Social media

We continued to primarily promote our editorial content on both Twitter and LinkedIn. As illustrated in the graph, IMI's social media channels continue to show a steady growth curve with the number of new members subscribing to both channels year-on-year, increasing at a regular pace.



Twitter

In 2021, @IMI_JU tweeted 512 original messages in addition to regular retweets, particularly from IMI projects, which resulted in over 782 000 impressions, 1 579 link clicks, 1 472 retweets and 2 744 likes, reaching 11 194 engagements. By the end of 2021, the IMI Twitter account had 11 827 followers, up from 11 095 the year before.

The news story with the furthest reach on Twitter was the announcement of the new members of the Governing Board, followed by a tweet about one of our AMR projects that examined doctors' level of confidence in antibiotic prescribing without testing (Value Dx). Other top performing themes that had high levels of reach on social media included the European Lead Factory drug discovery platform and the IMI coronavirus projects.

The @IMI_JU twitter handle was changed to @IHIEurope at the beginning of December.

LinkedIn

By the end of 2021, IHI had 7 634 followers on LinkedIn, up from 5 407 at the end of 2020. Engagement rates varied from around 3 % to over 5 %. 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 %). In December, the account was changed to Innovative Health Initiative.

Newsletter

In addition to our social media channels, the IMI newsletter, of which there were 10 issues throughout the year, plays a pivotal role in promoting our editorial content. By the end of 2021, there were 4 190 subscribers (compared to 3 825 in 2020). The breakdown of subscribers' organisations is as follows: 1 874 research organisations, universities and hospitals; 572 SMEs; 605 large industry (480 pharma industry subscribers and 125 other large industry subscribers) and 97 patient organisations. It is worth noting that over 500 subscribers come from organisations that act as amplifiers of IMI such as EU, national and regional authorities (245), consultancies (287) and press/PR agencies (33) As in previous years, the monthly tweet highlighting the newsletter stories featured consistently among the most popular in IMI's Twitter feed.

The transition to the new IHI newsletter went smoothly, with the first issue published in December 2021.

Press coverage

Throughout the year, the communications team tracked the number of press articles that mentioned IMI and/or its projects. There were 6 302 articles published worldwide, of which 853 were published in the EU (1 207 in the EU plus the UK, a figure that is useful for comparing coverage with years when the UK was a Member State). These figures are slightly below the number of articles published in 2020, a year in which IMI's COVID Call and projects were launched, but well above previous years.

Most of these articles talk about the challenges IMI projects are set to tackle and their expected impact in the development of more effective medicines and treatments. New evidence to back the performance of the JnJ Ebola vaccine has also made the headlines, as did the scientific expertise on the COVID pandemic of two IMI Executive Directors, Pierre Meulien and Michel Goldman.

IMI reached a 9 % headline / header presence, meaning IHI was mentioned in the headline or the opening part of the article.

Some key publications include:

- A silent tsunami is coming – it's time to stem the tide of AMR – Hospital Times
- How to stop the next pandemic -Wired
- Pharma's Blockchain Trials: Novartis, Merck Test The Tech Popularized By Bitcoin - Forbes
- The growing threat of antimicrobial resistance – Health Europa

- Nie konnten wir unsere Innovationskraft besser zeigen - Frankfurter Allgemeine Zeitung
- Une biotech française veut aider les patients cancéreux en soignant leur flore intestinale – Les Echos
- How protecting water can avert future global health crises - Euronews
- The tangled history of mRNA vaccines - Nature
- IMI successor to launch 30 large scale health innovation projects by 2030 – Science Business
- Council clears way for €22B industrial partnerships – Science Business

The communications team remained alert to issues that could damage IMI'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 95 % of news items, while the content of around 5 % of the pieces was positive. On Twitter a quarter of posts about IHI and a fifth of posts about IMI had a positive tonality, with the rest being largely neutral and just a small proportion with negative tonality.

2.5 Budgetary and financial management

2.5.1 2021 total budget

The total budget for 2021 was EUR **10 972 070** in commitment appropriations (CA) and EUR **210 351 818** in payment appropriations (PA). The budget execution of the commitment appropriations and the payment appropriations reached **75.91 %** and **95.39 %** respectively.

The 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 the functioning of the organisation such as renting of premises, IT needs, meetings, expenses related to external communication, expert fees, and costs of ex-post audits.

Titles 1 and 2 together form the administrative expenditure.

- Title 3 covers operational activities.

The IMI Governing Board approved the 2021 budget on 11 December 2020. The budget was subsequently amended during 2021, driven by revenue and expenditure updates as follows:

- to reflect the figures revised by the European Commission for 2021, in view of the transition to the new proposed cross-sectorial partnership in health under Horizon Europe - for this reason also the annual administrative budget was reduced by EUR 2 million;
- to enter in the budget the carry overs of the preceding financial year;
- to update the revised operational payments appropriations forecast for FP7 and H2020 related projects.

The Governing Board approved the first budget amendment on 23 April 2021 in order to reflect the figures revised by the European Commission for 2021, in view of the transition to the new proposed cross-sectorial partnership in health under Horizon Europe. As such, the first budget amendment reflected the reduction of the administrative budget by EUR 2 045 674, on both commitment and payment appropriations.

The Governing Board approved the second budget amendment on 23 July 2021 in order to reflect an increase of EUR 18 million in operational payment appropriations for FP7 and H2020 related projects and the carry overs to 2021.

On 30 November 2021, the Innovative Health Initiative Joint Undertaking (IHI JU) entered into force, being the legal successor of the Innovative Medicines Initiative (IMI2 JU).

The IHI Governing Board subsequently re-adopted the 2021 budget on 16 December 2021.

IHI JU is a partnership between the European Union and European industry associations representing the pharmaceutical, medical technology, biotechnology, digital health, and vaccine industries, namely COCIR, EFPIA, EuropaBio, MedTech Europe and Vaccines Europe.

IHI's total budget is EUR 2.4 billion. Half of this comes from Horizon Europe, the EU's research and innovation programme. The Union financial contribution from the Horizon Europe programme to the Innovative Health Initiative Joint Undertaking, including EFTA appropriations, will cover administrative costs and operational costs up to EUR 1.2 billion, including up to EUR 30.2 million for administrative costs. In addition, the EU will further contribute between 2021-2028 to the administrative budget with an amount of up to EUR 22.3 million, representing the carryover from IMI2 JU.

The IHI industry partners have committed EUR 1 billion to IHI JU, and a further 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. In addition, EFPIA will further contribute between 2021-2028 to the administrative budget with an amount of up to EUR 22.3 million, representing the carryover from IMI2 JU.

Overview of the total budget 2021 in EUR

Notes:

- CA = commitment appropriation, PA = payment appropriation.
- EC contribution includes EFTA contribution.
- Chapter 21 ('Subsidy from other members') refers to the subsidy from members other than the union and Associated Partners, constituent or affiliated.
- Assigned revenue (C4) refers to amounts recovered during the year from suppliers and projects.

STATEMENT OF REVENUE											
Chapter	Revenue	Budget 2021.0		Budget 2021 Amendment 1		Budget 2021 Amendment 2		Assigned revenue	Assigned revenue	Final budget 2021	
		CA	PA	CA	PA	CA	PA	CA	PA	CA	PA
10	EC 2021 contribution	5 572 837	185 572 837	-1 022 837	-1 022 837		18 000 000			4 550 000	202,550,000
10	Appropriations carried over from previous years					1 592 838	2 755 254			1 592 838	2,755,254
EC contribution		**5 572 837**	**185 572 837**	**-1 022 837**	**-1 022 837**	**1 592 838**	**20 755 254**			**6 142 838**	**205 305 254**
20	EFPIA 2021 contribution	5 572 837	5 572 837	-1 022 837	-1 022 837					4 550 000	4 550 000
20	Appropriations carried over from previous years						217 333			0	217 333
21	Subsidy from other members									0	0
EFPIA and other members' contributions		**5 572 837**	**5 572 837**	**-1 022 837**	**-1 022 837**	**0**	**217 333**			**4 550 000**	**4 767 333**
30	Associated Partner contributions									0	0
Associated Partner contributions		**0**	**0**	**0**	**0**	**0**	**0**			**0**	**0**

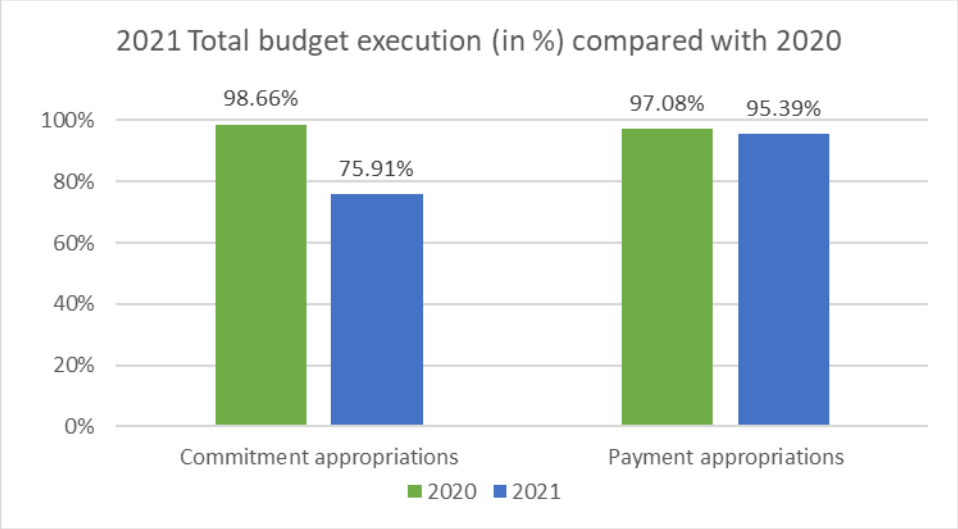
STATEMENT OF REVENUE											
Chapter	Revenue	Budget 2021.0		Budget 2021 Amendment 1		Budget 2021 Amendment 2		Assigned revenue	Assigned revenue	Final budget 2021	
		CA	PA	CA	PA	CA	PA	CA	PA	CA	PA
C4	Assigned revenue							279 232	279 232	279 232	279,232
Total revenue		**11 145 674**	**191 145 674**	**-2 045 674**	**-2 045 674**	**1 592 838**	**20 972 587**	**279 232**	**279 232**	**10 972 070**	**210 351 819**
Expenditure by title											
	1. Staff expenditure	6 564 153	6 564 153	-516 153	-516 153	-	60 698	12 642	12 642	6 060 642	6 121 340
	2. Infrastructure expenditure	4 581 521	4 581 521	-1 529 521	-1 529 521	-	373 968	15 205	15 205	3 067 205	3 441 173
	3. Operational expenditure	-	180 000 000	-	-	1 592 838	20 537 921	251 385	251 385	1 844 223	200 789 306
Total expenditure		**11 145 674**	**191 145 674**	**-2 045 674**	**-2 045 674**	**1 592 838**	**20 972 587**	**279 232**	**279 232**	**10 972 070**	**210 351 818**

2.5.2 Total budget execution

The table below shows the execution of the 2021 budget per Title in absolute amounts.

Title	CA	Execution	%	PA	Execution	%
Title 1	6 060 642	5 523 794	91.14	6 121 340	5 477 947	89.49
Title 2	3 067 205	2 769 289	90.29	3 441 173	2 352 171	68.35
Subtotal administrative expenditure	*9 127 847*	*8 293 083*	*90.85*	*9 562 513*	*7 830 118*	*81.88*
Title 3	1 844 223	36 120	1.96	200 789 306	192 831 090	96.04
Total (Title1, 2 and 3)	**10 972 070**	**8 329 203**	**75.91**	**210 351 818**	**200 661 207**	**95.39**

The graph below shows the 2021 total budget execution compared with 2020.



2.5.3 Budget transfers

In 2021, there were no budget transfers between titles. Budget transfers between chapters were authorised in 2021, 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**	5 651 000	-80 000	5 571 000
12	**Staff recruitments - miscellaneous expenditure**	10 000	0	10 000
13	**Mission expenses**	62 956	-19 012	43 944
14	**Socio-medical structure**	201 686	19 012	220 698

Chapter		Budget approved and assigned revenue (EUR)	Budget transfers (EUR)	Budget after transfers (EUR)
		Commitment Appropriations	Commitment Appropriations	Commitment Appropriations
15	External staff services	125 000	80 000	205 000
17	Representation	10 000	0	10 000
20	Office building and associated costs	650 000	-8 905	641 095
21	Information technology (hardware and software)	1 086 504	-11 100	1 075 404
22	Office equipment	5 000	-3 000	2 000
23	Current administrative expenditure	127 000	-23 095	103 905
24	Telecommunication and postal expenses	45 655	0	45 655
25	Formal meetings	28 046	28 000	56 046
26	Administrative expenditure in connection with operational activities	140 000	95 835	235 835
27	External communication, information and publicity	366 000	-51 000	315 000
28	Service contracts	419 000	104 100	523 100
29	Expert contracts and cost of evaluations	200 000	-130 835	69 165
	Total	**9 127 847**	**0**	**9 127 847**

2.5.4 Overview of total commitments outstanding

The table below shows the summary of commitments outstanding at the end of 2021, for administrative and operational expenditure.

	EUR
Commitments carried from previous year	901 099 341
De-commitments (-)	-3 600 110
Payments made during 2021 related to commitments carried forward (-)	-193 705 705
Commitments made during 2021	8 329 203
Payments made during 2021 related to commitments made during 2021 (-)	-6 955 503
Total commitments outstanding at the end of 2021	**705 167 227**

2.5.5 Operational budget

The total operational budget approved for 2021 was EUR 202.6 million including both the commitment and payment appropriations.

The 2021 commitment appropriations for operational activities were EUR 1.8 million. This amount resulted from EUR 1.6 million carry-over of 50 % unused administrative commitment appropriations in 2020, to the operational budget 2021, in view of the transition to the new proposed cross-sectorial partnership in health under Horizon Europe. In addition, the assigned revenue amounted to EUR 0.2 million.

The table below shows the execution of commitment appropriations for Title 3.

	Totals in EUR		%
	Appropriations	Execution	
FP7 *	250 818	36 120	*14.40 %*
H2020	1 593 405	-	*0.00 %*
Title 3 implementing the research agenda of JU	1 844 223	36 120	1.96 %

* FP7 appropriations - amount recovered during 2021 from projects (assigned revenue)

IMI2 JU launched its last Call for proposals in 2020. IHI JU started 30 November 2021 and before any Calls can be launched, all the new governance bodies need to be set up first. Therefore no new Calls were launched in 2021 under the Horizon Europe programme. As a result, the commitment appropriations execution reached 1.96 %. The unused commitment appropriations will be carried over to 2022, subject to Governing Board approval. In terms of operational payment appropriations, during 2021, the operational payment appropriations were increased by EUR 18 million, through a budget amendment, for FP7 and H2020 related projects.

The payment appropriations related to H2020 were mainly used by pre-financing, interim and final payments for projects of IMI2 - Calls 1-23.

The payment appropriations related to FP7 were mainly used by payments for periodic or final reports for projects of IMI1 - Calls 3, 5, 6, 9 and 11.

The operational payment appropriations rate reached 96.04 %, marking an excellent result for IHI. The significant achievement of payment execution rates shows a continuation of the previous year's trend in the absorption of operational appropriations, as a result of continuous actions taken in the budgetary planning and monitoring processes. In the context of year 2021, despite the exceptional circumstances created worldwide by the COVID19 pandemic, IHI has managed to achieve excellent results.

The table below indicates the operational budget execution (Title 3) per programme.

	Totals in EUR		%
	Appropriations	Execution	
FP7	12 861 407	10 242 451	79.64 %
H2020	187 927 899	182 588 639	97.16 %
Title 3 implementing the research agenda of the JU	**200 789 306**	**192 831 090**	**96.04 %**

The table below shows the summary of commitments outstanding for operational expenditure per programme at the end of 2021.

Commitments carried forward from previous year 2020	Commitment appropriations in EUR				
	Carry forward	Commitments made during 2021	De-commitments	Payments	Commitments outstanding at end 2021
FP7	94 941 054	36 120	0	-10 242 451	84 734 723
H2020	804 848 985	-	-3 358 948	-182 588 639	618 901 399
Total Title 3	**899 790 040**	**36 120**	**-3 358 948**	**-192 831 090**	**703 636 122**

As no Calls were launched during 2021, at the end of 2021 there were no level 1 commitments (related to Calls) open.

2.5.6 Operational budget per programme

IHI's operational budget (Title 3) reflects expenses linked to the implementation of the IHI and IMI research agenda. Here it should be noted that since 2014, IMI has managed two 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 contributes EUR 966 million to the IMI1 research programme.
- IMI2 (under Horizon 2020, H2020)

As initially foreseen 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 IMI2 JU (2014-2021) for operational activities amount to EUR 1.4566 billion.

This figure results from the initial EUR 1 595 million (as initially foreseen in Council Regulation 557/2014), minus EUR 139.1 million (reduction in 2019), minus EUR 6.7 million (redeployment to climate related activities under Horizon 2020), plus EUR 7.4 million (50% of unused commitments since 2014 transferred from the administrative budget to the operational budget).

At the end of 2021, the total committed EU funds under the H2020 programme for all 123 signed grants was EUR 1 452 million. In the meantime, the JU has de-committed EUR 0.9 million for closed grants which have underspent. The difference between commitments available and committed amounts, of EUR 5.5 million, represents de-committed amounts at the end of the programme. Of this, EUR 1.6 million will be further carried over to IHI for new Calls under Horizon Europe. Thus, the net de-committed amount under H2020 at the end of 2021 was EUR 3.9 million.

As of 30 November 2021, the Innovative Health Initiative Joint Undertaking (IHI JU), the legal successor of Innovative Medicines Initiative (IMI JU), manages a third programme, Horizon Europe.

As described in the 2021 Council Regulation, the EU has committed to contribute EUR 1.170 billion from Horizon Europe to the IHI programme, for operational activities.

The table below outlines the breakdown per Call of EU committed funds for IMI1 (FP7).

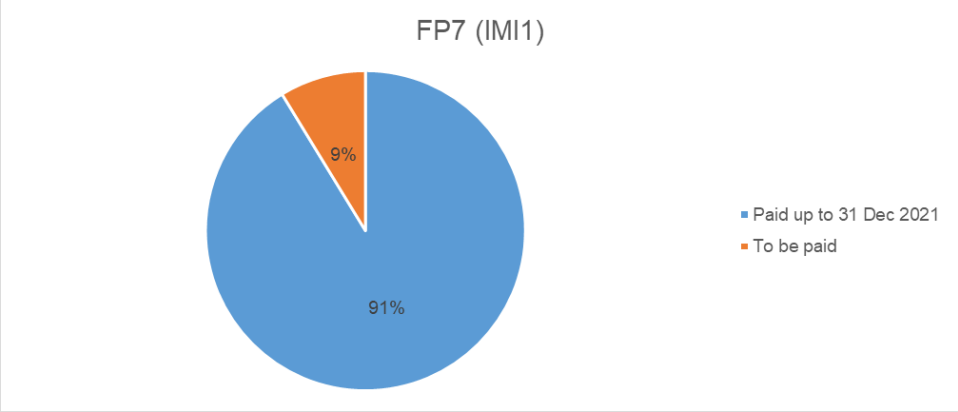
			EUR '000
FP7 (IMI1)	Committed	Paid up to 31/12/2021	To be paid
Call 1	116 082	114 607	1 475
Call 2	85 765	85 216	549

			EUR '000
FP7 (IMI1)	Committed	Paid up to 31/12/2021	To be paid
Call 3	112 854	112 548	306
Call 4	97 944	97 168	776
Call 5	80 021	79 377	644
Call 6	125 417	106 438	18 979
Call 7	13 000	12 064	936
Call 8	98 733	82 847	15 886
Call 9	56 441	50 127	6 314
Call 10	6 100	5 496	604
Call 11*	173 410	135 552	37 858
Total FP7 (IMI1)	**965 767**	**881 439**	**84 328**

In addition to the total amount to be paid, at the end of 2021, in ABAC there is the amount of EUR 401 675, representing the open amount of the ENSO (Exploring New Scientific Opportunities) Call.

At the end of 2021, 91 % 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 FP7.



The table below outlines the breakdown per Call of EU committed funds for H2020.

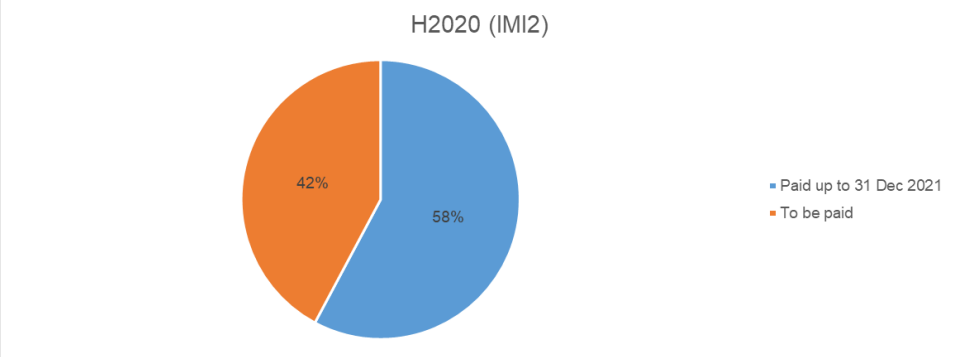
				EUR '000
H2020 (IMI2)	Committed EU	Committed AP and other members	Paid up to 31/12/2021	To be paid
Call 1	17 630		15 867	1 763
Call 2	113 954		103 842	10 112
Call 3	49 060	7 000	53 363	2 697
Call 4	1 078		1 078	-
Call 5	47 477		43 170	4 307
Call 6	46 343	200	41 116	5 427

				EUR '000
H2020 (IMI2)	Committed EU	Committed AP and other members	Paid up to 31/12/2021	To be paid
Call 7	46 429		40 200	6 229
Call 8	47 462		31 899	15 563
Call 9	53 606	4 000	47 491	10 115
Call 10	173 612		117 788	55 824
Call 11	3 266		3 092	174
Call 12	64 027		43 483	20 544
Call 13	114 152		66 029	48 123
Call 14	82 310		32 955	49 355
Call 15	165 608		58 382	107 226
Call 16	35 184		20 981	14 203
Call 17	40 786		14 958	25 828
Call 18	74 860		22 280	52 580
Call 19	12 715		6 809	5 906
Call 20	133 009		28 471	104 538
Call 21	71 998		34 777	37 221
Call 22	8 725		4 809	3 916
Call 23	47 788		12 637	35 151
Total H2020 (IMI2)	**1 451 079**	**11 200**	**845 478**	**616 801**

The Call 3 commitment includes a financial contribution from the Bill and Melinda Gates Foundation (BMGF), an IMI2 Associated Partner. The commitment for Calls 6 and 9 includes a financial contribution from EFPIA companies. In addition to the total amount to be paid, at the end of 2021, in ABAC there is the amount of EUR 2.1 million representing the open amount of the PERISCOPE project.

At the end of 2021, 58 % 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 H2020.

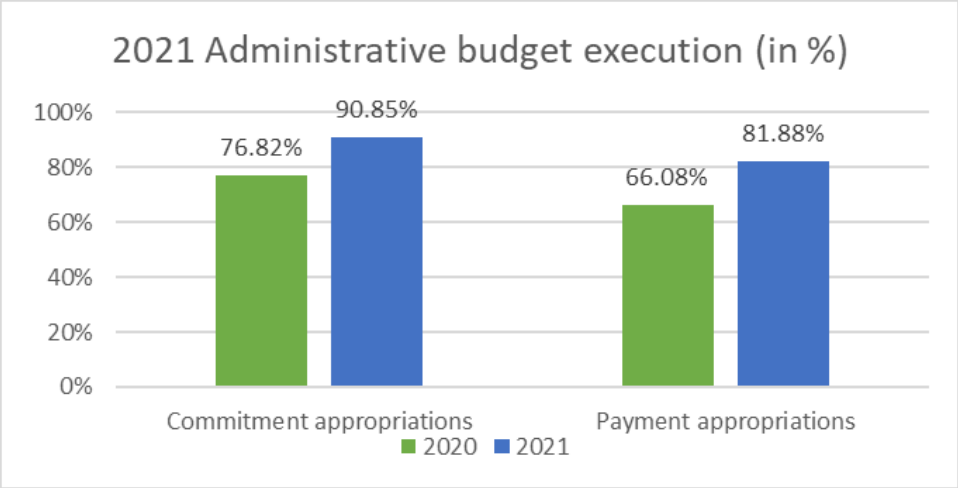


2.5.7 Administrative budget

The table below shows the execution of the 2021 administrative budget per Title in absolute amounts.

Title	Commitment appropriations	Execution	%	Payment appropriations	Execution	%
Title 1	6 060 642	5 523 794	91.14	6 121 340	5 477 947	89.49
Title 2	3 067 205	2 769 289	90.29	3 441 173	2 352 171	68.35
Total administrative expenditure	*9 127 847*	*8 293 083*	*90.85*	*9 562 513*	*7 830 118*	*81.88*

The graph below shows the 2021 budget execution for administrative costs (staff and infrastructure) compared with 2020.



The budget execution of the commitment and payment appropriations in 2021 reached a level of 90.85 % and 81.88 % respectively. The commitments and payments execution for administrative expenditure continued to be affected by the COVID-19 crisis. Areas directly affected by the Covid-19 crisis were missions, meetings and external events like Stakeholder Forum (chapter 27 - external communication).

Regardless of the effects of the COVID-19 crisis, the budget execution was significantly improved compared to 2020. This excellent achievement was largely due to the more efficient monitoring of the budget implementation.

The JU continued to execute its budget applying principles of sound financial management, which resulted in a number of budget transfers between budget chapters, in line with operational needs. In 2021, there were no budget transfers between titles.

2.5.8 Carry over of appropriations

Under the new program, the N+3 rule for JUs still applies. The N+3 rule states that the unused appropriations may be entered in the estimate of revenue and expenditure of up to the following three financial years.

Subject to Governing Board approval, IHI JU will re-enter into 2022 budget the administrative payment appropriations corresponding to commitments carried forward from 2021 of up to EUR 1.5 million and operational payment appropriations of EUR 7.951 million. On the commitment side, subject to Governing Board approval, IHI JU will re-enter into the 2022 budget 50 % of unused administrative commitment appropriations of EUR 0.5 million and unused operational commitment appropriations in 2021 of EUR 1.8 million.

2.5.9 Procurement and contracts

The majority of IMI's contractual commitments in 2021 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 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 2021 outside existing FWCs with a value exceeding EUR 15 000.

Subject	Procedure	Contractor	Value in EUR	Signature date
Legal support services	Negotiated	Ashurst Europe SRL	15 000	5 November 2021
Communication services	Open	ICF Next S.A.	79 886,40	21 May 2021

All procedures were administered in compliance with the IMI2 JU Financial Rules to ensure fair competition amongst economic operators, and the most sound and efficient use of IMI2 JU funds.

2.6 IMI EFPIA and Associated Partner contributions

IMI is a public-private partnership between the EU (represented by the European Commission) and the pharmaceutical sector (represented by EFPIA). Some IMI2 projects also include Associated Partners, in addition to EFPIA companies.

On the one hand, in IMI1 and IMI2 projects, legal entities eligible for JU funding (beneficiaries receiving JU funding) receive financial support from the JU to fund their activities[1].

On the other hand, IMI projects also benefit from contributions by EFPIA companies and (for IMI2) Associated Partners that do not receive any funding from the JU but contribute their own resources to the projects. These contributions consist of:

- in-kind contributions[2], i.e., costs incurred by EFPIA companies and Associated Partners in the implementation of the IMI projects for researchers, research equipment, and materials;
- financial contributions directly to the JU, or at project level to beneficiaries receiving JU funding.

This chapter presents the contributions of EFPIA companies and (for IMI2) Associated Partners, including commitments made at Call and project launch, and actual contributions made during the lifetime of the projects. The equivalent EU commitments / contributions are also provided throughout this chapter to facilitate comparison; for both IMI1 and IMI2, the public and private contributions should match by the end of the programmes.

EFPIA companies and Associated Partners are contractually obliged to report to the JU all costs that they incur in IMI projects. The JU controls the eligibility and regularity of the contributions and carefully monitors the development of the total contributions to both programmes (IMI1 and IMI2).

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

- IMI1: EC funding up to EUR 966 million, to match the equivalent contributions from EFPIA.
- IMI2: EC funding up to EUR 1.425 billion, to match the equivalent contributions from EFPIA companies. An additional EUR 213 million in EC funding may be provided to match additional contributions from other Members, Associated Partners, or from their constituent entities or their affiliated entities, bringing the maximum EC funding to EUR 1.638 million, of which EUR 1.596 for operational activities.

[1] The management of these funds is described in more detail in section 1.7 and section 4.
[2] In-kind contribution is defined as follows:
IMI1: 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'.
IMI2: Article 13(3)(b) of the IMI2 JU Statutes annexed to Council Regulation (EU) No 557/2014 - 'in kind contributions by the Members other than the Union and the Associated Partners, or their constituent entities or their affiliated entities, consisting of the costs incurred by them in implementing indirect actions, and in relation to advisory groups, if foreseen in the annual work plan, less the contribution of the IMI2 Joint Undertaking and any other Union financial contribution to those costs'.

IMI1 programme

IMI1 EU and EFPIA commitments

This section highlights the commitments pledged by EFPIA companies to the 59 projects in the IMI1 portfolio.

In 2020, IMI1 commitments were EUR 975.5 million for EFPIA in kind, and EUR 965.7 million for the EU, while in 2021 IMI1 commitments were EUR 913.0 million for EFPIA in kind, and EUR 937.1 million for the EU. The reduction of EUR 62.5 million in EFPIA commitments and EUR 28.6 million in EU commitments can be mainly attributed to the amendments approved for some projects in the antimicrobial resistance (AMR) portfolio.

Drug development in AMR is extremely complex, particularly in later stage clinical trials. However, in spite of the high levels of uncertainty in the field, the conviction that the challenges involved in discovering and developing new antibiotics are well suited for a public private partnership has led to the creation of a large IMI portfolio in AMR.

Aware of the risk that the clinical development of several of the compounds being studied by IMI projects might not complete or fail, the approach taken by the IMI Governing Board was, nevertheless, to commit a large enough amount of funding upfront. The intention was to make sure that if all the compounds were successfully tested, there would be sufficient funding to complete all the necessary clinical trials planned. This meant that the original budgets - from both public and private sources - in the Call topic texts for several AMR projects were highly indicative.

As the European Court of Auditors recognises, it is extremely difficult to pursue antibiotic drug discovery and development within the constraints of a traditional project-driven and grant-funding approach[3]. For instance, when faced with challenges that led to the termination of development programmes (e.g. toxicity or the lack of efficacy of some of the compounds under study), the original work plans in projects such as COMBACTE-NET, COMBACTE-MAGNET and iABC needed to be amended to either allow for the inclusion of substitute compounds, or reflect the fact that the planned clinical studies were not pursued.

In AMR projects, the IMI funding (public) is often used to fund the preparatory phase to allow compounds to enter the clinical trial, including observational studies to better understand the infections, while the in-kind (private) contribution is mainly to support the conduct of the clinical trial. Therefore, if the development of a compound is stopped for sound scientific reasons and the clinical trial is not executed, the expected in-kind contribution (private) is not used, leading to a mismatch between public and private funding.

In light of this, and in the interests of sound financial management, the Programme Office took the decision to reduce the original commitments to better reflect the amended descriptions of work for the projects affected.

IMI1 EU and EFPIA validated contributions - comparison by year

As of 31 December 2021, EFPIA contributions of EUR 776.0 million had been formally validated (checked by Programme Office staff and / or audited by external auditors). The table below gives an overview of validated IMI1 contributions for every year since the start of the programme.

Year	Validated cost claims from beneficiaries (*)	Validated EFPIA in-kind contributions
2010	0.5	
2011	15.2	
2012	33.5	52

[3] European court of Auditors Special Report *Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU*, p 32.

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
TOTAL	802.1	766.7

(*) excluding pre-financing

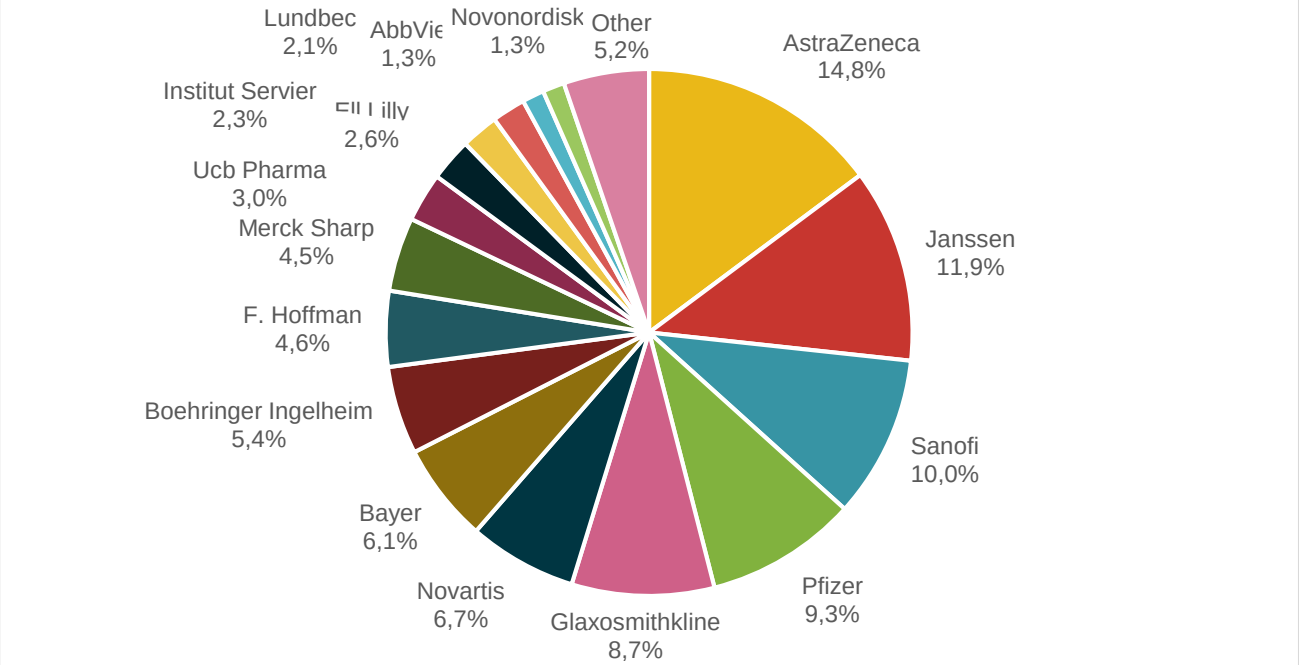
The difference between validated EU cost claims and EFPIA contributions results from the fact that, in some projects, tasks for the different consortium partners do not run in parallel but are often sequential.

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 2021, there were 5 projects still running out of the initial 59 IMI1 projects.

In 2021, the Programme Office continued to closely monitor the overall commitments of industry participants. 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 validated EFPIA companies' contributions to IMI1 projects since the start of the programme.



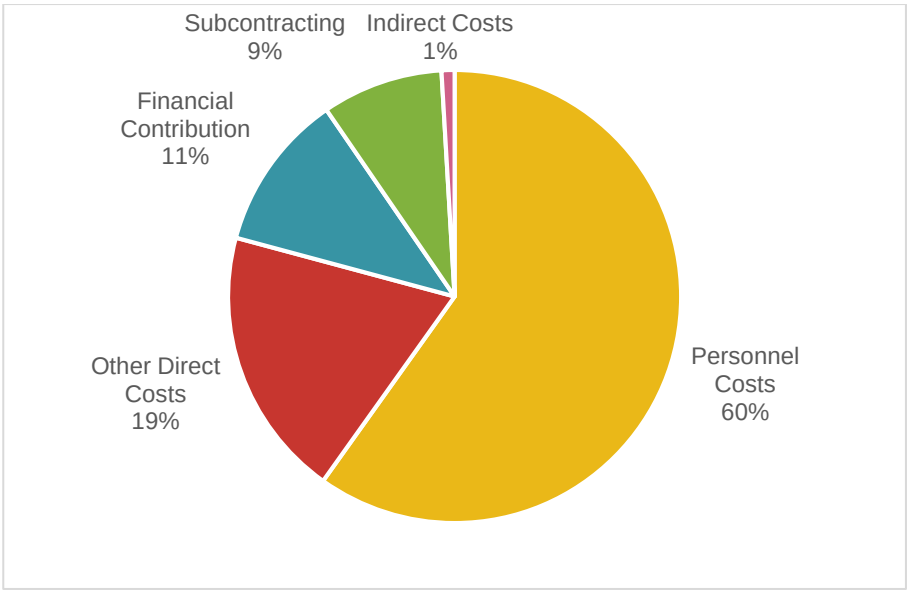
Companies listed under 'Others' are: Abbott, Amgen, AiCuris, Basilea Pharmaceutica, Bristol-Myers, Chiesi Farmaceutici, Da Volterra, Eisai, Employers' Union, Evotec, Farmaindustria, Genzyme, Grünenthal, Ipsen, Islensk, Laboratorios del Dr. Esteve, The Medicines Company, Orion, Polyphor, Seqirus, Sigma-Tau, 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.



IMI2 programme

During 2021, 15 Grant Agreements were signed, bringing the total number of IMI2 projects to 123. At the end of 2021, the total commitments for signed Grant Agreements in IMI2 were:

- EUR 1 452.1 million in EU funding.
- EUR 1 518.2 million commitments from EFPIA companies (EUR 1 315.2 million) and Associated Partners (EUR 203.0 million).

Both EFPIA and Associated Partner commitments include in-kind contributions, as well as financial contributions directly to the JU's operational costs, or at project level to beneficiaries receiving EU funding. The following table provides an overview of EU, EFPIA and Associated Partner commitments to signed IMI2 projects:

IMI2 million EUR	EFPIA commitment	AP commitment	Total EFPIA + AP commitment	EU commitment
Up to 31.12.2020	1 111.2	168.4	1 279.6	1 262.6
2021	204.0	34.6	238.6	189.5
TOTAL on 31/12/2021	1 315.2	203.0	1 518.2	1 452.1

The increase of commitments in 2021 of EUR 189.5 million (EU funding) and EUR 238.6 million (EFPIA and Associated Partner commitment), results mostly from the conclusions of 15 new signed Grant Agreements for IMI2 - Calls 20, 22, and 23.

Of the EUR 1 518.2 million committed by EFPIA and Associated Partners over the full IMI2 programme, EUR 1 051.7 million comes from the EU and H2020 associated countries; this represents 72.4 % of the EU's commitment (70 % of EUR 1 452.1 million is EUR 1 016.4 million). The remaining EFPIA and AP commitments come from outside the EU and H2020 associated countries.

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

In 2021, EFPIA companies and Associated Partners had contributed EUR 254.0 million to the IMI2 programme (amount certified by external auditors and validated by IMI). For comparison, accepted cost claims for JU funding from beneficiaries stood at EUR 161.8 million. The following table shows the validated EFPIA and Associated Partner contributions as well as cost claims from beneficiaries receiving EU funding.

	EFPIA contributions	Associated Partner contributions	Total validated EFPIA and Associated Partner contributions *	Validated cost claims from beneficiaries receiving EU funding **
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
TOTAL	**523.0**	**94.5**	**617.5**	**460.6**

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

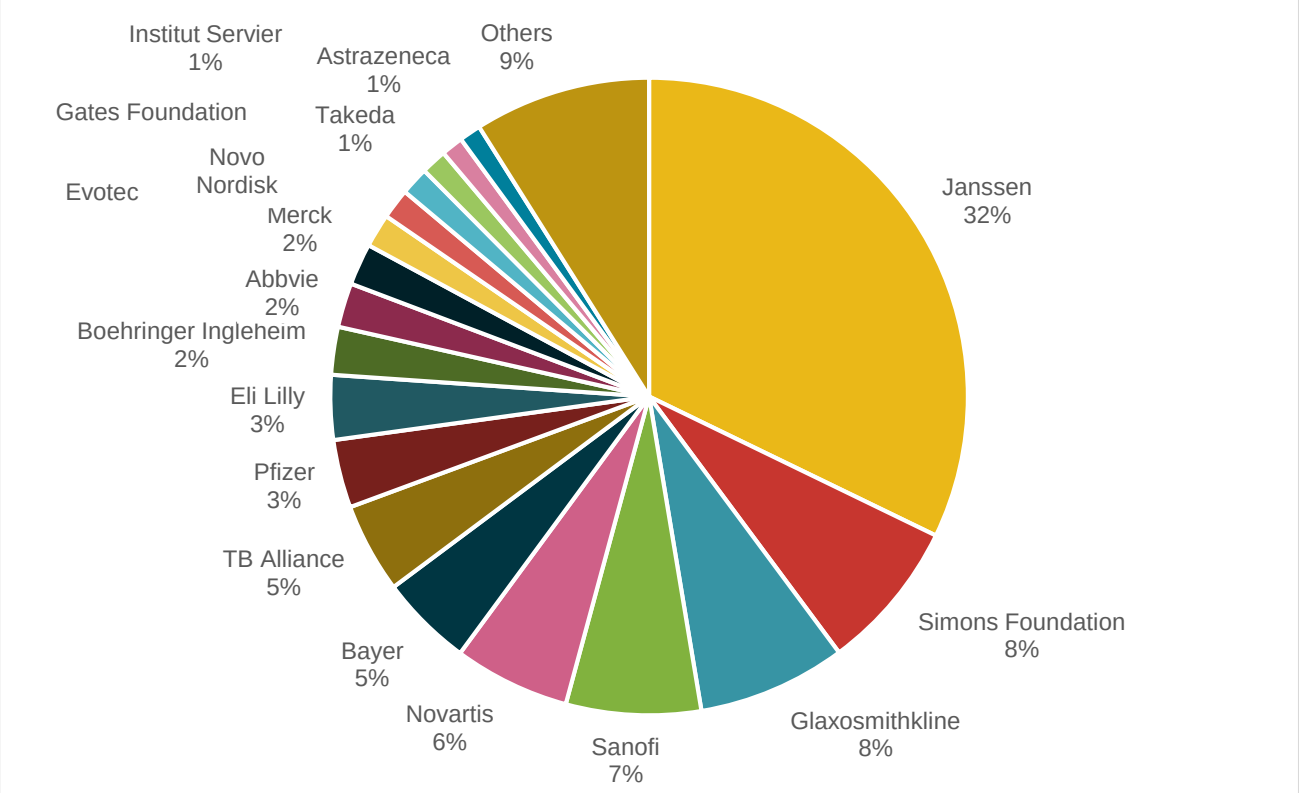
(**) excluding pre-financing

The significant increase of in-kind contributions and cost claims in 2021 compared to 2020 is due to the fact that the number of IMI2 running projects increased from 92 at the end of 2020 to 103 at the end of 2021 (final payments executed). In addition, there are more projects that are now at a more advanced stage (third, fourth or fifth reporting years), where their spending pattern is higher.

IMI2 validated EFPIA and Associated Partner contributions by organisation up to the end of 2021

There are now more than 60 EFPIA companies and Associated Partners contributing to IMI2 projects. As the organisational breakdown below shows, 32 % of the total validated 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 68 % contribution comes from other EFPIA companies and Associated Partners. Of note is the fact that some of the biggest contributors are Associated Partners, such as the Simons Foundation (8 %) and the TB Alliance (5 %).

The chart below includes both in-kind contributions and financial contributions at the level of the action to beneficiaries receiving IMI funding; this totals EUR 617.5 million certified by external auditors and validated by IMI.



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, Da Volterra, Diamond Light Source, EFPIA, Ellegaard Gottingen, Esteve Pharmaceuticals, Hoffmann-La Roche, Farmaindustria, GE Healthcare, Grünenthal, H. Lundbeck, Helmsley Charitable Trust, Icon Clinical Research, Imcyse, Institut Pierre Fabresas, Intercept Pharma Europe, Intervet, Ipsen, JDRF, Kungliga, Labcorp, Leo Pharma, Life Molecular Imaging, Lundbeck, Menarini, MSD, Merial, Ontario Institute for Cancer Research, Orion, Otsuka Novel Products, Pharmamar, Psychogenics, Rentschler, Seqirus, Teva, Transgene, UCB, VFA, Vifor, Zoetis.

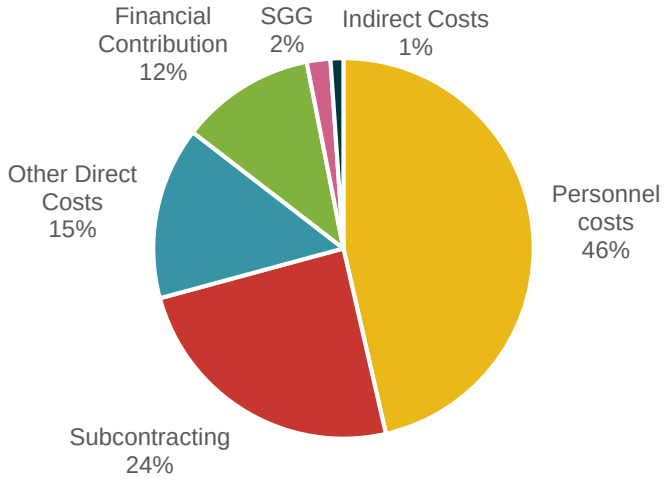
IMI2 EFPIA and Associated Partner reported contributions by cost category

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 and other direct 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), where significant tasks are subcontracted.

Ex-post controls of the in-kind contribution under IMI1

In addition to the ex-post audits covering IMI funding to beneficiaries, the Programme Office also continually conducts ex-post reviews and financial audits on the declared in-kind contributions by EFPIA companies participating in IMI projects. These companies do not receive any IMI funding, but contribute their own resources in kind to the projects in which they participate.

The purpose of these controls, using a risk-based approach as per the JU's audit strategy, is to independently verify that the in-kind contributions accepted by the JU have been effectively committed to the projects. Each control exercise consisted of two key elements: an ex-post review, followed by a financial audit.

Ex-post review: This is a review of the in-kind methodology used by the EFPIA companies to declare in-kind contributions for all the IMI1 projects in which they participate, applying agreed-upon procedures to confirm the factual basis of the responses and descriptions provided in the submitted certificate on in-kind contribution methodology. On this basis, the auditors are able to conclude whether:

- the approach and basis of the actual calculations were as originally described in the accepted methodology;
- whether any mathematical errors or other inconsistencies were noted in the actual calculations made relating to the direct personnel full time equivalent (FTE) daily cost rate;
- the in-kind methodology was consistently applied by the EFPIA company across all research and business activities and in accordance with its usual accounting and management principles and practices;
- the basis of the methodology and calculation was consistent with Article II.13.4 of the Grant Agreement and excludes ineligible costs.

Financial audit: This is a financial audit of a sample of in-kind contributions declared in the financial statements submitted by EFPIA companies to IHI in order to assess and present an opinion on whether these meet the conditions of the Grant Agreement.

Controls carried out by the JU on EFPIA companies' contributions are subject to scrutiny by the JU's internal and external auditors, namely the European Commission Internal Audit Service (IAS) and the European Court of Auditors (ECA).

Audit coverage of the in-kind contribution

To date, the JU has completed ex-post audits of 23 EFPIA companies, covering a total of EUR 753.3 million in accepted contributions to IMI1 projects or 98 % of all EFPIA contributions.

An overview of the audit coverage of the in-kind contribution (abbreviated to IKC in the tables below) provided by the EFPIA companies is detailed below:

Company	IKC validated as of 31/12/2021 (EUR million)
Total finalised audits	753.3
Total all EFPIA companies	766.7
Audit coverage	**98 %**

The audits finalised to date have identified adjustments, either positive ones thus increasing the contribution, or negative ones decreasing it, for a total value of EUR 7 562 476 corresponding to 1% of the total audited amounts.

Negative adjustments (EUR)	Positive adjustments (EUR)	Total absolute adjustments (EUR)	% of absolute adjustments
-5 362 344	2 200 131	7 562 476	1 %

2.7 Control systems and results

This section explains how the achievements described in the previous sections have been achieved by the Joint Undertaking[4]. It focuses on the control results and other relevant information that supports management's assurance on the achievement of the financial management and internal control objectives[5].

Assurance is an objective examination of evidence for the purpose of providing an assessment of the effectiveness of risk management, control, and governance processes. This examination is carried out by management who monitors the functioning of the internal control system on a continuous basis, and by internal and external auditors. The results are documented and reported to the Executive Director who periodically informs the Governing Board. The main elements examined are:

- management reports on control results, in particular the contribution of the Head of Unit in charge of Risk Management and Internal Control (RMIC), including the results of internal control monitoring, the annual self-assessment, the reports on recorded exceptions, non-compliance events and any cases of 'confirmation of instructions' (Art 92.3 FR);
- the reports on the ex-post audit results for FP7; and the CAS reports of the ex-post audits results for H2020;
- the observations and recommendations reported by the Internal Audit Service (IAS);
- the observations and the recommendations reported by the independent auditor and by the European Court of Auditors (ECA).

These reports stem from a systematic analysis of the evidence available. This approach provides sufficient guarantees regarding the completeness and reliability of the information reported and results in a complete coverage of the budget managed by the Authorising Officer.

The following paragraphs report about: (a) financial procedures, (b) control results, (c) and cost effectiveness of control procedures.

Financial procedures

In accordance with Art. 71 of the EU Financial Regulation 2018/1046 and Art. 60.2 of the Commission Delegated Regulation 2019/887, the JU adopted and implements appropriate financial rules, complemented by internal operating procedures. The key operational tool of the internal financial management is based on the Manual of Financial Circuits (including checklists and workflows) adopted by Executive Director (Decision No 55/2018).

These documents outline the financial processes applied and describe the responsibilities of the financial actors as well as the internal control framework applied to:

- ensure adequate management of the risks relating to the legality and regularity of the underlying transactions;
- safeguard IMI's assets;
- check the accuracy and reliability of recorded accounting data; and promote effectiveness and efficiency in financial operations.

The actions funded by IMI are managed through two different framework programmes - IMI1/FP7 and IMI2/H2020[6] - with different obligations and modus operandi. In this context, the activities embrace:

- continuous review and assessment of FP7 periodic and final reports (including updated templates for coordinators);
- effective implementation of the Commission IT operational tool for H2020 management (for Grant management, project monitoring, reporting and payment, audit implementation and recovery orders);

[4] Including both IMI2 JU up to 29.11.2021 and then the IHI JU as explained above.
[5] 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.
[6] See Section 2.5 'Budgetary and financial management'.

- active communication and cooperation with the CSC and working groups (e.g. the Common Legal Support Service, etc.), which enhance the common understanding of requirements and the management of H2020 workflows in the context of the JU environment.

2.7.1 Ex-ante controls on operational and administrative expenditure

In order to support the assurance on the achievement of the internal control objectives, this section is for reporting on and assessing the various kinds of expenditure (operational and administrative) and the programme management mode, with references to the budget coverage and the indicators set out.

In this report, assurance building, and materiality criteria are outlined in Chapter 4 and Annex 5.

The JU's annual budget is implemented through the administrative expenditure (related to staff and day-to-day activities – Titles 1 and 2 of the budget) and the operational expenditure (related to the management of the research programme and payments of beneficiaries - Title 3 of the budget)[7].

To assure the effective and efficient implementation of the operational expenditure, the Joint Undertaking has set out an internal control framework embedded across its organisational structure, which relies on a combination of ex-ante and ex-post controls as summarised in the following table. A key element of this system is the implementation of the Guidance of Horizon 2020 ex-ante controls on interim & final payments[8], which allows for a simplified and trust-based approach to beneficiary controls. In any case, based on lessons learned, the finance and the operational team performs ad hoc controls to ensure sound financial management and performs a proper risk assessment at the grant preparation phase.

	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 give 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.

[7] See Section 2.5 'Budget and financial management'.
[8] Adopted by the CSC Steering Board on 15 December 2016.

Overview of operational expenditure

The tables below show the balance between the actions implemented under the IMI1/FP7 and IMI2/H2020 programmes in terms of project portfolio and operational expenditure at the cut-off date of 31/12/2021.

IMI1 (FP7) project portfolio on 31/12/2021

Total projects funded			Pre-financing payments	Interim & final payments[9]
59	Running on 01/01/2021	8	10 242 451	10 242 451
	Ended[10] during 2021	(3)		
Total IMI1 projects running on 31/12/2021		**5**	**10 242 451**	**10 242 451**

IMI2 (H2020) projects portfolio on 31/12/2021

Total projects funded			Pre-financing payments	Interim & final payments	Total paid
123	Running on 01/01/2021	92	56 420 756	126 167 883	182,588,639
	Ended during 2021[11]	(9)			
	Signed in 2021	15			
Total IMI2 running on 31/12/2021		**98**	**56 420 756**	**126 167 883**	**182 588 639**

IMI1 and IMI2 full project portfolio on 31/12/2021

Total projects funded up to 31/12/2021			Pre-financing payments	Interim & final payments	Total paid
182	**Running on 31/12/2021**	**103**	**56 420 756**	**136 41 334**	**192 831 090**
	Ended during 2021	(12)	/	/	/

Control results on the operational budget implementation

The following sections provide an overview of the functioning and outcomes of the ex-ante controls performed on the overall management cycle implementing the JU's operational expenditure.

I - Call management, Selection and Evaluation phase (SEP)

The Joint Undertaking awards its grants to selected proposals in a competitive evaluation procedure following the publication of Calls for proposals. For each year, the Calls for proposals are established in the work plan adopted by the Governing Board. Annual work plans as well as announcements of individual Calls are published on the JU's website, and in the Commission 'Funding and Tenders Portal'.

[9]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).
[10] IMI1 projects which have ended their activities and presented or are yet to present their final report.
[11] IMI2 projects which have ended their activities and presented or are yet to present their final report.

The goal of controls performed at this stage is to make sure that the best proposals are selected; that they match the conditions set out in the Call for proposals; and that the beneficiaries can complete the projects successfully and on time. To this end, the following checks are performed:

- Eligibility checks, to make sure that the proposals are submitted according to the rules and that they follow the eligibility criteria defined in the work programme.
- Evaluation of the proposals by external experts. Controls ensure the quality of the experts selected to evaluate the proposals. IMI also makes sure that the experts do not have any conflict of interest.

In 2021 there were no new Calls launched due to the transition to the new research programme and the new Joint Undertaking, IHI JU. However, a large part of the year was devoted to finalising IMI2 - Calls 20, 21, 22 and 23, with a total of 14 topics launched in 2020. The results achieved in previous years - with 100 % of publication and relatively few percentages of redresses - show the robustness of the procedures set out by the JU.

Indicator	Results 2021	Results 2020	Results 2019	Results 2018	Results 2017
Coverage of Call topics planned in the AWP	**N/A**	100 %	100 %	100 %	100 %
No. redress procedures on the result of the evaluation	**4**	9	2	1	0

II - Grant Agreement preparation phase (GAP)

Grant Agreement preparation starts after the evaluation, and upon approval of the results by the Governing Board, with the GAP invitation letter, no later than 5 months after the Call deadline (time-to-inform / TTI). In this phase, the Grant Agreement (GA) is prepared and signed. The IMI Programme Office checks administrative data submitted – including the budget and the legal and financial status of each participant; gives consortia the opportunity to correct shortcomings identified by the independent experts in their evaluation; and ensures that the description of the action (DoA) matches the proposal. The result of the checks performed is documented in the grant preparation report. The pre-financing is transferred to the consortia as soon as the Grant Agreement is signed to enable the timely start of project activities.

In 2021, IMI2 JU confirmed and consolidated the efficiency and robustness of its granting process as reflected by the three performance indicators described in the following table. This is the result of the efficient management of the H2020 IT management tools, the quality control ensured by the grant coordinator, and the enhanced management supervision and regular monitoring.

- **Time to Inform (TTI)** represents the time needed by IMI2 JU to manage the evaluation and selection phase from the Call deadline to informing the participants. In 2021, the average TTI was 75 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 2021, the average TTG was 223 days, against the target of 245 days.

- **Time to Pay (TTP)** represents the outcome of the process for the payment of pre-financing to newly signed Grant Agreements and costs claimed by beneficiaries. The average TTP of costs claims and final payments (considering IMI1 and IMI2 together) was 61 days, continuing the positive trend of previous years.

Indicators	Target	Results 2021	2020	2019	2018	2017
Total average Time to Inform (TTI)	**153 days**	**75**	67	73	75	81
Total average Time to Grant (TTG)	**245 days**	**223**	190	210	232	270
Total average Time to Pay (TTP) for pre-financing	**30 days**	**10**	6	9	9	11
Total average Time to Pay (TTP) for cost-claims and final payments	**90 days**	**61**	63	57	59	/

III - Grant Agreement implementation phase

In this phase, the Programme Office plays a crucial role in forecasting, monitoring and checking the operational expenditure of both public funds and in-kind contributions related to the activities of its funded projects.

Scientific and Financial Officers check the projects' periodic reports to ensure that costs claimed by public beneficiaries are justified and that Grant Agreement rules are adhered to. The checks focus on the deliverables, the technical report summarising the work done, and the costs reported by beneficiaries as well as by (EFPIA) pharmaceutical companies (the in-kind contribution) and Associated Partners. As nearly 95 % of the annual budget is related to operational expenditures, a lot of effort goes into trying to get the closest estimate of our budget needs for the ongoing and coming years to reach the best budget execution rate, hence there is a close interaction with the budgeting and accounting functions of the Joint Undertaking.

In practice, the control of costs claimed by beneficiaries is triggered when the Programme Office receives the periodic or final report. The ex-ante control procedure is performed in accordance with the workflow, checklists and templates defined in the Vademecum on monitoring, reporting and payment, set out by the Common Support Centre of the EC. Before authorising any payment, the financial team verifies that:

- The project is progressing as planned and demonstrates the necessary level of achievement.
- Resources are being used according to the indicative plan in the description of work/action (DoW/DoA, e.g. FTEs associated to each of the work packages, subcontracts, 'other direct costs', etc.). In particular, costs are compared to the work done: if the costs (including person months per work package) are reasonable based on the work reported, and if there are significant deviations from the work as planned in the description of work (on the basis of the SO assessment report).

During the implementation of projects, the Programme Office monitors the progress of their work plan not only through the systematic review of the periodic (annual) technical reports, but also through interim reviews of each project. The review is performed by independent experts and their recommendations are closely followed up by the project managers[12].

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 costs paid is provided by the ex-post audits carried out at the beneficiaries' premises, after the costs have been incurred and declared (see Section 2.7.4). Ex-post audit can occur up to 5 years after a project is closed. In case of findings, they are also implemented as part of the project management cycle. This can result in the team working for many months on the file, even though the project has reached its official end date.

The following paragraphs report and assess the elements identified by management that support the assurance on the achievement of the internal control objectives regarding the grant management process.

[12] More information can be found in Section 1.4.2 above.

a) Volume of operational transactions

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

The tables below provide a multiannual overview of operational transactions, including both pre-financing payments (made to new projects selected) and interim and final transactions[13] made to ongoing projects funded under the FP7 and H2020 programmes. Having in mind the complexity embedded in the concept of 'transactions', the trend shows that in 2021 the number of financial transactions related to IMI projects has further increased.

Number of operational transactions

	2021	2020	2019	2018	2017	2016	2015
Pre-financing payments	**16**	25	29	20	16	16	16
Interim and final payments[14]	**83**	76	62	70	66	59	30
Total	**99[15]**	101	91	90	82	75	46

The number of transactions handled in 2021 confirms the peak of activities in the management of the research programmes (FP7 for IMI1 and H2020 for IMI2), and this trend will continue in the coming years with the start of the new Horizon Europe programme. That will represent an important challenge for the Programme Office of the IHI JU. The Programme Office was able to maintain a positive trend in the Time to Pay (61 days, see table above) regardless of the limitations due to the pandemic. This is a significant indicator of effectiveness and efficiency due to the complex nature of the projects implemented by IMI and the amounts at stake per project[16]. The verification process of each transaction is particularly extensive and time consuming. In addition, a portion of the processed operational transactions involves final payments to the projects (5 out of 99 in 2021); as a rule, the payment of the final balance needs a more in depth and extensive analysis and assurance elements in comparison to interim payments.

The table below give a picture of the modalities of the reporting process, where the number of cost claims processed (83, line 4) during the year may not match with the number of reports received (89, line 2). That 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.

Cost claims received with project reports against payments made

		2021	2020	2019	2018
1	**Cost claims received before 01.01.2021**	**16**	**14**	17	7
2	**Cost claims received during 2021**	**89**	**77**	57	80
3	**Cost claims not validated at the end of year 2021 (to be paid the following year)**	**22**	**16**	14	17
4	**Cost claims processed during the year (1+ 2 - 3)**	**83**	**75**	62	70

[13] 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 IMI. In technical terms, the clearing is the recognition of costs incurred against the pre-financing paid to projects.
[14] Including the clearings of pre-financing.
[15] Of which, 7 on IMI1 projects and 92 on IMI2 projects.
[16] Average EUR 30.3 million (with projects having a budget higher than EUR 200 million) and the high number of participants per project (average 26).

5	a. Pre-financing new projects	**15**	18	29	20
	b. Complementary pre-financing	**0**	7	0	0
	c. Pre-financing grant signed on previous year	**1**	NA	NA	NA
6	**Total Transactions (4 + 5)**	**99**	**101**	91	90
6	**Value of all transactions (in EUR)**	**242 114 926**	**260 m**	**245 m**	**254 m**

b) Value of operational transactions

The breakdown of the costs accepted and paid in 2021 based on the operational transactions described above is presented in the table below. In line with the increased volume of transactions, the value of payments reached the value of EUR 242 114 926, of which EUR 192 831 090 was actually paid to beneficiaries as pre-financing and interim/final payments, while EUR 48 877 536 are the result of full and partial clearing made against pre-financing paid at the beginning of the project.

Overall, it is worth noting that the continuous improvements in the project management workflow and the coordinated effort made by the staff overcame the difficulties linked to the COVID-19 pandemic period, ensuring business continuity and resulting in a considerable 96.04 % of operational budget execution in 2021. This demonstrates that staff high professionalism, cautious planning and enhanced monitoring of payment appropriation absorption yielded a positive result.

		No of transactions		Value of payments	Value of clearings[17]	Value of all transactions
IMI1 (FP7)	Pre-financing payments	0		0		0
	Interim payments	**5**	**7**	**10 242 451**	**13 170 598**	**23 413 049**
	Final payments	**1**				
	Full Clearing	**1**				
IMI2 (H2020)	Pre-financing payments	**16**	**92**	**56 420 756**	**N/A**	**56 420 756**
	Interim payments	**67**		**126 167 883**	**35 706 938**	**161 874 821**
	Final payments	**4**				
	Full Clearing	**5**				
TOTAL		**99**		**192 831 090**	**48 877 536**	**242 114 926**
Annual approved budget 2021				**200 537 921**		
Annual budget after recoveries				**200 781 983**		
Budget execution %				**96.04 %**		

[17] Which includes both full and partial clearing.

c) Costs rejected following ex-ante controls

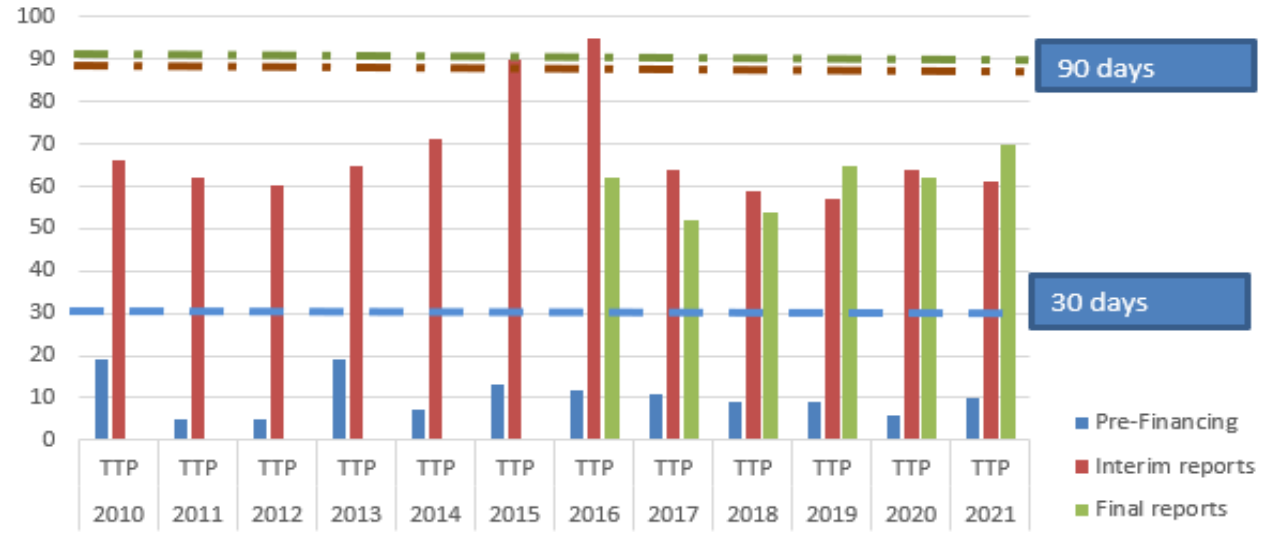
In order to monitor and measure the efficiency of the ex-ante controls, another key indicator is the percentage of declared costs considered ineligible (i.e. rejected) by the Programme Office. In 2021, the financial impact of the systematic ex-ante controls on the cost claims results were in line with previous years for the H2020 programme, while it is progressively reducing for FP7 as far as the grants are achieving their conclusion.

Total reported costs	**IMI1**	**24 127 767**	**187 314 509**	**100 %**
	IMI2	**163 186 742**		**100 %**
Accepted costs	**IMI1**	**23 413 050**	**185 287 871**	**97.04 %**
	IMI2	**161 874 821**		**99.20 %**
Rejection	**IMI1**	**714 717**	**2 026 638**	**2.96 %**
	IMI2	**1 311 921**		**0.80 %**

d) Time to Pay (TTP)

Figures of 2021 confirm the positive trend undertaken by IMI. The TTP average remains at a positive level for pre-financing with 10 days (out of 30 timeline), while we reached 61 days (out of 90 timeline) for interim/final payments, which need considerable checks and exchanges with the consortia. Within this global average, interim payments have been managed in 61 days, while final payments required 70 days to be finalised. The following chart summarises the average time to process payments against the deadlines set by the Financial Regulation and shows IMI's performance over the years.

Average TTP for operational transactions



Control results on administrative transactions

Regarding administrative expenditure, the indicator analysed is the TTP for all transactions, with a focus on expert payments. The commitment and payment execution for the overall administrative expenditure (Title 1 and 2) has been already presented above (Section 2.4.7). This section analyses the result of the control activities over 'running costs' i.e. costs related to Title 2 of IMI budget, which does not include staff-related costs. The purpose is to demonstrate the efficiency of the administrative financial activities of the JU and the effectiveness of the controls performed. As shown by the figures below, the JU continued to deliver very efficient services to its external or internal stakeholders through the timely payment of contractors and

experts as well as the revision of the procedures implemented, made more flexible and cost-effective to cope with the new socio-economic context created during the pandemic.

Administrative transactions made in 2021

	No.	%	TTP Average	Amount paid (EUR)	%
Total no. payments (including experts)	469	100 %	9 days	3 863 042	100 %
No. payments on time (within 30 days)	455	97 %		3 831 507	99 %
No. late payments	14	3 %		31 535	1 %

Expert payments made in 2021

No of payments	189	100 %
No of late payments	9	5 %
No of payments on time	180	95 %
Average time to pay	9	/
Total amount paid	EUR 338 535.00	/

Both the average TTP and the number of late payments for the administrative transactions improved in 2021 compared to the previous year. The average TTP in 2021 was 9 days against 12 days in 2020. Late administrative payments were furtherly reduced to 3 %, demonstrating that the measures taken to control the workflow and to deal with the impact of pandemic were effective[18].

[18] The 5 % of late payments (corresponding to 9 transactions) registered for experts were due to the year end operations. Those requests were received after the closure of the financial year 2021 and could therefore be paid only once the system was reopened in January.

2.7.2 Ex-post control 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 described in section 2.7.1

Since the legal basis and the budgetary frameworks are different, IHI reports separately on the IM1 programme under FP7 and the IMI2 programme under Horizon 2020. It should be noted that out of the cost claims paid out in 2021 for the total value of EUR 185 287 871[19], some 87 % of the costs (EUR 161 874 821) are paid under H2020 Grant Agreements, compared to EUR 23 413 050 under FP7 Grant Agreements.

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 and 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 the JU 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 IHI 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 5 – 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 5 – 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 the JU and the fact that the JU 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, the JU also works continuously to better inform beneficiaries of any pitfalls to help them report their costs correctly.

[19] This amount includes the costs accepted against pre-financing (clearing) but excludes pre-financings which remain IHI assets.

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

Resources

Since the lean structure of the JU 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 Programme Office remains responsible for the management of ex-post audits under FP7 operational expenditures, 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) compared to the total number of projects, in terms of the number of beneficiaries and projects as well as the accepted costs.

	Total population	Audited	Audit coverage
Beneficiaries	681	251	37 %
Projects	59	58	98 %
Contributions accepted by JU (EUR, cumulative)	**707 251 582**[20]	**123 856 206**	**17.51 %**

The following table gives an overview of the status of individual audit assignments as of 31 December 2021.

	Total audits	Audits finalised[21]	Audits ongoing
Representative	274	270	4
Risk-Based	21	17	4
Total	**295**	**287**	**8**

In 2021, 15 audits were finalised in total. One sample of representative audits was drawn in May 2021.

Representative and residual error rates as of 31 December 2021

At this point, the **cumulative Representative Error Rate** (RepER) resulting from all representative audits finalised by 31 December 2021 is 1.90 % in terms of JU contribution.

The **cumulative Residual Error Rate** (ResER: error remaining in the population after corrections and recoveries) is 0.81 % in terms of JU contribution. The residual error rate is thus below the 2 % materiality threshold established in Annex 5 of this report.

[20] Figure as of the cut-off date of 25 May 2021, corresponding to the last audit sample from which finalised audits were included in the current AAR.
[21] 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.

Implementation of audit results

When an audit report concludes that any amount has been unduly paid to a beneficiary, the JU launches the necessary corrective actions. Where the project is ongoing, the amount is offset against subsequent claims. Where the project is already closed, the JU 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 2021.

Number of cases of unduly paid amounts identified in audits	Number of cases implemented	Percentage of cases implemented	Amount implemented (EUR)
222	217	98 %	3 383 974

Extension of audit findings

When an audit detects findings of a systematic nature, the JU 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	287
Pre-information letters / letters of conclusion sent	287
Of which affected by systematic errors[22]	69
Extrapolation feedback received from beneficiary	69
Of which implemented	68
Amount implemented (EUR)	1 012 890

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

As regards the operational expenditure under H2020, the JU's ex-post controls of grants are aligned with the harmonised strategy adopted for the entire H2020 programme[23]. 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 for IMI2. The JU 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, the JU's cost claims are included in the programme level sampling, notably the H2020 common representative sample (CRS). Accordingly, the JU 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.

[22] This does not include positive systematic errors and systematic errors below the materiality threshold.
[23] Horizon 2020 Ex-post Audit Strategy (2016 – 2025).

However, as the IMI2 Regulation[24] 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 2021

The Horizon 2020 audit campaign started in 2016. At this stage, four Common Representative Samples with a total of 629 expected results have been selected. By the end of 2021, cost claims amounting to EUR 31.8 billion have been submitted by the beneficiaries to the services. The error rates on the H2020 programme level on 31 December 2021 are:

- Representative detected error rate: 2.29%[25]
- Cumulative residual error rate for the R&I family of DGs: 1.60 % (1.67 % for DG R&I).

Due to its multi-annual nature, the effectiveness of the control strategy of the Research and Innovation Directorates-General can only be fully measured and assessed in the final stages of the H2020 programme, once the ex-post control strategy has been fully implemented and systematic errors have been detected and corrected.

The above-presented error rates should be treated with caution. Since not all the results of the four CRS are available, the error rate is not fully representative of the expenditure under control. As H2020 is a multi-annual programme, the error rates, and especially the residual error rate, should be considered in 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.

Ex-post control specific to IHI's population in 2021

By 31 December 2021, the JU had launched seven individual representative samples (one sample of representative audits was drawn in June 2021). Audits were finalised from the first six samples. A total of 65 representative audits sampled by the JU were finalised. In addition, 8 risk-based audits were finalised by the end of 2021.

Audit coverage (cumulative)

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

	Total population	Audited	Audit coverage
Contributions accepted by IHI (EUR, cumulative)	**349 292 548[26]**	**54 394 102**	**15.57 %**

The following table gives an overview of the status of individual audit assignments as of 31 December 2021.

	Total audits	Audits finalised	Audits ongoing
Representative	90	65	25
Risk-Based	15	8	7
Total	**105**	**73**	**32**

[24] COUNCIL REGULATION (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking; Article 12.
[25] Based on the 418 representative results out of the 629 expected in the four CRS.
[26] Figure as of the cut-off date of 31 May 2021, corresponding to the last audit sample drawn in 2021.

Representative and residual error rates specific to the IMI2 population as of 31 December 2021

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

- Cumulative representative error rate (RepER) resulting from the 65 finalised audits considered representative is 0.97 % in terms of IHI contribution.
- Cumulative Residual Error Rate (ResER: error remaining in the population after corrections and recoveries) is 0.58 % in terms of IHI contribution.

Implementation of audit results and extension of audit findings

Following the finalisation of each audit by CAS, the JU 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 the implementation of audit results for the finalised audits on a cumulative basis, as of the cut-off reporting date of 31 December 2021.

Number of cases of unduly paid amounts identified in audits	Number of cases implemented	Percentage of cases implemented	Amount implemented (EUR)
39	35	90 %	915 147

Extension of audit findings

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	73
Pre-information letters / letters of conclusion sent	73
Of which affected by systematic errors[27]	8
Extrapolation feedback received from beneficiary	5
Of which implemented	5

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, the JU provides its opinion to the coordinating unit, the Common Audit Service, and implements the correction. As of 31/12/2021, the JU has implemented 10 out of the 13 extensions of audit findings triggered by audits performed by other EU services on IMI2 beneficiaries. The implemented amount of extensions of audit findings triggered by the JU or by other EU services on IMI2 beneficiaries is EUR 264 576.

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

2.7.3 Control efficiency and cost-effectiveness

The two sections below describe respectively the cost-effectiveness of the JU's controls related to the ex-ante phase and to the overall control cycle (including Call management and evaluation, and ex-post controls).

Cost-effectiveness of ex-ante controls on operational expenditure

The cost for ex-ante controls represents 1.06 % of operational expenditure in 2021 and can be quantified as EUR 21 877 per Grant Agreement.

Cost-effectiveness of all controls applied to the programme management cycle

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	Cost of overall controls / Total expenditure 2021 (Administrative and operational)	**1.12 %**
	Cost of overall controls / Operational expenditure 2021	**1.17 %**
	Cost of overall controls / Accepted cost 2021 (only beneficiaries' cost claims)	**1.27 %**
	Cost of overall controls / Total accepted cost 2021 (both beneficiaries' cost claims and validated industry contribution)	**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. In conclusion, the established control framework ensures the right balance between the efforts to simplify and minimise the administrative burden on beneficiaries, and the necessity to provide assurance as regards the sound financial management of the operational budget and the timely payments to beneficiaries, allowing them to conduct their research in line with the Grant Agreement.

Risk management

At the 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 objectives.

To that end, the JU implements a robust enterprise risk management (ERM) process based on the annual risk assessment exercise (RAE)[28]. The RAE is an important step in the definition of the annual objectives and priorities. It is also used as a key operational tool for day-to-day management. The RAE provides a comprehensive analysis of:

- the weaknesses and risks that might undermine the performance and capacity of the IMI2 JU to achieve its objectives;
- those risks that might be reduced and/or managed through mitigating measures.

Throughout the year, the Programme Office systematically monitored the evolution of the risks identified at corporate and operational levels in the annual RAE towards the AWP[29]. 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. This regular follow-up ensured that risk management was a

[28] The annual RAE is performed in accordance with the methodology defined in the IMI guidance for risk identification and assessment version 2013 DORA Ref. IMI/INT/2013-03397 and Risk Management in the Commission, Implementation guide version October 2018.
[29] RAE Report 2019/2020 of 16/10/2019 (ref. document: IMI2/INT/2019-01523; Ares: imi.admin(2019)6922591).

continuous, dynamic, and proactive process in view of evolving corporate priorities and considering that risks constantly develop, presenting new threats to the operations and strategy of the JU.

In a nutshell, the risk assessment for the achievement of the 2021 objectives identified seven corporate risks to be addressed, two of which were considered as critical by the management. The Strategic Risk Register provided detailed information about each one, the objectives affected, action taken and process owners.

Particular attention was dedicated during the year to the two critical risks, namely:

- COVID-19 pandemic: It continued to impact the implementation of all JU activities, putting at risk some objectives set out for the organisation. The Executive Director, supported by the Risk Management Working Group and relevant staff member continued to undertake pro-active actions to minimise the various impacts and, especially, the possible effect(s) on the business objectives.
- Uncertainties around the setting-up of the new European Partnership in Health within Horizon Europe might have challenged a smooth transition and had an impact on the IMI2 JU organisation and activities. The Executive Director, supported by the Risk Management Working Group and relevant staff members, has identified actions to be implemented in order to reduce the possible impacts.

For both those risks, the positive operational achievements of the year witness that they were well controlled, and the quality of the work done by the Programme Office was not impacted.

2.7.4 Fraud prevention and detection

The JU has an Anti-Fraud Strategy[30] aligned with the Commission Anti-Fraud Strategy (CAFS 2019) and the Common Anti-Fraud Strategy for the Research family (RAFS 2019), complemented by additional anti-fraud actions related to service contract management and administration.

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 2021, IMI's anti-fraud activities covered:

- Cooperation with the FAIR Committee activities,
- Increasing staff awareness on anti-fraud (including participation in the European Anti-Fraud Office (OLAF)'s conference: 'United against corruption – Upholding the ethical standards of EU Institutions' on 9 December 2021).
- Fraud risk assessment exercise. That task was twofold, one embedded in the annual anti-fraud 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.

Regular information on fraud-related risks and on the procedures to be used in case of suspicion of fraud/irregularities was communicated to the whole staff. Additionally, attention was given to cross-sectional issues such as risks linked with conflict of interest, delegation of authority, and segregation of duties.

As regards suspected fraud cases, the Programme Office made an internal analysis of a few suspicious cases identified during the ex-ante controls. The internal analysis did not identify any instances of irregularity or suspected fraud. No OLAF enquiries or requests for implementation or information have been received during the year.

[30] Adopted by IMI2 JU Governing Board on 27.04.2020 (IMI2-GB-DEC-2020-12) and extended to the IHI JU by GB Decision 03/2021.

2.8 Human resources management

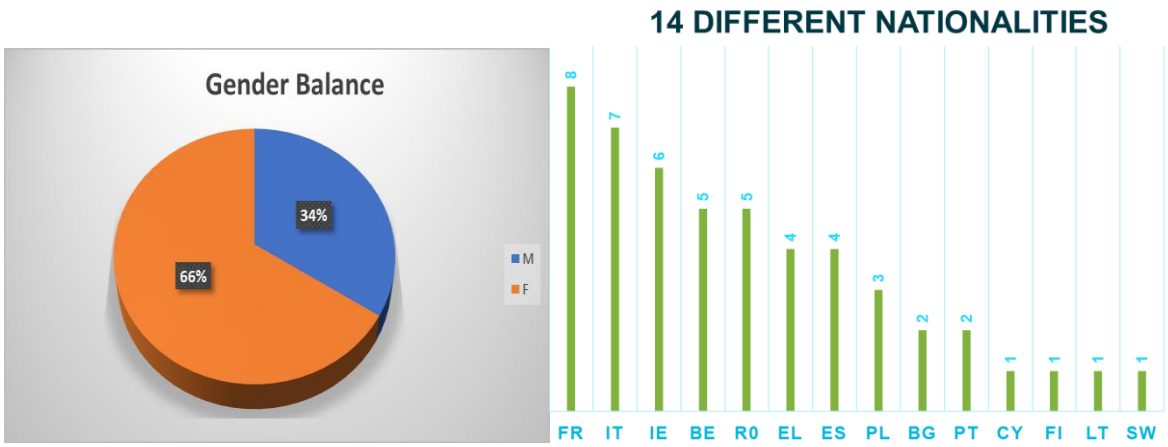
Staff and recruitment

The staff establishment plan (SEP) allows for 39 temporary agents, 15 contract agents and 2 seconded national experts (SNEs), in total 56 staff members. On 31/12/2021 there were 50 positions occupied: 36 out of 39 temporary agents (92.30 %), 13 out of 15 contract agents (86.70 %) and 1 out of 2 seconded national experts (50 %)[31]. The table below provides a summary of the staff planning.

	Positions planned in SEP	Positions filled on 01.01.2021	Resignations / end of service in 2021	Recruitment / appointment in 2021	Positions filled on 31.12.2021
Temporary Agents	39	37	3	2	36
Contract Agents	15	15	3	1	13
SNEs	2	1	N/A	0	1
Total	56	53	6	3	50

Due to the COVID-19 pandemic, all selection procedures were conducted remotely.

The two graphs below show the gender and geographical balance (14 EU nationalities were represented) within IHI on 31/12/2021.



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: in-kind contribution assessment, Qlik Sense training; some refresher training on monitoring project implementation in H2020 - risk module: EDES (Early Detection and Exclusion System), reinforced monitoring and double funding - recent developments. The HR and finance teams followed a tailor-made training course on payroll organised by PMO.

[31] Temporary Agents (TAs): the empty posts will be filled in 2022 as two selection procedures are on-going; Seconded National Experts (SNEs): in 2022 1 SNE post will be suppressed

- In-house soft skills and training courses such as appraisal exercise for all staff, performance management for managers, cybersecurity user awareness for JUs staff, Office 365; these sessions were delivered in cooperation with the other Joint Undertakings.
- Staff members also attended several online ‘soft’ and ‘hard’ skills courses, well-being lunchtime conferences and courses as well language training courses at the European Commission. The European Commission’s ‘EU Learn’ system helped IMI staff in the selection of their training needs, on both hard and soft skills.
- A specific well-being programme was developed for staff. It was composed of (i) 10 hour-long sessions on different well-being topics such as digital well-being, judgement detox, effective communication and active listening, individual and organisational resilience, dealing with disappointment, etc; (ii) a follow up coaching session on working in a time of COVID-19 for staff and managers organised at JU level; and (iii) online yoga sessions twice a week.
- 5 HR info sessions for staff and managers were organised in order to provide staff with a wider understanding of HR procedures and processes for example on teleworking, appraisal and reclassification exercises as well as induction training for newcomers.
- Weekly virtual staff check-in meetings were organised to ensure staff members’ well-being, to keep staff up to date on operational and HR matters, and to uphold the JU’s organisational culture also though virtual social events.

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 2021, in accordance with the Staff Regulations. As a result, 6 staff members (5 temporary agents and 1 contract agent) were reclassified to the immediate higher grade.

Staff regulations and implementing rules

During 2021, the JU continued working on the implementing rules in line with the new Staff Regulations and the EC Human Resources and Security Directorate General (DG HR) guidelines. In particular, comments were provided to the Standing Working Party (SWP) on two important draft COMMS decision on (i) laying down general implementing provisions on the conduct of administrative inquiries and disciplinary proceedings, to develop a specific model decision on administrative enquiries and disciplinary procedures for the EU Agencies and Joint Undertakings; and (ii) the implementation of working time and hybrid working.

2.9 IT and logistics

In the context of the ongoing COVID-19 pandemic and teleworking as a norm for the staff, IT activities in 2021 remain focused on maintenance and further development of appropriate and secure IT infrastructure and business support tools, in order to provide remote access, smooth collaboration and business continuity. Another major topic was IT's contribution to the transition to the new partnership.

Transition to IHI

The technology side of the organisational transition from IMI to IHI involved the following change enablement stages:

- Assessment and planning – during this phase we assessed the impact and potential risks on the IT environment and software system in place with the main objective to ensure that changes are made with as little disruption to the organisation as possible. Following the initial analysis, we identified two main areas of activities:
  - adjustments and re-configurations in the common JUs IT infrastructure, M365 tenant and own applications and platforms with new email addresses, domain name and corporate identity;
  - coordination with different EC services (EU Login, COMREF, EU Sign, eGrants etc.).

In the further detailed study, we engaged as main stakeholders some key business users from the programme office, external IT service providers (managed services, infrastructure architect, software development etc.) and relevant EC teams in charge of the shared services in place. We discussed and tested different technical approaches and finally came up with a detailed plan with expected technical steps (DNS records, domain certificates, system reconfigurations etc.), outcomes, resources, timeline, testing requirements, and ways to roll back the change if needed.

- Implementation – before proceeding with planned technical implementations, we communicated to the internal users all the details on anticipated downtimes and what to expect from the change, both in the short-term and over time (as per the change plan). Execution was done in a staging environment for different areas, mainly outside business hours, with the scheduled time for testing and validation, which is vital to ensure functional and non-functional requirements.
- Post-evaluation review determined that the transition:
  - met original objectives that were recorded and approved;
  - went smoothly, in a timely and effective manner;
  - without any significant unexpected side effects, user impact or service outages.

The IT team supported the procurement and development of the new website, including the data flow with the data warehouse.

Common IT infrastructure and Microsoft 365 online services

We share a common IT infrastructure and facilities with five other joint undertakings co-located in the White Atrium building and participate in formally established common IT governance. In 2021 we completed the implementation of all IT mitigation measures, recommended by the previously conducted data protection impact analysis (DPIA) and risk assessment on Microsoft 365's online services.

Based on the risk analysis outcome, a security implementation plan (SIP) was defined to ensure effective implementation of the M365 IT Security Plan. The SIP indicates details on the implementation of risk treatment plans where actions are defined to mitigate the risk to an acceptable level.

We organised series of tailored to our environment trainings, on OneDrive and SharePoint.

In line with the continual improvement principle and order to facilitate modern and flexible workplace, we delivered the following new services:

- Teams Voice (Unified communications) – integration of our landlines in MS Teams via SBC (session border controller) allowing standard phone calls directly from any device with MS Teams application.

- Virtual desktop - virtualisation technology that hosts a desktop operating system with predefined set of customised software on a centralised server in our IaaS (Infrastructure as a Service) data centre. It can be used as a BCP solution to allow users to work securely from any device via a standard internet browser, providing full access to the JUs' common IT infrastructure and EC internal applications (ARES, SYSPER, eGrants etc.).
- New VPN – Windows 10 VPN replaced deprecated Direct Access technology, providing a secure remote connection to JUs' infrastructure from all corporate windows devices.
- Teams meeting rooms – all meeting rooms are equipped with MS Teams natively compatible devices, offering a rich, collaborative experience whether users join remotely or from in the room (hybrid meetings).
- SharePoint collaborative platforms - as one of the first use case of M365, we initiated developments of collaborative platforms for the new governance bodies of IHI – the Governing Board and States Representatives Group.

Business support tools

In line with the current trend, the Programme Office continues to implement more and more EC tools to support the core business and administrative and financial workflows. In 2021 we were one of the first successful EUIBA to onboard the EUSIGN not only as a standalone tool but also as an integrated service in ARES. This new functionality simplifies the use of Qualified Electronic Signature (QES) for the responsible Authorising Officers and automatically generates the organisation ID (seal certificate) for the JU when needed. By adopting three internal workflows, the JU replaced blue-ink signatures with QES, which contributes significantly to the concept of a completely paperless office. Another important development in the integration towards the EC objective of digital transformation is the use of eProcurement with the e-Invoice as an example of another important tool adopted in 2021.

SYSTAL, common inter-JUs project for adopting Oracle SaaS Talent acquisition system, was completed successfully in 2021, replacing our internal outdated vacancies portal.

Enhancements of in-house applications

The following major new enhancements and change requests regarding the further development and maintenance of in-house applications were implemented.

- SOFIA (Submission of Information Application)
  - finalisation of major redesign and component updates following findings and recommendations from the vulnerability assessment carried out by CERT-EU (Computer Emergency Response Team);
  - improvements in the KPI (project outputs report) tool.
- Data Warehouse (DW)
  Our data warehouse was further extended with several new data sources, and now in addition to:
  - SOFIA - IMI1 projects and proposals, IMI2 proposals up to call 9
  - SEP DS – IMI2 proposals and evaluations after call 9 (including Stage 1 and Stage 2)
  - CORDA – IMI2 Projects (SyGMa/Compass) and reference data (PDM, countries, etc.)
  - website content management system (CMS) - tags assigned to projects (tools, programmes, disease areas, products, twitter etc.)
  - reference files (mainly data not available in our source systems) - e.g. groups of EFPIA companies, Partners in Research, ORG type grouping, SGG/SRA/WHO categories etc.
- It also includes:
  - publications data from Clarivate's annual report
  - project results from all previous AARs
  - news and success stories from the website CMS.

In-kind report monitoring tool – in order to monitor development of committed and reported in-kind contribution, with particular focus on non-EU, we added data on the Grant agreement stage in the data warehouse and developed a dedicated Qlik sense application.

Cybersecurity and collaboration with CERT-EU

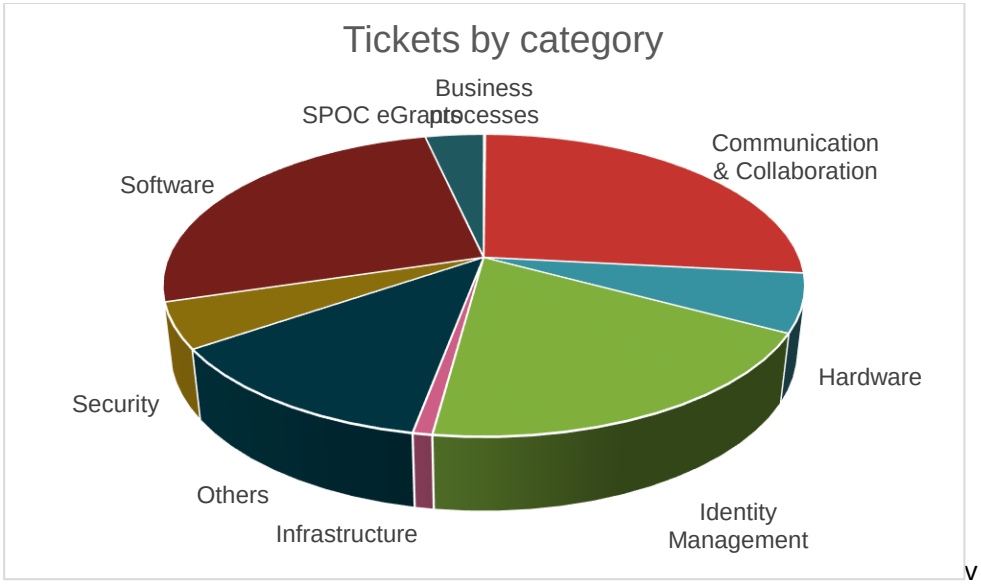
As coordinator for collaboration with CERT-EU on behalf of the 6 JUs, we organised four cybersecurity awareness sessions. Phishing exercises performed before and after those sessions clearly proved their efficiency and positive impact on general cybersecurity users' knowledge and responsible behaviour.

CERT-EU performed a web application security test on our web site, which provided useful input for security updates and improvements. We also benefited from information provide in their service portal, Malware Information Sharing Platform (MISP), announcements, advisories, and briefings. We participated in several workshops, seminars and an annual conference providing details on cyber threats and reinforced security policies.

We concluded separate SLA for a social media assurance service – a social media monitoring service that covers our brand (organisation accounts) and persons (Executive Director).

Servicedesk support

In 2021, a total of 967 requests for support were handled by the IT Helpdesk. The following graph depicts the various categories assigned to the tickets.



2.10 Data protection

In 2021, the JU pursued its efforts to render its processes and working methods fully compliant with Regulation (EU) 2018/1725, particularly as regards the use of its ICT assets. The JU participated in various interinstitutional data protection activities, including events held by the European Data Protection Supervisor (EDPS).

Following the release of the Microsoft 365 DPIA, the Data Protection (DP) team, in conjunction with teams from the other JUs, prepared and oversaw the adoption of a range of mitigating measures.

Most of the measures required the drafting of privacy statements and guidance on the use of M365. They have been adopted and registered on ARES with the cooperation of the JU teams involved.

In June 2021, a series of staff trainings on DP relating to M365 were held by the external contractor for all JUs' staff.

All the JUs' DP and IT Teams, through horizontal meetings, followed up the implementation of the mitigation measures and monitored the updates stemming from the contract between Microsoft and DIGIT.

In September, the IMI Data Protection team took over leadership role in the Joint JU Data Protection group until Spring 2022.

2.11 Access to documents

The JU registered one application for access to documents in 2021, pursuant to Regulation (EC) No 1049/2001. This request resulted in the partial disclosure of the documents sought.

2.12 Assessment of audit and ex-post evaluation results during the reporting year

2.12.1 Internal Audit Service (IAS)

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[32].

In 2021, IAS concluded an audit on Horizon 2020 grant implementation in IMI2 JU as originally planned in 2019-2021 Strategic Internal Audit Plan[33]. The objective of this audit was to assess the adequacy of the design and the efficiency and effectiveness of the internal control system in place in for the implementation of Grant Agreements under Horizon 2020 programme.

The scope of the audit covered the overall control strategy of IMI2 JU for grant implementation. It included controls on monitoring, reporting and payments as well as dissemination, communication and exploitation, suspensions and early termination of Grant Agreements, the management of amendments, and recovery orders.

The auditors recognised the ongoing efforts made by IMI2 JU to ensure exemplary management of grant implementation. According to the final audit report, the overriding strength of the JU is the commitment and dedication of the project officers and financial officers, and their line managers, who oversee the implementation of the Grant Agreements.

The final IAS audit report[34] importantly concludes that the internal controls put in place by the Joint Undertaking for the implementation of Grant Agreements under Horizon 2020 are overall adequately designed and efficiently and effectively implemented.

The audit did not identify any critical or very important issues. However, the IAS considered that there was some room for further improvement and issued five 'important' recommendations[35] on fraud risk assessment, the implementation of ex ante controls before payment, the modalities of project monitoring, managing and processing requests for amendments to Grant Agreements, and the monitoring and enforcement of dissemination and exploitation requirements.

[32] IAS note on Organisational Independence of the Internal Auditor and results of the External Quality Assessment Ares (2021)439646 of 20/01/2022.
[33] Ares(2019)4058461 - 26/06/2019
[34] Ares(2021)659720 – 27/01/2022
[35] IAS classification of audit recommendations – Levels of significance are categorised as 'critical', very important', 'important'.

2.12.2 European Court of Auditors (ECA)

Audit on IMI2 JU annual accounts for the financial year 2020

On 12 November 2021, the European Court of Auditors (ECA) published a specific 'Annual report on the EU Joint Undertakings for the financial year 2020'[36] as well as the summary document '2020 audit of EU Joint Undertakings in brief'[37].

While the audit work for the financial year 2020 was performed by a dedicated ECA team, no individual report was issued on IMI. IMI is presented in the dedicated paragraphs of the joint report.

The ECA gave a clean bill of health for IMI2 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 on the following subjects:

- *Implementation of the 2020 budget* – the auditors noted that Title 2 (infrastructure expenditure, representing around 3 % of the JU's total available payment budget) budget execution was low (51 %) because of the accumulation of unused payment appropriations and aggravated by the impact of the COVID-19 pandemic on planned costs for IT, communication, meetings, events, and other services.
- *Internal controls* – the auditors confirmed that ex-ante control procedures based on financial and operational desk reviews are reliable; the internal control framework is implemented. As part of the operational payment controls, the auditors randomly sampled Horizon 2020 payments made in 2020 at the level of the final beneficiaries, to corroborate the ex-post audit error rates. These detailed audits revealed only one case with an error above 1 % of the audited costs related to the declared direct costs.

Audit on IMI2 JU annual accounts for the financial year 2021

In accordance with Article 54 of the JU Financial Rules, the 2021 annual accounts are audited by the external audit company. The specific contract signed in 2020 with Baker Tilly Belgium[38] covers the financial years 2020 and 2021. The audit work for the accounts for 2021 will be completed by issuing an opinion on the final accounts by 15 June 2022.

The Court of Auditors will draw the final audit opinion on the 2021 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 2022.

ECA performance audit

In 2021, the JU was selected for an in-depth review in the context of a performance audit on the cybersecurity of EU institutions, bodies and agencies[39]. The Programme Office responded to the questionnaire on cybersecurity arrangements as well as cooperation arrangements between EUIBAs. In subsequent interviews, the Programme Office explained common IT arrangements for the six JUs located in the same building. The audit team noted that sharing IT governance, infrastructure and services is a relevant synergy and serves as a good practice.

[36] www.eca.europa.eu/en/Pages/DocItem.aspx?did=59817
[37] www.eca.europa.eu/en/Pages/DocItem.aspx?did=59967
[38] Implementing Framework contract BUDG19P014
[39] ECA Special report 05/2022: Cybersecurity of EU institutions, bodies and agencies : Level of preparedness overall not commensurate with the threats published on 29 March 2022. See also https://www.eca.europa.eu/en/Pages/DocItem.aspx?did=60922

2.13 Follow up of recommendations and action plans for audits and evaluations

The JU prepared an action plan that was approved by the IAS on 2 June 2021. All five accepted recommendations were translated into 27 actions. 26 actions (addressing four and a half recommendations) were implemented by the end of 2021 in accordance with the agreed deadlines. One remaining action is ongoing with the implementation deadline in 2022.

The JU has provided evidence of the action plan implementation and requested IAS to review the documentation. The IAS performed the assessment and closed four recommendations. The closure was confirmed by an IAS letter in March 2022[40].

IMI acted upon the ECA's comments on administrative budget implementation and took immediate measures. For 2021, IMI2 carried over a lower amount of administrative payment appropriations than the amount of commitments carried forward to 2021 under Title 2. The difference was paid out of 2021 fresh credits (C1).

The corrective measures put in place yielded results. In 2021, budget implementation for Title 2 reached 68 % and 81.88 % for title 1 and 2 together (the so-called administrative budget). In other words, the JU has honoured the commitment expressed in the replies to ECA 2020 report.

2.14 Follow up of recommendations issued following investigations by the European Anti-Fraud Office

There are no pending recommendations from any investigation, and no follow up actions were required.

2.15 Follow up of observations from the Discharge authority

The European Parliament decided to grant the Executive Director of IMI2 JU discharge regarding the implementation of the JU's budget for the financial year 2019 by an ample majority. Following the European Parliament vote on the 28 April 2021[41], the accounts for 2019 were closed and approved.

In the framework of the 2019 budgetary discharge, the European Parliament also adopted a resolution[42] containing a series of observations. In accordance with Articles 55 and 57 of JU's Financial Rules, the Executive Director informed the Governing Board and sent to the European Parliament the report on measures taken in light of the Discharge Authority's observations on the implementation of the budget of 2019 with the aim of further improving IMI's operations[43].

[40] See ARES (2022)2393054 of 31/03/2022
[41] Decision (EU, EURATOM) 2021/1670 of the European Parliament of 28 April 2021 and Decision (EU, Euratom) 2021/1671 of the European Parliament of 28 April 2021. See full text: eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2021:340:TOC
[42] Resolution (EU) 2021/1672 of the European Parliament of 29 April 2021 with observations forming an integral part of the decision on discharge in respect of the implementation of the budget for the Innovative Medicines Initiative 2 Joint Undertaking for the financial year 2019
[43] https://www.europarl.europa.eu/committees/en/cont/discharge-procedure/discharge-2019?tabCode=jus

3 Assessment of the effectiveness of the internal control system

3.1 Effectiveness of the internal control system

The internal control framework (ICF) implemented throughout the JU is intended as a process applicable at all levels of management and designed to provide reasonable assurance that:

- operations are effective, efficient and aligned with the strategy;
- financial reporting is reliable; and
- the JU complies with the applicable laws and regulations.

The JU's internal control framework[44] is based on 17 control principles aligned with the Commission control framework[45]. All the principles of the new 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, and promotion of ethical behaviour.

Within this context, the Executive Director steers and supervises the risk and internal control management assisted by the Head of Administration and Finance - as risk management and internal control manager (RMIC) - the management team and the audit manager. The Programme Office at all levels ensures the implementation of the internal control framework.

Management assessment of the effectiveness of the internal control system

The self-assessment of the effectiveness of the internal control framework in 2021 is based on the criteria set out in the implementation guidance, namely:

- a set of pre-defined indicators complemented by targets and baselines;
- interviews with the management team and analysis of the results of the questionnaire on the functioning of internal control;
- implementation of the operating procedures developed or revised in 2021;
- an objective examination of reports and assessments carried out by management and by internal (Internal Audit Service) and external auditors (independent financial auditors and the European Court of Auditors) as well as a management's overview on progress made on the implementation of the corresponding action plans.

In order to assure that all aspects of the operations and control (financial management, governance, administration and horizontal support, procurement and contracts, HR, IT, communication) were covered by the assessment, the 17 control principles have been analysed both individually and as part of the corresponding control component[46].

Register of exceptions and non-compliance events

The Programme Office keeps a register of all exceptions and non-compliance events; reports are entered into the register through a dedicated procedure and using pre-defined templates. The register is reviewed regularly by the risk management and internal control (RMIC) manager, the Internal Audit Service (IAS) and, in the course of the Declaration of Assurance (DAS) procedure, by the European Court of Auditors (ECA).

In 2021 two register of Exceptions and Non-Compliance Reports were managed:

[44] GB Decision of 20 December 2017 (IMI2-GB-DEC-2017-28) and extended to the IHI JU by GB Decision 03/2021.
[45] Adopted by the European Commission on 19 April 2017. The revised ICF moves away from a compliance-based to a principle-based system. It provides the necessary flexibility to adapt to specific characteristics and circumstances while ensuring a robust internal control with a consistent assessment throughout the IMI2 JU. This approach aims at helping the organisation to achieve its objectives and sustain operational and financial performance.
[46] The IHI ICF consists of 5 internal control components: "Control environment", Risk assessment", "Control activities", "Information and Communication" and "Monitoring activities".

- one related to IMI2 JU activities until its transition to the new IHI JU on 29.11.2021;
- one related to IHI JU activities as from the 30.11.2021 till 31.12.2021.

The reasons of the events reported have been analysed by the management in order to further strengthen the internal control system, ensure compliance with rules and procedures, and further improve the efficiency and effectiveness of the operations. Related risks and financial impacts have been assessed and monitored when material, corrective measures were introduced (e.g. training for staff, internal instructions, etc.). IHI JU will continue to raise awareness among the staff and encourage them to participate in trainings on financial procedures and the payment life cycle.

Safeguard of JU assets

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 foreseen in the internal procedure.

Annual evaluation of the IMI local financial systems by DG BUDG

The 2021 annual evaluation (related to financial year 2020) of IMI local financial systems was performed by DG BUDG according to Article 25 (d)of the JU Financial Rules. The evaluation has not identified 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.

3.2 Conclusions of assessment of the internal control system

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. The continuous efforts to improve quality management allowed the Programme Office to implement a number of specific actions (such as targeted presentations to staff, trainings on operating procedures adopted, etc.) that ensured the compliance of the overall control system and allowed the JU to improve its efficiency, and to better cope with the particular circumstances of 2021. In this context, risks that might pose a threat to the achievement of the JU objectives were systematically managed and controlled.

In conclusion, the JU has assessed its internal control system during the reporting year and has concluded that it is effective, and the components and principles are present and functioning well. Areas where further improvements can be made have been identified and will be prioritised in 2022.

4 Management assurance

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 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 management team[47];
- reporting by the internal control and risk manager;
- results of ex post control (ex-post audits on beneficiaries and verifications of industry partners' contributions);
- Governing Board assessment;
- Stakeholder Forum feedback.

Findings and opinions from internal and external audits:

- reports and follow up notes by the Internal Audit Service;
- recommendations by the JU audit manager;
- reports by independent financial auditors;
- reports by the European Court of Auditors.

External verifications and investigations:

- 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.

The information gathered from the sources of assurance covers both the operational budget related to the FP7 and H2020 programmes, as well as the administrative budget managed in 2021, and supports the statement of the Declaration of Assurance. Management assessment provides the results of key indicators related to budget execution, addressing the statement on the 'use of resources for the intended purpose'. It further assesses the 'sound financial management' and the 'legality and regularity of underlying transactions' per process stage and reports on measures implemented to prevent, detect and correct fraud.

No significant weaknesses were identified or reported. 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 5.

[47] Head of Administration and Finance, Head of Scientific Operations, Head of Communications and Institutional Relations

The overall cumulative residual error rate is below 2 % for both operational programmes. The control strategy foresees 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.

4.2 Reservations

There are no reasons for introducing any reservations.

4.3 Overall conclusion

In conclusion, management has reasonable assurance that, overall, suitable controls are in place and work as intended; risks are being appropriately assessed, monitored and mitigated; necessary process improvements and reinforcements are being implemented. The Executive Director, in his capacity as the Authorising Officer, has signed the Declaration of Assurance.

4.4 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 Revision of IMI2JU 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, June 2022

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, June 2022

signed

Hugh Laverty, Head of Scientific Operations

5 Declaration of assurance

I, the undersigned,

Executive Director 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 [48].

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, June 2022

signed

Pierre Meulien

48 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: Key performance indicators

- Table I - Horizon 2020 Key Performance Indicators common to all JTI JUs
- Table II - Indicators for monitoring H2020 Cross-Cutting Issues common to all JTI JUs
- Table III - KPIs specific to each single JU

Annex 2: Project outputs

Annex 3: Publications from projects

Annex 4: Patents from projects

Annex 5: Materiality criteria

Annex 6: Organisational chart

Annex 7: Staff establishment plan

Annex 8: Annual Accounts

Annex 9: List of projects

Annex 10: List of acronyms

Annex 11 Analysis and assessment of the Consolidated Annual Activity Report 2021 (CAAR 2021) by the IHI JU Governing Board

Annex 1: Key performance indicators

This annex sets out the key performance indicators relating to the IMI2 programme and Horizon 2020. We will report on Horizon Europe / IHI indicators once we have data on them.

Table I - Horizon 2020 Key Performance Indicators common to all JTI JUs[49]

	Correspondence to general Annex 1	Key Performance Indicator	Definition / responding to question	Type of data required	Target at the end of H2020	Results in 2021
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)	[On average, 20 publications per EUR 10 million funding (for all societal challenges)]	30.54 %

[49] Table I 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 tables I and II, 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 2021
				data to be collected by commercially available bibliometric databases.		
	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 5 patents awarded
	16	Number of prototypes testing activities and clinical trials[50]	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: Prototypes: 116 Testing activities: 170 Clinical trials: 88
	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]	529 27.24%
	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: New products: 35 New processes: 23 New methods: 25
EVALUATION	**NA**	Time to inform (TTI) all applicants of the outcome of the evaluation of their application from the final date for	To provide applicants with high quality and timely evaluation results and feedback after each	Number and % of information letters sent to applicants within target	153 calendar days	No. of Short Proposal information letters: 0 No. information letters for Full Proposals: 12 (100 % on time)

[50] Clinical trials are IMI specific.

	Correspondence to general Annex 1	Key Performance Indicator	Definition / responding to question	Type of data required	Target at the end of H2020	Results in 2021
		submission of completed proposals	evaluation step by implementing and monitoring a high scientific level peer reviewed process	Average TTI (calendar days) Maximum TTI (calendar days)		Average TTI: 74.5 days
	NA	Redress after evaluations	To provide applicants with high quality and timely evaluation results and feedback after each evaluation step by implementing and monitoring a high scientific level peer reviewed process	Number of redresses requested		There were 4 redress requests in 2021. For 3 cases, no grounds were found to support any of the complaints. For 1 case, the redress committee considered that the complaint was founded and a re-evaluation of the specific criterion affected was carried out. The results of this re-evaluation had no impact on the final ranking of the evaluation.
GRANTS	**NA**	Time to grant (TTG) measured (average) from call deadline to signature of grants	To minimise the duration of the granting process aiming at ensuring a prompt implementation of the Grant Agreements through a simple and transparent grant preparation process	Number and % of grants signed within target Average TTG in calendar days Maximum TTG in calendar days	TTG < 245 days (as % of GAs signed)	15 out of 15 (100 %) were signed within the target Average TTG: 223 days. Maximum TTG: 242 days
	NA	Time to sign (TTS) Grant Agreements from the date of informing successful applicants (information letters)		Number and % of grants signed within target Average TTS in calendar days	TTS 92 calendar days	15 out of 15 (100 %) were signed within the target.[51] Average TTS: 151 days Maximum TTS: 171 days

[51] IMI can only sign a Grant Agreement once the consortium has signed its own consortium agreement. Given the size and complexity of IMI consortia, it is rarely possible for these multi-stakeholder, multi-disciplinary teams to conclude their own consortium agreement (covering issues such as intellectual property and governance) within 92 days. This in turn impacts on the time to sign the Grant Agreement.

	Correspondence to general Annex 1	Key Performance Indicator	Definition / responding to question	Type of data required	Target at the end of H2020	Results in 2021
				Maximum TTS in calendar days		
PAYMENTS	**NA**	Time to pay (TTP) (% made on time) Pre-financing Interim payment Final payment	To optimise the operational payments circuits	Average number of days for Grants pre-financing, interim payments and final payments	Pre-financing: 30 days Interim payment: 90 days Final payment: 90 days	Pre-financing: 10 days (100 % on time) Interim payments: 61 days (100 % on time) Final payments: 70 days (100 % on time)
HR	**NA**	Vacancy rate (%)		% of posts filled in, composition of the JU staff		Overall vacancy rate: 10.71 % TAs: 7.7 % CAs: 13.30% SNEs: 50 %
JU EFFICIENCY	**NA**	Budget implementation / execution:	Realistic yearly budget proposal, possibility to monitor and report on its execution, both in commitment (CA) and payments (PA), in line with sound financial management principle	% of CA and PA	100 % in CA and PA	75.91 % CA to total budget 95.39 % PA to total budget
	NA	Administrative Budget: Number and % of total of late payments	realistic yearly budget proposal, possibility to monitor and report on its execution in line with sound financial management principle	Number of delayed payments % of delayed payments (of the total)		437 payments of which 14 were late (3.2 %)

Notes:

18* This indicator is not legally compulsory, but it covers several additional specific indicators requested for more societal challenges by the EC services in charge.

Table II - Indicators for monitoring H2020 Cross-Cutting Issues common to all JTI JUs[52]

<table>
<tr><th>Correspondence in the general Annex 2</th><th>Cross-cutting issue</th><th>Definition / responding to question</th><th>Type of data required</th><th>Direct contribution to ERA</th><th>Results in 2021</th></tr>
<tr><td>2</td><td>Widening the participation</td><td>2.1 Total number of participations by EU-28 Member State</td><td>Nationality of H2020 applicants & beneficiaries (number of)</td><td>YES</td><td>Eligible proposals:
Applications: 7079
Applicants: 2505
Beneficiaries: 2661
<table><tr><th>Country</th><th>Participations (Participants)</th></tr><tr><td>Austria</td><td>57 (25)</td></tr><tr><td>Belgium</td><td>257 (79)</td></tr><tr><td>Bulgaria</td><td>2 (2)</td></tr><tr><td>Croatia</td><td>4 (4)</td></tr><tr><td>Czechia</td><td>12 (7)</td></tr><tr><td>Denmark</td><td>94 (31)</td></tr><tr><td>Estonia</td><td>6 (3)</td></tr><tr><td>Finland</td><td>44 (13)</td></tr><tr><td>France</td><td>305 (119)</td></tr><tr><td>Germany</td><td>428 (151)</td></tr><tr><td>Greece</td><td>11 (7)</td></tr><tr><td>Hungary</td><td>8 (5)</td></tr><tr><td>Ireland</td><td>32 (18)</td></tr><tr><td>Italy</td><td>181 (92)</td></tr><tr><td>Latvia</td><td>1 (1)</td></tr></table></td></tr>
</table>

[52] Table II presents all indicators for monitoring of cross-cutting issues which apply to JTI JUs (Annex III - Council Decision 2013/743/EU).
In tables I and II, 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 2021
					Lithuania 1 (1) Luxembourg 34 (6) Netherlands 310 (98) Poland 8 (6) Portugal 28 (27) Romania 3 (3) Slovenia 8 (6) Spain 173 (77) Sweden 118 (29) UK[53] 536 (144) Total EU-28: 2661 (954) (Cumulative figures as of 31/12/2021)
		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 / IMI contrib., M EUR (%) Austria 36.6 (2.7%) Belgium 77.4 (5.8%) Bulgaria 0.2 (0%) Croatia 0.2 (0%) Czechia 3.1 (0.2%) Denmark 22.2 (1.7%) Estonia 2.8 (0.2%) Finland 19.1 (1.4%) France 133.4 (9.9%) Germany 164.6 (12.2%)

[53] 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 2021
					Greece 3.6 (0.3%) Hungary 3.7 (0.3%) Ireland 26.2 (1.9%) Italy 70.8 (5.3%) Latvia 0.3 (0%) Lithuania 0.1 (0%) Luxembourg 12.5 (0.9%) Netherlands 275.6 (20.5%) Poland 1.9 (0.1%) Portugal 9.7 (0.7%) Romania 1.6 (0.1%) Slovenia 1.3 (0.1%) Spain 115 (8.5%) Sweden 53.8 (4%) UK 309.3 (23%) Total EU-28 1344.9 (100%) (Cumulative figures as of 31/12/2021)
NA		Total number of participations by Associated Countries	Nationality of H2020 applicants & beneficiaries (number of)	YES	Eligible proposals: Applications: 541 Applicants: 226 Beneficiaries: 255 Country — Participations (Participants) Iceland 1 (1) Israel 22 (12) Norway 28 (13) Serbia 4 (4) Switzerland 198 (51)

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
					Turkey 2 (2) Total Assoc. countries 255 (83) (Cumulative figures as of 31/12/2021)
NA		Total amount of EU financial contribution by Associated Country (EUR millions)	Nationality of H2020 beneficiaries and corresponding EU financial contribution	YES	Country / IMI contrib., M EUR (%) Iceland 0.1 (0.1%) Israel 3.6 (4.6%) Norway 11.4 (14.5%) Serbia 1.1 (1.4%) Switzerland 62.3 (79.4%) Turkey 0.03 (0.0%) Total Assoc. countries: 78.5 (100%) (Cumulative figures as of 31/12/2021)
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 % of EU contribution going to beneficiaries flagged as SME		Participations: 364 out of 2269 (16.0 %) Participants: 239 out of 960 (24.9 %) EU funding: EUR 178.0 million (12.2 %) (Cumulative figures as of 31/12/2021, beneficiaries receiving EU funding only)
6	Gender	6.1 Percentage of women participants in H2020 projects	Gender of participants in H2020 projects	YES	52 % of the total workforce working in IMI2 projects is female.

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
		6.2 Percentage of women project coordinators in H2020	Gender of MSC fellows, ERC principal investigators and scientific coordinators in other H2020 activities	YES	25 %
		6.3 Percentage of women in EC advisory groups, expert groups, evaluation panels, individual experts, etc.	Gender of memberships in advisory groups, panels, etc.	YES	SRG: 24 out of 39 appointed nominees (61,5%) SC: 5 out of 12 full members (41,7 %) Expert evaluators: 22 out of 40 experts (55%) Interim review experts: 38 out of 86 experts (43%)
7	International cooperation	7.1 Share of third-country participants in Horizon 2020	Nationality of H2020 beneficiaries	YES	Eligible proposals: Applications: 234 Applicants: 158 Beneficiaries: 130 Country — Participations (Participants): Australia 2 (2) Benin 1 (1) Brazil 1 (1) Burkina Faso 1 (1) Canada 7 (7) China (People's Republic of) 1 (1) Congo (Democratic Republic of) 1 (1) Gabon 2 (1) Japan 2 (2)

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
					Russian Federation 1 (1) Senegal 2 (1) Sierra Leone 3 (2) Singapore 1 (1) South Africa 3 (3) Tanzania (United Republic of) 1 (1) United States 101 (51) Total for third countries 130 (77) (Cumulative figures as of 31/12/2021)
		7.2 Percentage of EU financial contribution attributed to third country participants	Nationality of H2020 beneficiaries and corresponding EU financial contribution	YES	Country — IMI contrib. M EUR (%) Australia 0.3 (0.7%) Benin 0.6 (1.4%) Brazil 0.3 (0.7%) Burkina Faso 3.8 (9.2%) Canada 0.4 (1.1%) China (People's Republic of) 0 (0%) Congo (Democratic Republic of) 3 (7.3%) Gabon 0.8 (2%) Japan 0 (0%) Russian Federation 0.1 (0.3%) Senegal 0.4 (0.9%) Sierra Leone 20 (48.5%)

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
					Singapore 0 (0%) South Africa 1.5 (3.7%) Tanzania (United Republic of) 0.5 (1.2%) United States 9.5 (23.1%) Total for third countries 41.3 (100%) (Cumulative figures as of 31/12/2021)
9	Bridging from discovery to market [54]	9.1 Share of projects and EU financial contribution allocated to Innovation Actions (IAs)	Number of IA proposals and projects properly flagged in the WP; follow up at grant level.		n/a
		9.2 Within the innovation actions, share of EU financial contribution focused on demonstration and first-of-a-kind activities	Topics properly flagged in the WP; follow-up at grant level		n/a
NA		Scale of impact of projects (High Technology Readiness Level)	Number of projects addressing TRL[55] between (4-6, 5-7)		2 projects TRL 4 3 projects TRL 5 1 project TRL 6 5 project 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: 1 168 of 3 046 (38.4 %) Participants: 410 out of 1 114 (38.8 %)

[54] This indicator (9.2) is initially intended to monitor the Digital Agenda (its applicability could be only partial).
[55] 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 2021
					(Cumulative figures as of 31/12/2021)
		11.2 Share of EU financial contribution going to private for-profit entities (Enabling & industrial tech and Part III of Horizon 2020)	H2020 beneficiaries classified by type of activity; corresponding EU contribution		EUR 195.3 million out of EUR 1 464.7 million (13.3 %) (Cumulative figures as of 31/12/2021)
12	Funding for PPPs	12.1 EU financial contribution for PPP (Art 187)	EU contribution to PPP (Art 187)		EUR 202.1 million (total cash contribution EC at the end of 2021)
		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 - in-kind contribution already committed by private members in project selected for funding - additional activities (i.e. research expenditures/investment of industry in the sector, compared to previous year)		EFPIA & Associated Partners contribution (EUR 1 582 million) divided by EU contribution (EUR 1 452.1 million) = leverage of 1.09
13	Communication 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: 15 629 Total funding amounts: EUR 10 005 549
14	Participation pattern	14.2 Proposal evaluators by country	Nationality of proposal evaluators		20 countries[56] (34 experts)

[56] Austria (1), Belgium (2), Bosnia and Herzegovina (1), Finland (1), France (3), Germany (2), Greece (1), Hungary (1), Ireland (1), Italy (1), Luxembourg (1), Philippines (1), Poland (2), Portugal (4), Romania (1), Spain (3), Sweden (1), Switzerland (2), United Kingdom (4), United States (1).

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
		14.3 Proposal evaluators by organisations' type of activity	Type of activity of evaluators' organisations	YES	12 – HES: higher or secondary education establishment 7 – REC: research organisations 3 – PUB: public bodies 8 – PRC: private for-profit entities 4 – OTH: other type of organisations
NA	Participation of RTOs and Universities	Participation of RTOs[57] and Universities in PPPs (Art 187 initiatives)	Number of participations of RTOs to funded projects and % of the total Number of participations of universities to funded projects and % of the total % of budget allocated to RTOs and to universities	YES	Participations: Research org: 557 (18.3 %) HES: 976 (32.0 %) % budget allocated: Res. org: EUR 344.0 million (23.5 %) HES: EUR 777.4 million (53.1 %) (Cumulative figures as of 31/12/2021)
NA	Ethics	The objective is ensuring that research projects funded are compliant with provisions on ethics efficiently	% of proposals not granted because non-compliance with ethical rules/proposals invited to grant (target 0%); time to ethics clearance (target 45 days)[58]		0 % of proposals not granted because non-compliance with ethical rules/proposals invited to grant. Time to ethics clearance in line with Grant Agreement Preparation timelines.
NA	Audit	Error rates	% of common representative error; % residual error		Representative error rate: 0.97 % Residual error rate: 0.58 %

[57] RTO: Research and Technology Organisation.
[58] Data relates to pre-granting ethics review. This time span runs in parallel to granting process.

Correspondence in the general Annex 2	Cross-cutting issue	Definition / responding to question	Type of data required	Direct contribution to ERA	Results in 2021
NA		Implementation	Number of cases implemented; in total EUR million; ´of cases implemented/total cases		Cases implemented 35 (90 %) Amount: EUR 915 147

Table III - KPIs specific to each single JU[59]

Reporting methodology: cumulatively reporting from the beginning of IMI2 until 31/12/2021.

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: - Expressed as a number of areas reflected in the IMI2 portfolio. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective b1: 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. Number of projects: 80 Budget committed: EUR 2 223 715 537	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: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' b2: 'reduce the time to reach clinical proof of concept in medicine development…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks'	50	275	425

[59] Table III presents the KPI specific for each JU, as transmitted by the Programme Offices or the operational services.
In this table, the budgets given include the EFPIA and Associated Partner contributions to the projects.

KPI	Definition	Comment	Relates to	IMI2 target	IMI2 results	IMI1 + IMI2 results
			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: - new tools for preclinical drug development, - biomarkers and tools developed to predict clinical outcomes, - improved protocols to design and process of clinical trials, - 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). - Complemented by number of qualification procedures launched. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objectives b1, b2, b4, b5 and b6: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' b2: 'reduce the time to reach clinical proof of concept in medicine development…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks' 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 (for completed procedures)	20 completed procedures: CE mark: 3 Inclusion in regulatory guidelines: 4 Regulatory letter of support: 1 Regulatory qualified opinion: 10 Submission for qualification opinion: 2 Number of projects: 14 Projects' budget: EUR 363 611 297	43 completed procedures: CE mark: 3 Inclusion in regulatory guidelines: 17 Regulatory letter of support: 5 Regulatory qualified opinion : 13 Submission for qualification opinion: 5 Number of projects: 29 Projects budget: EUR 1 009 512 988
4	New taxonomies of diseases and new stratifications (such as the definition of patient subpopulations, development, validation and use of new diagnostics) developed.	- Expressed as net figure. - As published and/or implemented by industrial partners and evidenced in annual reporting. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objectives b3 and b4: b3: 'develop new therapies for diseases for which there is a high unmet need…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'	30	34 Number of projects: 14 Projects' budget: EUR 429 174 550	47 Number of projects: 20 Projects' budget: EUR 792 078 134

KPI	Definition	Comment	Relates to	IMI2 target	IMI2 results	IMI1 + IMI2 results
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: 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…' and IMI2 Regulation recital 8: '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 270.0 million (AP: EUR 203.0 million; Partners in Research: EUR 67.0 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. - Accessibility to be evidenced by online availability (with or without fee), and documented by project reports.	IMI2 Regulation objectives a, b2 and b6: 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…' b2: 'reduce the time to reach clinical proof of concept in medicine development' 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%	48.51% Number of projects: 49 Budget committed: EUR 1 197 679 215	57.96 % Number of projects: 91 Budget committed: EUR 2 661 506 918
7	Co-authorships and cross-sector publications between European researchers on IMI2 projects (sectors include academia, small and mid-sized companies, pharma, regulators,	- Expressed as net figure - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective a: 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…'	1 500	1 457	5 119

KPI	Definition	Comment	Relates to	IMI2 target	IMI2 results	IMI1 + IMI2 results
	patient organisations, etc.).					
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. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. - Assessment based on yearly reporting by industrial partners until the project close-out meetings.	IMI2 Regulation objectives a, b2 and b6: 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…' b2: 'reduce the time to reach clinical proof of concept in medicine development' 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	350 Number of projects: 46 Budget committed: EUR 1 141 285 811	669 Number of projects: 85 Budget committed: EUR 2 656 592 231
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: 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…' b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'	80 %	60,40% Number of projects: 61 Projects' budget: EUR 1 773 893 401	56.69 % Number of projects: 89 Projects' budget: EUR 2 612 863 464
10	Support to SMEs: share of SMEs participating as formal IMI project beneficiaries.	- To be complemented by the number of SMEs benefitting from IMI project support in other ways.	H2020 priority; IMI2 Regulation recital 9 '(…) 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'	20 %	16.0 % (364 out of 2 269) (IMI2 cumulative figures until 31/12/2021, beneficiaries receiving EU funding only)[12]	SME participations: 16.0 % (562 out of 3 517) (IMI1 and IMI2 cumulative figures until 31/12/2021, beneficiaries receiving EU funding only)

Annex 2: Project outputs

In order to track progress against its ambitious goals, IMI categorises project outputs 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 IMI website includes a catalogue of accessible results, including a brief description of each resource and a link for more information. The list, which is not exhaustive, can be found in the 'projects and results' section of the IMI website.

IMI1 project outputs

New tools/resources for drug discovery & preclinical drug development

Project title	Description of result(s)
ENABLE	Mutabilis' EBL-1463 has been progressed from hit to candidate within the ENABLE project. EBL-1463 is a novel class of non-beta-lactam inhibitor of penicillin-binding proteins (PBPs) called dabocins. It kills bacteria by interfering with the cell wall synthesis of the bacteria. EBL-1463 continues to progress with funding and support from CARB-X, a global non-profit partnership led by Boston University, dedicated to accelerating early development antibacterial R&D. The funding from CARB-X will support the continued development of EBL-1463 beyond the ENABLE funding period.
ENABLE and ELF	A new class of potential antibiotics has been discovered by the University of Oxford through the ENABLE and ELF projects. A programme lead by the University of Oxford has screened their target against compounds of the ELF collection. The screening results indicated highly potent and selective compounds that have the potential to reverse antibiotic resistance in bacteria that causes conditions such as sepsis, pneumonia, and urinary tract infections. This new class of enzyme blockers, called indole carboxylates, can stop metallo-beta-lactamases (MBL) resistance enzymes allowing the antibiotic to attack and kill bacteria such as *E. coli* in the lab and in infections in mice. This collaborative research was published in Nature Chemistry. The press release can be found here.

Biomarkers and tools developed to predict clinical outcomes (efficacy and safety)

Project title	Description of result(s)
APPROACH	The project tested a non-invasive, user-friendly and commercially available motion analysis technique (GaitSmart®) to assess osteoarthritis progression in the APPROACH cohort (297 subjects), in combination with standard outcome measures such as radiographic parameters and patient reported outcome measures. Results have been published and show that the use of gait analysis improves the assessment of presence of tissue damage and may also improve the assessment of disease severity and progression.

New taxonomies of diseases and new stratifications of patient sub-populations

Project title	Description of result(s)

SPRINTT	Results of the SPRINTT clinical trial confirmed:
	• the definition of a population of sarcopenia with functional as well as anatomic criteria;
	• the feasibility of recruiting this population in a multinational, multicentre trial – (operationalising this definition);
	• and extended the results of the LIFE study:
	  ○ sarcopenia is reversible with a multimodal intervention;
	  ○ a multicomponent intervention based on physical activity, nutrition counselling and ICT can be delivered in outpatient settings with good risk-benefit;
	  ○ SPRINTT nutrition intervention is feasible and able to adapt flexibly to varying needs of this heterogeneous population – as described in European Geriatric Medicine.
	These results set the bar for future development of pharmacological therapies.

Development and use of cohorts, registries and clinical networks for clinical studies and trials

Project title	Description of result(s)
APPROACH	To respond to the challenge of selecting the right patients in knee osteoarthritis clinical trials, the APPROACH consortium combined a multistep participant selection with machine learning models to include people with an increased likelihood of structural progression and/or pain progression. The selected cohort consists of patients with high pain levels and low structural damage, suitable for evaluation of treatment modalities that decrease pain and arrest or slow-down tissue structural damage.
COMBACTE-CARE	Ongoing enrolment in 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). Of the 168 sites selected globally, 121 have been activated for enrolment, nearly half within the COMBACTE clinical trial network. As of December 2021, 222 patients had been randomised globally, despite the constraints of the global pandemic and the related operational hurdles. A number of initiatives were taken in order to drive enrolment and minimise delays in the completion of the study including site support initiatives, training, and ongoing feasibility/site selection.
COMBACTE-MAGNET	Launch of the EPI-Net Excellence Centres, a network of healthcare centres sharing epidemiology data and surveillance data for epidemiological research. Over 60 centres from 22 countries expressed interest in participation in the network, and recruitment is ongoing.
COMBACTE-NET	The results from ANTICIPATE's prospective observational cohort study, published in two papers in Nature Communications, provide important information that can be used to inform future study design, to enrich for high-risk patients in prospective clinical trials, and to develop predictive microbiota-based diagnostics for management of patients at risk for *Clostridioides difficile* infection (CDI): • Microbiota-based markers predictive of development of Clostridioides difficile infection | Nature Communications • Incidence and predictive biomarkers of Clostridioides difficile infection in hospitalized patients receiving broad-spectrum antibiotics | Nature Communications Notably, the results were essential to design MICROCARE, the phase 3 trial evaluating the efficacy of DAV132, a microbiota-protective therapy in preventing the occurrence of CDI in patients with haematologic malignancies. The study is progressing, with the first patient randomised in July 2021. There are more than 20 activated sites in over 10 countries, half of them from COMBACTE's clinical network (Clin-NET). The trial is described in the journal Blood.
COMBACTE-NET	Publication in the Lancet Infectious Diseases of the results from the SAATELLITE randomised phase 2 clinical trial looking at the efficacy and safety of suvratoxumab for prevention of *Staphylococcus aureus* ventilator-associated pneumonia (VAP).

Project title	Description of result(s)
	The data supported the potential role of monoclonal antibodies in preventing VAP in intensive care unit patients using a pre-emptive treatment approach and to move to the phase 3 clinical trial, SAATELLITE-2, sponsored by ARIDIS Pharmaceuticals. EMA and FDA advice was obtained on the protocol of the SAATELLITE-2 phase 3 trial, a randomised, double-blind, placebo-controlled, single-dosed trial, focusing on a human monoclonal antibody against *Staphylococcus aureus* alpha toxin in mechanically ventilated adult and adolescent subjects, and clinical sites are being activated.
COMBACTE-NET	Completion of the 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 the predictors of treatment failure of SA-PJI after a primary hip and knee arthroplasty. The preliminary results on the identified risk factors of *S. aureus*-PJI were presented at the 2021 ECCMID congress and will be published soon. The results will help the design of preventive measures and improve the medical prognosis of this disease.
iABC	The clinical trials parts of the project are progressing: • Clinical trial approval granted by the regulatory bodies in the UK and France to carry out the phase I study to test the first in class compound ALX-009 sponsored by Alaxia. Completion of the phase I, single-centre, double-blind, placebo-controlled, randomised, parallel group, multiple ascending doses study in healthy volunteers and results being analysed. • Further to the clinical trial approval granted by the UK regulatory authority, the phase I study of Polyphor's novel class antibiotic murepavadin, delivered via the oral inhalation route, has started. Completion of the healthy volunteers' recruitment (12) for the run-in phase (randomised double-blind, placebo-controlled, single-ascending dose) to assess the safety, PK, and local tolerability of single low doses. • Approval granted by the regulatory bodies in the UK, Germany and Spain to carry out a phase II study sponsored by Novartis the explore the efficacy and safety of QBW251 in the patients with bronchiectasis. 13 clinical sites have been initiated; patient screening is ongoing and to date 5 patients have been randomised out of the 72 planned. (clinicalTrials.gov NCT04396366)

Education and training for new and existing R&D scientists and stakeholders

Project title	Description of result(s)
APPROACH	The consortium published an article explaining the activities, lessons learned and challenges from the involvement of a Patient Council in the project, with the goal to help other research projects to integrate the patient perspective effectively. They cover both the formal processes of involvement (organisational structure, budget, meetings) and informal processes (building relationships, changing researcher perceptions). Among the learnings reported they also include the challenges, such as effective integration of the Patient Council with researchers' work in the early phase of the project.

Accessibility of resources/outputs beyond consortium

Project title	Description of result(s)
COMBACTE-MAGNET	Through the EPI-Net's surveillance-dedicated website, antifungal resistance data set made freely accessible for public consultation, including 53 910 isolates from 8 European countries. Data are available for five different target fungi: *Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida krusei* and three different drug classes.
SPRINTT	Produced the SPRINTT Physical Booklet that proposes a safe and effective home-based physical activity programme for reducing the risk of loss in mobility. Produced the SPRINTT Nutrition Workbook that provides nutritional recommendations for active and healthy aging – it also give useful information about nutrition for older people with or without physical frailty and sarcopenia.

IMI2 project outputs

New tools/resources for drug discovery & preclinical drug development

Project title	Description of result(s)
AIMS-2-TRIALS	Identified a developmental sensory processing difference (in pre-pulse inhibition) across three genetic mouse models (Cntnap2, Nrxn1, and Shank3) and applied the learning to human studies incorporating sensory processing measures to identify convergent mechanisms and intervention possibilities. This may lead to identification of novel drug targets and of the best developmental time window for successful treatment.
ARDAT	Work began on the development of standardised models to predict product immunogenicity, with all necessary ethical approvals in place. The first steps were initiated to set up a sustainable biobank repository that can accept samples from gene therapy patients, with a lab manual for operational procedures completed and the ARDAT Biorepository Governance Board in place. Engagement with regulatory bodies was initiated through a meeting held with the EMA Innovation Task Force (ITF), with valuable feedback obtained for the preparation of formal scientific advice from national competent authorities.
BEAT-DKD	Developed an automated deep learning image analysis for immunohistochemical validation of markers, as well as a novel fluorescent profile peak-to-peak confocal imaging to quantify glomerular endothelial glycocalyx damage. These tools were successfully used to validate BEAT-DKD's first candidate targets indicating their usefulness to support drug discovery campaigns. The automated image analysis will be now applied to spatial transcriptomics to further increase the resolution for understanding molecular phenotypes of healthy vs diseased cells, and the novel confocal approach will be used to characterise glycocalyx dysregulation in diabetes and assess effectiveness of drugs in glycocalyx protection.
BEAT-DKD	Established a comprehensive 'cell encyclopaedia' of the kidney, and high-throughput cell type-specific isolation techniques useful to unravel the molecular changes linked to diabetic kidney disease (DKD). These were applied to identify common and cell-specific insulin resistance and DKD molecular programmes, leading to the identification of the molecular mechanisms of sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibitors, which are an important drug class for these patients. A paper on the cell encyclopaedia is under development. Once published, it will become a powerful resource of cell-specific RNAseq and proteomic data for other investigators.
BEAT-DKD	Identified a novel potential therapeutic target in the context of renal fibrosis associated with human chronic kidney disease progression. This may open a new avenue for therapeutic intervention.
BEAT-DKD	Identified a microRNA (miRNA) candidate biomarker in transgenic mice models of early diabetic nephropathy which is being further validated in early human diabetic kidney disease (DKD). This will support the identification of high-risk patients for disease progression in the early stages of the disease.
BIOMAP	The BIOMAP glossary for the harmonisation of clinical variables related to atopic dermatitis and psoriasis facilitating comparative analyses across diverse cohorts was established and made publicly available. A corresponding glossary for the harmonisation of molecular data is being developed.
CARE	SARS-CoV-2 Syrian hamsters infection model established. After intranasal inoculation, high viral loads are detected in the lungs within 4 days causing pathological changes resembling bronchopneumonia observed in human patients. Model used to study the replication of variants of concern (VoCs), to demonstrate the efficacy of antivirals, antibodies and vaccines, and to evaluate the effect of antivirals on transmission.
CARE	CARE demonstrated that cynomolgus macaque are susceptible to SARS-CoV-2 infection, including the VOCs, and represent a relevant non-human primate (NHP) model of human infection. The project has reproduced the course of SARS-CoV2 infection with different VOC as characterised by: • viral load quantification (RTqPCR) • computerized tomography scan imagery • antibody response • cellular response (ICS/ELISpot).
CARE	Luciferase-encoding pseudoviruses carrying spike proteins of SARS-CoV-2 variants, or individual amino acid mutations, have been constructed. This versatile pseudovirus system

Project title	Description of result(s)
	can be used for (high throughput) testing of neutralising activity by polyclonal and monoclonal antibodies against emerging SARS-coV-2 variants of concern.
CARE	To identify drugs to combat COVID-19, Janssen Pharmaceutica NV and the REGA Institute developed a high throughput screening (HTS) assay based on a fluorescent read-out in VeroE6-eGFP cells. Using current scientific data, Janssen developed another HTS platform in A549-hACE2 cells using the power of high-content imaging to find antivirals.
COMBINE	Ran a 2-day online workshop on the standardisation of animal models, including 15 external speakers and up to 159 participants: the consortium has developed an experimental protocol for a standardised mouse pneumonia model for PK/PD studies on Gram-negative bacteria. This will be shared with the scientific community as a publication (manuscript in preparation). The COMBINE project will now determine reproducibility of results from lab-to-lab using the standard protocol, and use this protocol to assess preclinical PK/PD of benchmark small molecule antibiotics and improve preclinical-to-clinical translation.
ConcePTION	Method developed to produce pure primary mammary epithelial cells cultures from the mammary glands of conventional pigs as a valid tool to study the mammary epithelial barrier function in vitro and therefore understand how medicines transfer to breast milk. The method is described in the journal Animals.
EBiSC2	To accelerate human induced pluripotent stem cells (iPSC) differentiation and disease modelling with inputs from public and private partners, EBiSC continued to expand the EBiSC repository with 5 novel iPSC lines (see cells.ebisc.org/search and key novelty below). The use of inducible differentiation factors reduces the time required to generate the required cell types with accelerated maturity status. Key novelty - 5 iPSC-derived cell models established using control and disease iPSC lines: • cardiomyocytes generated from control and LQTS1 iPSC lines • hepatocyte-like cells • co-culture models using fully humanised neural + astrocyte cells • dopaminergic neurons • aggregation models assessing role between α-synuclein pathology + GBA activity.
EBiSC2	Aligned IT infrastructure wherein the EBiSC Information Management System (IMS) is migrated to a new programming backend synchronised with the human pluripotent stem cell registry (hPSCreg). This reduces maintenance efforts while streamlining the implementation of new future functionalities based on EBiSC2 customer needs.
EBiSC2	A fully functional biobank, operative across two central banking facilities in the UK and Germany with updated documentation and processes aligned with GDPR. Monitors and controls towards improvement of EBiSC banking operations across 2 different organisations: Coherent quality system implemented including 10 key standard operating procedures (SOPs).
ERA4TB	Regarding TB *in vivo* imaging, the consortium has designed and constructed a positron emission tomography–computed tomography (PET-CT) imager for mouse models to be installed in biosafety level (BSL) 3 facilities. This key equipment will allow non-invasive PK/PD data to be used in response prediction models, ensuring a faster, safer regime translation to humans. Moreover, the equipment will make it possible to develop new image biomarkers with translational potential that could be eventually used in the accurate diagnosis of TB patients.
ERA4TB	In the area of *in-vivo* imaging, in the frame of single cell time-lapse microscopy for *Mycobacterium tuberculosis* (Mtb), ERA4TB has designed and fabricated microfluidic platforms for carrying out PK/PD experiments with TB strains and constructed a dual reporter plasmid to facilitate characterisation of the different bacterial sub-populations that arise upon drug treatment (killed, non-growing metabolically active, actively growing). These developments will contribute to the project's impact by enabling a faster, accurate assessment of drug efficacy at *in vitro* level that can lead to more rigorous PK/PD models that will be key in informing the design of clinical studies on compounds and regimes.
ESCulab	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. The ELF screening programme for the SME Metabomed has previously identified potent and selective acetyl-CoA short-chain synthase 2 (ACSS2) inhibitors for the potential treatment of cancer. The company has secured more than US$ 12 million to fund the further development of a clinical candidate. MTB-9655, one of the compounds based on this series, is currently in phase I trials in USA and Israel.

Project title	Description of result(s)
ESCulab	Merck KGaA is developing a hit originally derived from the ELF, M4205, which is a selective inhibitor of disease-associated cKIT (a receptor tyrosine kinase) mutants in unresectable metastatic or recurrent gastrointestinal stromal tumours. A phase I trial is in preparation.
EUbOPEN	First set of chemogenomics candidate compounds covering >300 targets acquired and assessed for compound purity and cytotoxicity New technologies and assays for compound profiling established (see also Wells et al., Int J Mol Sci, 2021). Through these resources, EUbOPEN is working towards its objective of developing high quality chemical tool compounds for 1 000 human proteins, which represents one third of the druggable genome. Researchers in academia and industry alike will therefore be able to use the tools to study diseases, and identify proteins that play a key role in disease development and so could be targeted by drugs. The tools will also help scientists to design drugs capable of blocking specific proteins involved in diseases.
EUbOPEN	• 10 recombinant antibodies for EUbOPEN target proteins generated. • *In-vitro* assays for 56 targets and cellular assays for 44 targets established. • 40 CRISPR knockout cell lines generated to support chemical probe validation. • 60 chemical starting points identified.
FAIRplus	The FAIRplus project worked on making the data from the IMI1 project eTOX more findable, accessible, interoperable, and reusable (FAIR). The eTOX database covers 8.8 million pre-clinical data points on nearly 2 000 chemicals from 8 196 studies that included predictions on health effects. The FAIRplus work has made these data easier to use in future research. They have captured the lessons learned and hurdles found in their FAIR Cookbook.
GNA NOW	The consortium delivered one *ex vivo* culture of rat mast cells to better anticipate the risk of pseudo-allergic reaction, thus de-risking unexplained acute toxicity of novel antibiotic scaffold. The assay has been applied to at least three antibacterial drug discovery programmes.
HARMONY	The HARMONY Alliance has developed a machine learning researching tool prototype to predict the risk of relapse after first remission in acute myeloid leukaemia (AML) patients treated without allogenic hematopoietic stem cell transplant (alloHSCT). The aim of this tool is to create a more accurate risk prediction in this setting, based on the analysis of the clinical outcome of specific genetic alterations and the development of an online tool that can be implemented in mobile devices, where to visualise the likelihood of relapse and thereby help determining in which patients alloHSCT should be performed.
iConsensus	The project has developed an integrated platform including several automatic analyses from mammalian cell culture such as detection of important proteins by micro-fluidics and detection of metabolites by capillary electrophoresis chip. These are promising tools for bioprocess monitoring and contribute towards the development of simple, rapid, and cost-effective devices, allowing routine at-line monitoring of specific proteins during process development and production.
IM2PACT	Several tools/resources have been produced by the IM2PACT project (e.g. antibodies, cell lines, single cell enrichment protocols and candidate blood brain barrier -BBB- transport targets). Some of these have been validated, while others require further validation before sharing as a publication. For instance, an induced pluripotent stem cells (iPSC) – brain capillary endothelial-like cells (BCEC) differentiation model has been produced and validated. This is useful for scientists to develop functional assays that will be used to assess small molecule transport in the brain. More detailed information can be found here. The tools developed within IM2PACT will provide a rich resource to advance research on the BBB by better understating how it works, what are the potential targets and how to improve central nervous system (CNS) distribution.
IMMUcan	IMMUcan's inclusive and integrated European immuno-oncology tumour profiling pipeline platform is up and running. This platform has access to high-quality human biological material (tissue, blood, stool and saliva) and clinical data from patients with colorectal, lung, head & neck, breast, renal cancers, and immune checkpoint inhibitor failures. Biological material is subject to detailed molecular analysis and immuno-profiling with cutting edge technologies. As of December 2021, 782 patients have been screened by the platform.
IMPRiND	The project has come up with a working laboratory model of Parkinson's disease. The consortium used induced pluripotent stem cells (iPSCs) derived from both healthy subjects and patients with the alpha-synuclein gene defects to generate human dopaminergic neurons that are primarily affected in Parkinson's disease. They found a way of 'amplifying', in a fairly

Project title	Description of result(s)
	pure form, the main constituent, called fibril, of alpha-synuclein clumps directly from post-mortem Parkinson's brains. When they added these brain-derived fibrils onto the human dopaminergic neurons, they successfully triggered the aggregation of alpha-synuclein inside the cells and observed progressive neuronal loss. These findings are important because they provide a fully human model to decipher how alpha-synuclein clumps cause nerve damage. This model will allow researchers to start targeting the toxic effects of alpha-synuclein clumps with novel therapeutics.
ITCC-P4	Using the consortium's target actionability reviews (TAR) methodology to match mechanism-of-action-based anti-cancer drugs with specific cancer subtypes based on preclinical studies, the consortium created a comprehensive overview of targeting replication stress across 16 paediatric tumour types, which can be explored using the publicly available interactive heatmap on the R2 target actionability review platform. The results, published in the European Journal of Cancer, showed that ATR, CHK1, PARP or WEE1 are the most promising drug targets using either single agents or in combination with chemotherapy or radiotherapy in neuroblastoma, osteosarcoma, high-grade glioma or medulloblastoma.
ITCC-P4	Over 600 patient derived xenograft (PDX) models are registered in the IT resource R2, and over 250 of these are fully established spanning all major paediatric tumour types including rare entities. Over 240 of these models are also fully molecularly characterized. Thanks to the addition of 3 new EFPIA partners in the consortium (Amgen, Sanofi and Servier), the platform is enriched with a wider organoid repertoire, with models for leukaemias and lymphomas as well as rarer entities. The *in vivo* testing has started in more than 100 models at different sites and includes innovative combination testing (drug-drug and radiotherapy-drug).
MAD-CoV 2	The project published a paper in Science Advances identifying 200 approved drugs appropriate for repurposing against COVID-19, 40 of which are already in COVID-19 clinical trials. Using artificial neural network analysis, they classified these 200 drugs into 9 distinct pathways, within two overarching mechanisms of action: viral replication (126) and immune response (74). Two drugs (proguanil and sulfasalazine) implicated in viral replication were shown to inhibit replication in cell assays. This analysis opens new avenues for the rapid repurposing of approved drugs into clinical trials.
MAD-CoV 2	In the treatment of COVID-19, remdesivir has received authorisation for COVID-19 and has been shown to improve outcomes but not decrease mortality. The project has demonstrated an additive effect of combination therapy using remdesivir with recombinant soluble Angiotensin-converting enzyme 2 (ACE2). This combination treatment markedly improved their therapeutic windows against SARS-CoV-2. This data lays the groundwork for the study of combinatorial regimens in future COVID-19 clinical trials.
MELLODDY	In their second year, the MELLODDY project trained the drug discovery models of 10 pharmaceutical partners via federated multi-task machine learning without compromising privacy. This involved more than 100 000 machine learning tasks, transferring 713 796 GB of data and spanned over 3 months on the Amazon cloud infrastructure. The resulting multi-partner models showed an improvement over single-party derived models, demonstrating the advantage of this form of competitive collaboration.
PIONEER	PIONEER has reached a consensus on recommendations for the definitions and measures of clinician-reported outcomes. These recommendations helped to inform on the patient-reported outcome measures that should be used in both research and routine care settings. The findings are summarised in this article, published in the European Oncology Journal.
PIONEER	PIONEER has developed an online search tool for prostate cancer diagnostic and prognostic factors (DPF). The tool, which is open access, allows users to identify prostate cancer DPFs underpinned by the PIONEER Core Outcome Sets for prostate cancer. All DPFs in the tool have an associated quality assessment. The tool will be officially launched at the end of January 2022.
PREMIER	New tools have been developed to better understand how active pharmaceutical ingredients (APIs) may be taken up by fish, including a new model to predict bioaccumulation through a quantitative structure activity relationship models (QSAR) approach and a physiological based kinetic model of uptake into a generic (universal) fish, that will be used to support prediction of internal concentrations.
PREMIER	Two *in silico* models have been generated: a fish PBK (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. The updated

Project title	Description of result(s)
	ePiE model is used to develop a European spatial exposure modelling framework for APIs and transformation products in surface waters, sediments, soils and biota.
RESOLUTE	The project has generated tools to advance research on solute carriers (SLCs) and, ultimately, make use of them as targets for drug development. More precisely, the RESOLUTE plasmid collection has been enriched with 447 new (894 in total) codon-optimised sequences of human SLCs inserted in a vector compatible with the gateway system, which allows a fast and efficient cloning as well as providing higher protein expression in human cells. These are available through Addgene. The immediate impact on the scientific community is a reduced barrier for entry into the SLC field and standardised reagent quality.
RESOLUTE	The project has released a set of SLC-knockout cell lines (30 clones) to the ATCC (American Type Culture Collection) cell repository. This will ensure the longevity and long-term impact of the resources generated for the benefit of the wider scientific community. Cells will be made available after quality control by ATCC.
RESOLUTE	The project has published a review article providing an overview of cellular assay technologies for SLCs, which are being applied and further developed within the RESOLUTE project. The review provides a comprehensive overview of the state of the art for cellular assay technologies for SLC research, and discusses relevant SLC characteristics enabling the choice of an optimal assay technology.
RTCure	Development of *in vitro* and *in vivo* systems for screening of molecular constructs (potential drugs) that target antigen-specific T cell activation in systems where T cells expressing antigen-specific T cell receptors cloned from single T-cells from rheumatoid arthritis (RA) patients are used. These systems are used to screen potential new drugs and to better understand T cell biology in RA and could potentially lead to new tolerising drugs for the treatment of RA. The systems are described in papers in Scientific Reports, the Journal of Translational Autoimmunity, and Clinical and Experimental Immunology.
RTCure	Development of animal models for the testing of antigen-specific tolerance with ovalbumin (OVA) reactivity as a triggering event. Tolerance induction studies using this OVA breach of tolerance model show that the timing of application of tolerogenic therapies is key to successful outcome. This is an important tool to learn more about the immunological triggering events leading to RA. For example, the consortium started evaluations of tolDC (tolerogenic dendritic cells) therapy in the OVA breach of tolerance model.
TransQST	The early prediction of drug adverse effects is of great interest to pharmaceutical research, as toxicity is one of the leading reasons for drug attrition. Understanding the cell signalling and regulatory pathways affected by a drug candidate is crucial to the study of drug toxicity. In a paper in Frontiers in Pharmacology, TransQST presents a computational technique that employs the propagation of drug-protein interactions to connect compounds to biological pathways. The analysis pipeline was implemented in an open-source KNIME workflow called Path4Drug to allow automated data retrieval and reconstruction for any given drug present in ChEMBL. The pipeline was applied to withdrawn drugs and cardio- and hepatotoxic drugs with black box warnings to identify biochemical pathways they affect and to find pathways that can be potentially connected to the toxic events. The tool is openly available and modifiable to support other systems biology analyses.
TransQST	Drug toxicity class curation in ChEMBL: Drug safety data curation: toxicity class(es) for boxed warnings and withdrawn drugs. 17 toxicity classes curated for 176 withdrawn drugs and 438 drugs with black box warning. The paper is available in Chemical Research in Toxicology.
TransQST	New release of the DisGeNET Cytoscape App. The App enables analysis of the DisGeNET database on disease genomics through the Cytoscape software for network analysis and offers functions to query, analyse, and visualise different network representations of the gene-disease and variant-disease associations available in DisGeNET. As main features it includes: visualisation and analysis of variant-disease networks, disease enrichment analysis for genes and variants, annotation of user's own data with DisGeNET and analytic support through Cytoscape Automation. The DisGeNET Cytoscape App is available through the Cytoscape App Store. New REST API available, including endpoint for performing disease enrichment analysis for genes and variants.
VAC2VAC	The consortium has successfully developed animal-free methods for potency testing of several vaccines currently commercialised by industry partners: For human diphtheria, tetanus and acellular pertussis (DTaP) vaccine, a physicochemical method based on proteolytic degradation and LC-MS. In addition, monoclonal antibodies have been characterised and selected for use in immunochemical methods such as ELISA

Project title	Description of result(s)
	(enzyme-linked immunosorbent assay) to determine quantity/quality of diphtheria and tetanus antigens. For tick-borne encephalitis (TBE) vaccine, a proof of principle has been reached for PBMC-based gene expression assay assessing the potency of the inactivated virus component. A better understanding of how infectious bronchitis virus (IBV) and other poultry vaccines activate immune cells has been reached and a nitric oxide production/phagocytosis assay developed with the aim to vaccine quality testing *in vitro*. These physiochemical/immunochemical/ cell-based multiparametric methods developed to ensure consistency among different vaccine batches could potentially replace animal tests currently used by industries and therefore strongly impact the 3Rs policy.
VSV EBOPLUS	The consortium has developed an internal database for data sharing that can be adapted to other consortia. Therefore, it may serve as data manager tool for consortia that need to share data among their members in a secure manner. The consortium has also developed the computational tool BioFeatS, specifically 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)
3TR	The identification of urinary leukotriene E4 and prostaglandin D2 metabolites in severe childhood and adult asthma, methodology for their detection and importance as severity prognostic biomarker. The findings, published in the American Journal of Respiratory and Critical Care Medicine, also builds on work carried out in the IMI1 severe asthma project U-BIOPRED.
3TR	Whole blood is often collected for large-scale immune monitoring studies to track changes in cell frequencies and responses using flow (FC) or mass cytometry (MC). In order to preserve sample composition and phenotype, blood samples should be analysed within 24 hours after bleeding, restricting the recruitment, analysis protocols, and biobanking. In a paper in Cytometry Part A, 3TR evaluated two whole blood preservation protocols that allow rapid sample processing and long-term stability. This setting constitutes a valuable tool for multicentric and retrospective studies.
AB-DIRECT	Two mathematical models have been built to describe the effects of novel antibacterial agent gepotidacin over time *in vitro* on the bacteria *Escherichia coli* and *Neisseria gonorrhoeae*. Although the models have several limitations, they can play a valuable role in estimation of the dosage regimens needed to eradicate these bacteria.
AIMS-2-TRIALS	Carried out a large imaging study involving 362 males and 82 females with autism; and 409 males and 166 females without autism. In both not-autistic males and autistic people, they found reduced resting-state brain function in the so-called 'default network', a network that is active when we engage in social cognition or thoughts about ourselves. Additionally, connections across brain hemispheres in the visual cortex are reduced in autistic females, while autistic males are not different from males who are not autistic. These findings may shed light on the mechanisms underlying sex-differences in autism, fostering the development of better gender-tailored treatments.
AIMS-2-TRIALS	Showed in a study of 104 infants with and without a family history of autism, using the electroencephalography (EEG) biomarker N170, that infants with genetic differences related to autism responded to faces differently, even at a very young age, before signs of autism might be noticeable. The finding may pave the way to a more reliable and early diagnosis of infants at high risk of autism.
BEAT-DKD	Discovered and validated 4 biomarkers that predict the response of patients with diabetic kidney disease (DKD) to an endothelin receptor antagonist. These biomarkers will enable the selection of patients more likely to respond to this drug class, thereby reducing the size and costs of clinical trials.
BEAT-DKD	Validated tumour necrosis factor (TNF) receptor markers that can be used to monitor the response to sodium-glucose cotransporter-2 inhibitors (SGLT2) inhibitors, now part of the

Project title	Description of result(s)
	guideline recommended treatment for patients with DKD. Changes in these TNF markers during treatment can predict the long-term risk of kidney injury and will inform decision making in clinical practice.
BEAT-DKD	Evaluated 19 plasma biomarkers for their ability to predict fast renal decline in patients with low urine albumin-to-creatinine ratio (used to follow risk of progression to kidney disease). Elevated plasma levels of kidney injury molecule-1 (KIM-1) was an especially strong predictor of future renal decline in these patients, supporting use of this biomarker to identify patients at risk for declining glomerular filtration, which otherwise would go undetected.
BEAT-DKD	Identified several gene candidates that predicted hyperglycaemia and decline of kidney function in diabetic kidney disease (DKD) patients via measurement of mRNA expression in urine vesicles extracted from patient urine. This may pave the way for the clinical use of urine, which is an easily collected biofluid, to measure biomarkers of DKD.
BIOMAP	Core transcriptomic signatures of atopic dermatitis and biomarker candidates predicting clinical outcomes were identified and published in the Journal of Allergy and Clinical Immunology. Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder, affecting up to 20 % of children and 10 % of adults. Its pathophysiology results from a complex interaction of genetic and environmental factors leading to epidermal dysfunction and cutaneous inflammation. This study will allow better understanding of atopic dermatitis and its clinical and lifestyle complexity, and better prediction of future treatments.
CARE	An integrative analysis of immune markers in COVID-19 patients highlights neutrophil activation as a hallmark of severe disease. Longitudinal measurements of CD177, a specific marker of neutrophil activation, discriminated between patients with the worst prognosis and those who recovered. CD177 would be a reliable prognostic marker for routine care. Published in iScience.
EU-PEARL	Completed a systematic review to assess the currently available biomarkers able to predict tuberculosis end-of-treatment outcomes. The review captured a total of 129 unique biomarkers or biomarker combinations and identified 59 of the most promising.
HYPO-RESOLVE	By using a new simulation tool, a new mathematical methodology was devised and implemented to assess and rank the impact of behavioural risk factors (11 parameters reflecting 6 different actions made by patients) on hypoglycaemia. These results are valuable for better monitoring of treatment with sugar lowering drugs.
HYPO-RESOLVE	Showed that none of the hypoglycaemia-specific patient reported outcome measures (PROMs) currently available has sufficient validity, reliability, and responsiveness to accurately assess the impact of hypoglycaemia on quality of life (QoL) in people with diabetes, which restricts their utility in the clinic or research setting. The findings are published in Diabetologia.
HYPO-RESOLVE	Examined how hyperinsulinemia–hypoglycaemic glucose clamp technique has been developed and applied in humans to assess effects of and responses to hypoglycaemia under standardised conditions. The conclusions are that despite this technique being considered a ‘gold standard’, a uniform standard with key elements on how to perform these experiments is lacking which is needed for reproducible application in clinical trials. The findings are published in Diabetologia.
IMI-PainCare	Postoperative pain management is still sub-optimal, causing problems including patient suffering, impaired surgical recovery, long-term opioid intake, and post-surgical chronic pain. IMI-PainCare published a paper describing an international, stepwise consensus process on outcome domains for pain management after surgery. The process was conducted at a face-to-face meeting and involved nine international stakeholder groups and patient representatives. This process resulted in an overall core outcome set for perioperative pain management with five core outcome domains.
Immune-Image	The ideal set of multi-modality molecular imaging for immune cell tracking has been defined. Multimodal whole-body PET/MRI and PET/CT are optimal tools for quantitative whole-body cell tracking studies due to the superior temporal and spatial resolution and high sensitivity of positron emission tomography (PET).
imSAVAR	The consortium developed immune related adverse outcome pathways (irAOPs) for different organs to predict key events and subsequently identify putative biomarkers with an improvement of non-clinical test systems. The conception and application of the irAOP as a tool enables the definition of the current state of knowledge regarding the respective pathologies. Moreover, this results in a thorough

Project title	Description of result(s)
	gap analysis and the conceptual framework of the irAOP guides the refinement of improved non-clinical test systems and helps identifying suitable biomarkers. • Generation of an irAOP (graphical) indicating the key events to the induction of interleukin (IL)-2 mediated severe advents (1 molecular initiating event (binding of IL-2 to its receptor), 3-4 key events (activation of IL-2 receptor expressing cells; release of cytokines/migration of immune cells, tissue resident cell activation; tissue specific toxicity), 4 pathological outcomes (vascular leakage, dermatoxicity, skin rash, hepatotoxicity). • Development of an irAOP (graphic) indicating the key events leading to the adverse outcome cytokine release syndrome [CRS]: 1 molecular initiating event (binding of CAR to its specific target), 4 key events (activation of CAR-T cells, release of cytokines/migration of leukocytes, tissue resident/endothelial cell activation, systemic inflammation), 1 pathological outcome (CRS). • Development of an irAOP (graphic) indicating the key events leading to the adverse outcome cytokine release syndrome [CRS]: 1 molecular initiating event (formation of immune synapse with antigen expressing cell), 4 key events (activation of T cells/migration of leukocytes, increased pro-inflammatory mediators, activation of endothelial cells/macrophages/dendritic cells, systemic inflammatory response), 1 pathological outcome (CRS).
imSAVAR	The consortium started a scientific study to identify molecular biomarkers in patient samples to predict immune related adverse events (irAEs), with 7 patients included so far.
LITMUS	In a paper in the Journal of Hepatology, LITMUS researchers summarised how a number of imaging biomarkers, particularly those that measure liver stiffness (elastography), can be helpful in efforts to improve diagnosis of non-alcoholic steatohepatitis (NASH). Vibration-controlled transient elastography (VCTE), point shear wave elastography (pSWE), 2-dimensional shear wave elastography (2DSWE), magnetic resonance elastography (MRE), and magnetic resonance imaging (MRI) were evaluated for their diagnostic accuracy for liver fibrosis and NASH.
LITMUS	Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide and is often associated with aspects of metabolic syndrome. Despite its prevalence and the importance of early diagnosis, there is a lack of robustly validated biomarkers for diagnosis, prognosis and monitoring of disease progression in response to a given treatment. LITMUS researchers published an overview of the contribution of metabolomics and lipidomics in clinical studies to identify biomarkers associated with NAFLD and non-alcoholic steatohepatitis (NASH). They found that, although several studies have identified potential biomarkers, few have been validated. The paper is published in Nature Reviews Gastroenterology and Hepatology.
LITMUS	The LITMUS consortium assessed 13 non-invasive tests (NITs) to discriminate simple steatosis from non-alcoholic steatohepatitis (NASH). They found that fibrosis targeted biomarkers and single biomarkers showed limited performance in detecting NASH. However, combinations produced more promising results. Among these, the SomaScan algorithm, a novel proteomics panel specifically developed to detect NASH, and the ADAPT algorithm significantly outperformed the Fibrosis-4 index. The results were presented in a poster at the International Liver Congress. Validation of these findings in an expanded cohort is underway.
LITMUS	The LITMUS consortium has proposed several potential biomarkers for non-alcoholic fatty liver disease (NAFLD): • Serum miR-193a-5p levels were shown to correlate strongly with NAFLD activity grade and fibrosis stage and may have a role in the hepatic response to oxidative stress and is a potential clinically tractable circulating biomarker for progressive NAFLD. SomaScan analysis in more than 300 NAFLD serum samples confirmed that circulating concentrations of proteins AKR1B10 and GDF15 were strongly associated with disease activity and fibrosis stage.
LITMUS	The consortium identified PRO-C4 as a blood-based biomarker of fibrotic non-alcoholic steatohepatitis (NASH) which has the potential be used as screening tool.
MACUSTAR	MACUSTAR aims to develop novel clinical endpoints in patients with intermediate age-related macular degeneration (iAMD). The consortium is overseeing a low-interventional clinical multicentre study with a cross-sectional part and a longitudinal part. Statistical analysis of the cross-sectional part indicated that all selected functional tests demonstrated a sufficient performance and discriminant ability and can therefore be included in the longitudinal part of the study.

Project title	Description of result(s)
	A further interaction with EMA was initiated during 2021 to receive feedback on the results of the statistical analysis of the cross-sectional data and its implementation in the longitudinal part of the study.
Mobilise-D	There is a lack of agreed definitions about what constitutes real-world walking, impeding the comparison and interpretation of data acquired across systems and studies. Mobilise-D published a study in which expert-based consensus on specific aspects of real-world walking was sought via an online survey involving 162 participants. The set of real-world walking definitions identified will serve as a common framework for implementing digital and mobile technologies for gait assessment and are an important step in the transition from supervised to unsupervised gait assessment.
NECESSITY	The consortium developed a tool for assessing response index in Sjögren's patients (STAR). Unlike current measures, STAR will accelerate drug development in Sjögren's by assessing the efficacy of drugs on all aspects of the disease.
PERISCOPE	A novel assay was developed to identify infection-induced mucosal antibodies against non-vaccine pertussis antigens. This assay could yield a biomarker of pertussis infection in populations vaccinated with acellular pertussis vaccines.
RESCEU	Published an article examining within-host diversity of respiratory syncytial virus (RSV). Data from 319 nasopharyngeal swabs indicated that RSV-B had lower consensus diversity than RSV-A at the population level, while exhibiting greater within-host diversity. The differences found in within-host virus populations highlight the importance of monitoring for RSV vaccine efficacy.
RHAPSODY	RHAPSODY established a diabetes biomarker prioritisation matrix and a web-based prioritisation tool to enable: • the systematic evaluation of biomarker candidates with relation to relevant external data sources; • the consideration of candidate biomarkers in the context of all RHAPSODY data generated and visualisation of the results across multiple experiments. Together with the federated database, these resources provided a platform for biomarker discovery.
RHAPSODY	Paired plasma and islets samples were obtained from diabetic, glucose intolerant and non-diabetic patients undergoing partial pancreatectomy for islet transcriptome and proteome analysis and for plasma lipidomic analysis. Integrated data analysis identified islet gene co-expression modules that correlate with type 2 diabetes (T2D) progression, and which provide a mechanistic model of beta-cell failure in T2D.
RHAPSODY	Human islet transcriptomic, proteomic and lipidomic data analysis identified (i) islet cell mechanisms that lead to amyloid plaque deposition (type 2 diabetes islets marker); and (ii) mechanisms by which gluco-lipotoxic conditions induce irreversible beta-cell dysfunction. These findings aid in our understanding of the development of diabetes.
RHAPSODY	Analysis of plasma lipidomics and islets and liver transcriptomic data from mouse models of prediabetes identified a link between plasma triglycerides, the liver ß-oxidation pathway and key genes controlling insulin secretion by beta cells. Similar correlations were found using human lipidomic and islet transcriptomic data. This study also identified a novel regulator of insulin secretion. Thus, circulating triglycerides are part of a liver-to-beta-cell axis and are biomarkers of beta cell function.
RHAPSODY	Newly developed unsupervised and supervised multiblock analysis bioinformatic tools were used to visualise and analyse how changes in islet-liver-fat-muscle gene module interaction networks underlie multi-organ deregulation in type 2 diabetes progression. Spt2 was one of the specific genes studied, revealing a link between ceramide production, bile acids, Fgf15 action and glucose homeostasis.
RTCure	RTCure has defined an immunological panel of more than 20 antibodies for leucocytes in blood in well validated flow cytometry analysis. This panel has been validated in 4 partner sites and will be used to define tolerogenic signatures and for functional phenotyping of immune cells in RA. RTCure has also demonstrated an expansion of a population of NK cells in RA in that are in stable remission; this result describes a signature of the tolerant state.
RTCure	Identification of several biomarkers predictive for the development of rheumatoid arthritis, which will make it possible to identify people at greater risk of developing RA: • N-Linked Glycans in the Variable Domain of IgG Anti–Citrullinated Protein Antibodies (published in Arthritis & Rheumatology).

Project title	Description of result(s)
	• A panel of 24 antibody targets (and non-modified 'control' variants) to post translationally modified antigens in RA has been developed and validated. • Ultrasound emergence of tenosynovitis as a predictor for RA development in at risk for RA individuals has been validated.
RTCure	Identification of several biomarkers may be used to help diagnose RA in the future: • Identification of more than 100 possible candidate antigens for autoantibodies in RA using protein and peptide array technology. • The consortium established the citrullinated/native index of autoantibodies against hnRNP-DL to predict an individual 'window of treatment success' in RA patients. The difference in autoantibody signal against citrullinated hnRNP-DL versus native hnRNP-DL (the CNDL-index) can be used as a biomarker to identify patients 'at risk' of rheumatoid arthritis (published in Arthritis Research & Therapy). • A multiplex serology panel for the detection of approximately 70 antibody targets has been developed for the identification of individuals at risk of RA or with early signs of RA.
RTCure	The consortium has established several cell lines that can be used to study the development of RA: • Identification and isolation of more than 30 monoclonal ACPAs from single B cells or plasma cells from blood, synovial fluids, bone marrow, lungs and gingival tissues from patients with ACPA-positive RA and from individuals at high risk for this disease. Fine specificities of the monoclonals for a large number of post-translationally modified peptides and proteins have been determined. • Established neutrophil progenitor cell lines. • Established cell lines expressing human antigen specific TCR isolated and from single T cells from patients with RA.
RTCure	The consortium has developed several animal models that can be used to study the development of RA: • HLA-DR4 transgenic model of collagen induced arthritis (CIA); • mouse model of inflammatory memory; • *in vivo* model of autoimmune skin blistering; • mouse model for pain, bone loss and tenosynovitis after transfer of monoclonal ACPA; • mouse model expressing TCRs recognising citrullinated peptides (HLA DR4 transgenic model).
TransQST	Kidney quantitative systems toxicology (QST) model: The project established an improved version of proof-of-concept pharmacodynamic/QST model of drug-induced kidney injury. Integrated species-specific physiological parameters to enhance the accuracy of translational predictions of renal injury markers, e.g. urinary Kim-1 in patients. New time-course data from cisplatin study in the rat were generated and are now being applied to re-parameterise the model.
TRISTAN	Programmed cell death protein 1 (PD-1) antibody treatment is the standard of care for melanoma and non-small-cell lung cancer (NSCLC). However, accurately predicting which patients will benefit is currently not possible. Tumour uptake and biodistribution of the PD-1 antibody might play a role. The project carried out a positron emission tomography (PET) imaging study with zirconium-89 (89Zr)-labelled pembrolizumab before PD-1 antibody treatment and demonstrated that: 1) 89Zr-pembrolizumab PET imaging is safe and feasible in patients with metastatic melanoma and NSCLC; 2) 89Zr-pembrolizumab uptake in tumour lesions correlates with response to PD-1 antibody treatment; and 3) patients with high 89Zr-pembrolizumab tumour uptake experience longer progression-free survival and overall survival.
VSV EBOPLUS	Molecular signatures induced by rVSV-ZEBOV vaccination were analysed in adult cohorts in Europe, Africa and North America and reported in The Lancet Microbe. Results show a gene signature associated with immunogenicity (common to all four cohorts) was identified correlating gene expression profiles with ZEBOV-GP antibody titres and a gene signature associated with reactogenicity (Geneva cohort) was identified correlating gene expression profiles with an adverse event (arthritis). Detailed analyses of immune and molecular signatures of immune responses elicited by rVSV-ZEBOV in humans have been conducted. Transcriptomic analysis identified an rVSV-ZEBOV-induced signature and demonstrated a direct correlation of blood transcriptomic changes with ZEBOV glycoprotein-specific antibody titres as reported in the journal Vaccines. This is the first study profiling the blood transcriptomic response up to one month after rVSVΔG-ZEBOV-GP vaccination, providing an important contribution to the identification of

Project title	Description of result(s)
	immune signatures of the rVSVΔG-ZEBOV-GP that is the first Ebola vaccine approved for clinical use. This information could also have broader implications to support the identification of immune signatures of other Ebola vaccines. Despite the efficacy and safety profile of this vaccine demonstrated in clinical studies conducted in North America, Europe and Africa, the precise mechanisms of inducing protective immunity remain unclear, and these results help our understanding of the precise mechanisms.

Improved protocols for clinical trial design and processes

Project title	Description of result(s)
3TR	Designs of prospective clinical trials have been finalised for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD) and asthma – analysis will enable the identification of super responders, personalisation of treatment and linking clinical phenotypes to different mode of actions.
AB-Direct	Microdialysis process for the determination of *ex-vivo* gepotidacin tissue concentrations in humans has been optimised by reducing probe flow rates as much as possible. The efficiency of this new procedure has been confirmed by complementary experiments in rats.
c4c	Strategic Feasibility Advice operationalised. 25 expert groups set up with access to over 300 clinical and methodological paediatric experts as well as parents and young patients to provide expert advice on paediatric drug development. To date 30 requests have been received and for more than half, the advice has been finalised. A couple of these expert advices have been used by sponsors when discussing their paediatric investigation plan with the Paediatric Committee at the European Medicines Agency (EMA).
c4c	Held the project's first multistakeholder meeting on paediatric inflammatory bowel disease (PIBD) 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 IBD and to agree on a new development path.
EBiSC2	Further improved human induced pluripotent stem cells (iPSC) biobanking processes under a coherent quality management system to ensure consistent standards, efficiency of processing, and improved product delivery to users: • Culture protocols • Guidance on how to deposit lines (cells.ebisc.org/depositors/ and cells.ebisc.org/faq/) • Guidance on how to QC iPSC lines + related tissue (cells.ebisc.org/faq/ and cells.ebisc.org/customer-information/)
EBiSC2	To meet iPSC end-user needs, establishment of: • protocol optimisations for high volume iPSC scalable expansion and differentiation for iPSCs, neuronal, cardiac, and hepatic cell models and to support proof-of-concept (PoC) studies in terms of reproducibility, sustainability, and reliability; • additional protocols to generate tissue specific cell types from healthy and disease relevant iPSC lines at high volume. To meet iPSC end-user needs, establishment of testing of developed QC regimes for early progenitors and more mature cell types. To meet iPSC end-user needs, establishment of a protocol for high-volume cell cryopreservation (including alternative cryopreservation formats) as well as criteria for bulk QC testing of iPSC expansion and differentiation for iNGN2 neurons, cardiac, definitive endoderm, hepatocyte progenitor and hepatocyte-like cell populations. To enable downstream evaluation, disease-relevant iPSCs (e.g., cardiac disease) have been included in protocol optimisations to allow disease phenotyping.
ERA4TB	Start of clinical trials with two new compounds with anti-TB activity. In relation to this main outcome, the definition of the units' validation criteria for the development of first-time-in-Human (FTIH) within the project constitute an innovation in themselves because there was no standard before.

Project title	Description of result(s)
EU-PEARL	First draft of the master protocol with intervention specific appendix template for integrated research platforms (IRPs) was completed with input from disease experts and regulatory stakeholders.
IDEA-FAST	The IDEA-FAST project has assessed several sensors and devices used to monitor fatigue and sleep. In one of the first studies at scale, the performance of commercially available sensors against technical and patient-usability criteria for the specific disease cohorts present in the IDEA-FAST project has been assessed. The devices included a headband sleep monitor, activity monitors, and bed sensors, amongst others. Testers worked closely with the technologies during a 4 to 8 week testing period and reported their experience through diaries and detailed questionnaires. The results have been used to prepare for a feasibility study and are reported on the project website.
IMI-PainCare	Published the BioPain study protocol to validate human biomarkers of nociceptive processing based on non-invasive electroencephalographic recordings. These pharmacodynamic biomarkers will improve future analgesic drug development by allowing pharmacokinetic-pharmacodynamic evaluation of drug effects in early-stage drug development.
INNODIA	Antithymocyte globulin (ATG), Thymoglobuline, an immunosuppressive agent used in one of the INNODIA clinical trials, has recently shown promise in the treatment of new-onset T1D subjects aged 12–45 years. The study protocol 'Minimum effective low dose Anti-human Thymocyte Globulin (MELD-ATG)', based on the INNODIA master protocol, has been published in BMJ Open.
Mobilise-D	Published the protocol of the MOBILISE-D technical validation study to demonstrate the technical validity of measuring digital mobility outcomes (DMOs) in the real world using wearable devices including inertial measurement units (IMUs). The procedures for the validation of an IMU-based device's ability to measure gait / walking are defined and the experimental procedures for the validation of algorithms used to calculate the DMOs are presented.
PERISCOPE	An outpatient controlled human infection study was initiated to confirm results obtained previously in in-patient studies and evaluate the risk of asymptomatic transmission to household contacts.
PERISCOPE	Approved and launched a randomised clinical trial to investigate and compare immunogenicity of acellular pertussis (aP) vaccines vs whole-cell (wP) vaccines in infants born to aP-vaccinated mothers.
PharmaLedger	The PharmaLedger project applied its blockchain platform to several clinical trials use cases, including: Clinical trial e-recruitment: this use case uses blockchain to match patients with relevant clinical trials from multiple sponsors. Clinical trial eConsent: streamlines the informed consent for clinical trials, including allowing for remote clinical trials. Internet of Things for Medical Devices: allows clinical trial participants to easily use electronic diaries, devices, and sensors while also ensuring the data obtained is obtained, analysed, and stored in a GDPR compliant manner.
PIONEER	PIONEER, with the help of patient representatives, has developed a core outcome set (COS) for localised and metastatic prostate cancer relevant to all stakeholders, in particular patients. This publication showcases the process for COS development and highlights the most important recommendations to ultimately inform future research projects co-created between patients and other stakeholders.
RADAR-AD	RADAR-AD published its trial protocol for evaluating remote monitoring technologies (RMTs) such as smartphone applications, wearables, and home-based sensors to measure functional decline in Alzheimer's disease.
RTCure	Development of a protocol for a long term follow up study of the Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept (APIPPRA) trial. APIPPRA investigates if the drug abatacept could prevent development of RA and in this follow up study, called ALTO (Arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept Long-Term Outcome study), the same participants will be followed on a more long-term basis to investigate whether abatacept treatment prevents or delays additional joints being affected by pain or inflammation and whether prevention of RA in a patient group is a sustained feature of the abatacept treatment.

Project title	Description of result(s)
	Trials@Home has developed the protocol for their decentralised clinical trial, which is a proof-of-concept study to test how clinical trials can be run in the future. RADIAL (Remote And Decentralised Innovative Approaches to Clinical Trials) is a three-arm study comparing decentralised and hybrid clinical trial approaches with a conventional approach. The trial will focus on people living with type 2 diabetes and will take place in several countries across Europe. A total of 400 people will take part in the decentralised arm, 200 in the standard arm and 200 in the hybrid arm. The trial will last for six months. When drafting the protocol and creating training materials, people living with type 2 diabetes were closely consulted on both the trial design and on the way information about the trial is explained.
Trials@Home	Trials@Home completed a series of interviews with clinical trial personnel, patient representatives and other decentralised clinical trial (DCT) stakeholders to inform the design of their RADIAL trial. 48 stakeholders from 20 case studies were interviewed. Key findings were that: • patient involvement and participant engagement are critical to the success of DCTs; • building strong relationships early with trial partners supports DCT conduct; • multiple modes of capturing information, including patient-reported outcomes (PROs) and routinely collected data, contribute to data completeness. The full report is available in the British Journal of Clinical Pharmacology.
Trials@Home	As a result of the COVID-19 pandemic, many clinical trials have shifted from in-person to remote. Trials@Home assessed the regulatory response to the COVID-19 pandemic regarding ongoing clinical trials. They found that 24 of the 27 EU national competent authorities published country-specific clinical trial guidance. This guidance was provided most frequently for regulatory management (24/24), safety management (23/24), documentation management (22/24), and CT monitoring (22/24). The regulatory guidance provided during the pandemic, ensuring participant safety and data integrity, may now be the starting point to innovate future CT conduct. The research is published in Clinical Pharmacology and Therapeutics.
TRIC-TB	The first in human (FiH) study for the TRIC-TB molecule was approved by the Spanish regulatory agency (AEMPS) and the Ethics Committee of hospital Sant Pau in Barcelona in October 2020. In December 2020, the first healthy volunteer was dosed. The TRIC-TB molecule is the first small molecule targeting bacterial transcription regulators that is currently in clinical development and, hopefully, to reach the market.

Biomarkers for the efficacy and safety of vaccine candidates

Project title	Description of result(s)
PERISCOPE	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.

New taxonomies of diseases and new stratifications of patient sub-populations

Project title	Description of result(s)
COMBACTE-CDI	Completion of the project and all key results grouped and presented as an infographic on the project website. The highlights include: • identification of the burden of *Clostridioides difficile i*nfections (CDI) across the European healthcare economies; • dynamic transmission model which demonstrates that the true incidence of colonised and infected cases in the hospital setting in different European countries can be predicted; • marked variation in the healthcare costs of CDI diagnostic and treatment measures; • hight costs and overall stay of a patient with a recurrence of CDI; • power of whole genome sequencing for *C. difficile* shown and consequently the possibility to move away from standard ribotyping to study the epidemiology of CDI; • for the first time, epidemiology of CDI uniquely identified per different setting (humans (community and hospital), animals and food); • understanding of the gaps in current guidance and compliance for diagnosis and clinical management of CDI. Overall the results have significant impact for guideline development in terms of testing and treatment, as well as focusing on the need for education and training to ensure compliance with guidelines and for aiding the design of clinical trials of CDI treatment or management options.
EU-PEARL	Published a manuscript in which consensus definitions for treatment-resistant (TRD) and partially-responsive depression (PRD) were developed with input from experts in the treatment of depression, encompassing a broad range of expertise. A total of 25 consensus recommendations resulted. A key take-away from this work is that a definition of TRD that is distinguishable from PRD is recommended.
RHAPSODY	The use of the federated database to model type 2 diabetes progression using genetics and omics data in combination with the clinical measurements allowed the consortium to: (i) refine the previously characterised 5 patient subgroups; and (ii) identify the underlying molecular mechanisms related to islets, liver and adipose tissue metabolism, which provide novel insights into the diverse aetiological processes. This will provide insights into type 2 diabetes progression.
RTCure	Subdivision of RA patients based on refined serology: the consortium used the multiplex serology kit to describe novel serologically defined subsets of RA. The results, published in Frontiers in Immunology, will facilitate patient stratification so that patients can get more targeted treatments for their specific condition.
SOPHIA	Federated database of observational studies and clinical trial cohorts set up, including the necessary computational infrastructure (database and tools) at each local site. Clinical data from more than 20 cohorts extracted and half of them already aligned to a standard data model (OMOP common data model). This is a critical step to allow analysis to identify biomarkers for patient stratification in terms of risk of obesity and response to treatment, including patients with diabetes.

Development and use of cohorts, registries and clinical networks for clinical studies and trials

Project title	Description of result(s)
3TR	3TR has been setting up a clinical network to facilitate clinical studies of 7 immune-mediated, allergic and inflammatory diseases. The network now has 44 centres in 9 countries participating in 3TR prospective studies: • rheumatoid arthritis (RA): 9 centres in 6 countries; • multiple sclerosis (MS): 6 centres in 5 countries; • systemic lupus erythematosus (SLE): 10 centres in 6 countries; • inflammatory bowel disease (IBD): 5 centres in 5 countries; • asthma/chronic obstructive pulmonary disease (COPD): 14 centres in 8 countries.

Project title	Description of result(s)
AB-DIRECT	A phase 1 human clinical study, to investigate tissue distribution of the novel antibiotic gepotidacin, has been launched at the beginning of February 2021 at the Department of Clinical Pharmacology, Medical University of Vienna, with Inserm as study sponsor. The first subjects for tonsillectomy and prostatectomy have been enrolled.
AIMS-2-TRIALS	The phase 2 trial to explore the efficacy, safety, and tolerability of arbaclofen in children and adolescents (ages 5-18) for the treatment of social adaptive behaviour disorders in autism has achieved ~50 % of the recruitment target. This study will provide critical data for the validation of the N170 biomarker and the Vineland Socialisation composite score in the context of use of stratification of the autistic population in a trial. The trial incorporates 'wearable' measures (e.g. smart watches) of physiology in everyday life, which will show if physiological responses are a valid, objective measure of intervention effects.
AIMS-2-TRIALS	Approximately 20 % of infants with a sibling diagnosed with autism will also receive an autism diagnosis. Autism's core features emerge from genetic and environmental likelihood factors that most likely primarily act during the first 1 000 days from conception. The prospective longitudinal study of foetuses/neonates and infants has completed N=51 foetal scans, N=141 neonatal scans (approximately 40 % with elevated likelihood for autism) and recruited 180 infants with elevated familial likelihood for autism (HR), and 45 controls (LR). These studies will pave the way for early-life intervention that could impact across the lifespan and provide the earliest information on both typical and atypical brain development to date.
AIMS-2-TRIALS	The Preschool Brain Imaging and Behaviour Project (PIP) is the first Europe-wide study to track the development of preschool children with and without autism and related neurodevelopmental conditions. 118 participants have been enrolled into the PIP study (including those with visits scheduled), and 96 have completed initial assessments (N = 24 autism; 72 typical development, target N = 180 autism, N = 180 typical development (TD)).
AIMS-2-TRIALS	The Safe Passage study cohort (run in South Africa) investigates the role of environmental factors in social, cognitive, and emotional development and neurodevelopmental conditions (including autism) in a non-western, low-income context. To date, a total of 141 participants have been enrolled into the main study and are undergoing testing using the same biomarkers measures as in the project's European cohort study. There have been no withdrawals to date and recruitment is ongoing. The results will be very valuable in unravelling the role of environment risk factors in autism, as well as the usability of biomarkers measures in a context with limited resources.
AMYPAD	Amyloid imaging is an important tool for patient diagnosis, but its value in guiding patient management is not clear. In 2021, the diagnostic and patient management study (DPMS) reached the end of the clinical phase, with all patients having completed protocol visits and scans. Of the 900 initially planned, 844 patients were recruited (94 % completion). In total, 850 scans were collected and are now part of the DPMS dataset.
AMYPAD	Amyloid imaging is an important tool for identifying patients with Alzheimer's disease for clinical trials and detecting the efficacy of a treatment. The prognostic and natural history study (PNHS) was again impacted by COVID-19 in 2021, but sites were able to recover by doubling the scanning rate of patients. 8 parent cohorts (PC) were active within PHNS and as of the end of December 2021, 1 181 participants consented and 1 220 underwent PET imaging.
BIGPICTURE	The BIGPICTURE project created an overview report (available via CORDIS) of the legal frameworks of seven countries involved in the project. The focus is on those legal requirements that are relevant for the processing and re-use of health data for scientific purposes. These obligations are fragmented and vary to a great extent, depending on the country of the data submitter, the type of data submitter, and the context. Nevertheless, some high-level recommendations are provided.
BIOMAP	BIOMAP finalised a mapping exercise on 60 cohorts and developed a glossary for clinical and -OMICS data. This glossary has been published (and is used to harmonise cohorts analysed in BIOMAP. Harmonised datasets are also accessible to the consortium via a centralised database at the University of Luxembourg.
c4c	Consolidation of the pan-European paediatric clinical trial network (19 national hubs across 21 European countries providing access to over 250 clinical sites) with: • a unique confidential disclosure agreement cascade process and related templates put in place allowing fast and very efficient exchange of confidential information between the study sponsor and single point of contact (SPoC), national hubs (NHs) and sites during site feasibility, study start-up and conduct; • updated standardised template for clinical trials agreement (CTA) to promote timely completion of preparations for site opening;

Project title	Description of result(s)
	• core set of performance metrics for NHs and sites defined, with targets and ranges specified; • the 3 non-industry proof of viability studies were initiated and sites have started to recruit patients; • site selection and trial feasibility testing ongoing for the industry proof of viability studies.
CARE	Set-up of a clinical trial platform for early phase COVID-19 trials. The platform has five partner sites which have been validated as expert centres for the conduct of early trials in humans and which have ample clinical and research experience with this disease.
COVID-RED	Completed the COVID-RED study of the Ava wearable device and associated app to detect COVID cases early. The first participant registered on 19 February and the last one joined on 3 June. All in all, 17 824 people registered for the study, of which over 12 000 people made it to the finish.
DRIVE	For the 2020/21 season, DRIVE faced its fourth influenza season with the uncertainties posed by the COVID-19 pandemic and the unforeseen changes in the influenza circulation patterns. An expanded study network involving 13 research sites in 8 European countries, covering 24 hospitals and more than 500 general practitioners worked together to collect the data necessary for the DRIVE studies for the flu season 2020/21.
EBiSC2	Updated the cell line catalogue so that it is easier for researchers to search for specific cell line data to identify and access human induced pluripotent stem cell (iPSC) lines to meet their research needs, since EBiSC2 intensified interactions with the human Pluripotent Stem Cell Registry (hPSCreg). The freely accessible online registry for human pluripotent stem cell lines (hPSC) with global reach is linked to the EBiSC repository (and others). EBiSC allows researchers to deposit their cell lines into the centralised public online repository; EBiSC reviews the consent used to collect the original biosamples, records all details and registers them in 'hPSCreg' with a unique identifier to support traceability. Depositors can then simply direct other researchers to EBiSC to access their lines. Depositors retain full ownership rights on their lines and can continue using and sharing them as they choose.
EBiSC2	To simplify research using iPSCs (particularly for non-expert users), EBiSC has collected and safeguarded >900 iPSC lines in the centralised non-profit repository, generated from >740 primary tissue samples collected across >27 clinical sites (within >30 different clinical studies incl. lines generated by publicly funded projects ADAPTED, StemBANCC, HipSci), shared by >20 different depositing institutions (academic, commercial, SME, EFPIA) from Europe and US.

EBiSC2	Thanks to improvements made in 2021, EBiSC customers can quickly access iPSC lines from the desired donor background, selecting for age, sex, disease, or phenotype, as well as familial or isogenic controls:
	• Healthy 'control' iPSC lines available from the catalogue include cells donated from individuals ranging from 15 to 89 years of age and both male and female biological sex.
	• Disease associated iPSC lines from >35 disease areas include:
	  ○ 17 % Parkinson's disease
	  ○ 15 % additional neurological diseases i.e. Dravet syndrome, migraine, pain, etc.
	  ○ 13 % Alzheimer's disease
	  ○ 13 % diabetes
	  ○ 8% neurodegenerative diseases, i.e. Huntington's, Gaucher's etc.
	  ○ 6% cardiovascular diseases.

EBOVAC1	The project set up the EBL2010 study in Kenya and Uganda. The study teams have successfully recruited 26 HIV-positive adults who previously received the Janssen 2 dose Ebola vaccine regimen as part of the EBL2002 trial. In the EBL2010 study, the trial teams successfully administered a booster dose to the HIV-positive participants. All safety follow-up visits have been completed. No serious adverse events have been reported. The booster dose was well tolerated, and the trial is now awaiting immunogenicity results. EBL2010 is registered on clinicaltrials.gov (NCT05064956). In the EBL2011 study, EBOVAC1 has recruited 50 children who previously received the Janssen 2 dose Ebola vaccine regimen in the EBL3001 study conducted in Sierra Leone. These 50 children received a booster dose and were followed for 28 days after the booster vaccination. All safety follow-up visits have been completed. No serious adverse events have been reported. The booster dose was well tolerated, and the trial is now awaiting the immunogenicity results. EBL2011 is registered on clinicaltrials.gov (NCT04711356).

Project title	Description of result(s)
EBOVAC3	This study evaluates the Janssen 2 dose Ebola vaccine regimen (Ad26,MVA) in infants under 1 year old. A total of 108 infants have been enrolled and randomised in Guinea and Sierra Leone. 75 participants received Ad26,MVA and 33 received a control vaccine (a meningococcal conjugate vaccine). The Ad26,MVA vaccine regimen was well tolerated. The safety profile consists of mild to moderate adverse events (AEs). The frequency of unsolicited AEs was similar in active and control groups. No serious adverse events (SAEs) were related to the Ad26,MVA vaccine regimen. The Ad26,MVA vaccine regimen induced strong humoral immune responses in all active group infants at 21 days post dose 2, and persisted up to one year in 96 % of active participants. Binding antibody responses were comparable to levels previously reported in African children (1-3 years) and higher than the response in older children and adults. In conclusion, the Ad26,MVA Ebola vaccine is suitable for preventing Ebola in infant populations.
EBOVAC3	In the EBOVAC-Salone Extension study (EBL3005), 652 participants who previously received the Janssen 2 dose Ebola vaccine regimen in the EBOVAC-Salone (EBL3001) study were recruited in Cohort 1. Of the 652 participants recruited, 449 have completed the study; 17 exited before completion; and 186 are currently in the study. EBL3005 also recruited one child who was exposed to the Ebola vaccine regimen at conception (Cohort 2) and is currently still in the study. In this open-label phase 2 vaccine trial, healthcare workers and frontliners from the Tshuapa province in the Democratic Republic of the Congo (DRC) were vaccinated with the Janssen 2 dose Ebola vaccine regimen and were randomised to receive a booster dose either at 1- or 2-years post dose 1. In total 699 participants were enrolled in this trial. The study aims to assess the safety and immunogenicity of the Ebola vaccine regimen and the Ad26.ZEBOV booster.
H2O	The project aims to set up independent, patient-centred health outcomes observatories (H2Os) in four European countries and three diseases initially. The observatories will then equip patients with tools to measure these outcomes and implement a governance model that will allow for ethically and legally appropriate data sharing. So far, an architecture model for the technical infrastructure of H2O has been designed. National data observatory associations are currently forming in partnership with sister organisations and 7 new collaborators have joined the consortium including government agencies and research institutes.
IMMUcan	IMMUcan is accessing patient biological material and linked clinical data via the EORTC SPECTA platform. 129 principal investigators from 78 clinical sites from 17 countries have been authorised to recruit patients in SPECTA as of December 2021.
ImmUniverse	The network of clinical centres involved in the recruitment of patients has been successfully established. It includes four centres for atopic dermatitis (AD) and five centres for ulcerative colitis (UC). The collection of prospective cohorts has successfully been initiated. A total of 36 AD patients (out of 300 expected in total) and 43 UC patients (out of 270 expected in total).
Impentri	The CounterCOVID study, assessing the efficacy and safety of oral imatinib, has been completed. The results (from 385 patients) suggest that although imatinib administration does not change the time to discontinuation of supplemental oxygen and ventilation compared to placebo, the analysis of secondary outcomes indicate that the mortality is lower in the imatinib group than in the placebo group. The findings were published in the Lancet Respiratory Medicine.
ImSAVAR	The consortium characterised the immune system of patients undergoing CAR T cell therapy to identify molecular biomarkers for prediction of irAEs. To date, two study centres are involved to correlate cellular and genomic readouts to specific adverse events to be used as benchmarks for refined *in vitro* and *in vivo* models.
INNODIA	INNODIA reached an important milestone by passing the mark of 5 000 recruited participants. With 652 newly diagnosed people with type 1 diabetes (T1D) and 4 405 unaffected family members (UFM), the consortium keeps paving the way for better treatment and prevention of the disease. Out of 4 405 UFM, 350 have been found to be auto-antibody (AA) positive, and so far 269 are in follow-up.
NEURONET	NEURONET has developed the NEURO cohort initiative, an open network of 40 clinical sites across 13 countries representing over 25 000 participants, as a virtual European parent cohort that facilitates feasibility assessment and recruitment for new research projects, through collection of a harmonised minimal data set.
PERISCOPE	A clinical network was established in Finland to perform a maternal-infant vaccination study. In total, 47 vaccinated and 22 unvaccinated infant-mother pairs completed follow-up. Mothers

Project title	Description of result(s)
	were recruited during pregnancy and either vaccinated with Tdap-IPV or not. Infants were vaccinated at 3 and 5 months of age. Clinical samples were collected at multiple time points before and after vaccination, both from mothers and infants.
PIONEER	PIONEER organised a study-a-thon to characterise different populations of prostate cancer patients. The team developed 25 cohorts of patients, 38 stratifications and 7 outcomes. Currently 12 datasets have run this analysis and the results are available freely in the Shiny apps. All developed resources are open source in GitHub. Access to the development tools, environment and material can be granted upon request.
PIONEER	The study-a-thon team successfully developed packages and Shiny apps to collate cohort diagnostics and characterisation results. Federated data sites have successfully deployed the package and ran the analyses. The results app contains patient counts, time to event analysis for 7 outcomes, metrics distribution and functionality to compare results between the cohorts in all databases.
RESCEU	RESCEU helped set up the BronchStart study, a multi-centre prospective observational cohort study. This study aims to monitor out of season RSV transmission. Study data is made available on a live online dashboard. Data was collected on 10 347 infants and children from 44 study sites for the period 1 June to 5 December 2021.
RHAPSODY	The RHAPSODY consortium reported in Diabetologia the use of their cohort to replicate and cross-validate type 2 diabetes subtypes based on clinical variables (age, BMI, HbA1c, random or fasting C-peptide, and HDL-cholesterol). This clustering may aid in the prediction of disease progression and best treatment options.
RTCure	Establishment of the RTCure at-risk for rheumatoid arthritis (RA) cohort registry, a European registry that can be used as a clinical trial infrastructure and for development of algorithms that will predict the likelihood of developing RA within the coming 1, 2 or 3 years. (Publication under review in Frontiers Rheumatology.)
RTCure	Developed and validated new methods to identify individuals at risk of RA and developed tools to monitor disease progression. The consortium also expanded and further developed cohorts suitable for these purposes. Furthermore, they have also developed standard operating procedures (SOPs) for assays that are and will be used to monitor effects of immune interventions, including tolerising therapies that are used in clinical trials for RA. The same SOPs are and will be used in clinical trials for prevention in individuals at high risk for RA.
RTCure	Initial results of the Abatacept Reversing subclinical Inflammation as measured by MRI in ACPA positive Arthralgia (ARIAA) trial demonstrating the benefits of abatacept in people at risk for RA. The aim of ARIAA is to test whether abatacept, compared to placebo, reverses subclinical arthritis in individuals with antibodies to citrullinated protein antigens (ACPA) and magnetic resonances imaging (MRI) signs of inflammation, but who have not developed RA. After 6 months, 61 % of the individuals in the abatacept group improved in at least one of the MRI parameters (synovitis, tenosynovitis, and osteitis) compared to only 31 % in the placebo group (p=0.0043). Also, arthritis developed in 17 patients in the placebo group (34.7 %) but only 4 patients (8.2 %) in the abatacept group (p= 0.0025), showing that abatacept significantly improves subclinical arthritis in patients at high risk of developing RA, and that early intervention may prevent or at least delay the development of RA. The results are presented in a video.
STOPFOP	The aim of this study 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. The clinical study has started (six patients recruited) but not completed yet. If positive, this study will provide data to treat a very serious condition for which no treatment currently exists.
VALUE-Dx	The first point prevalence audit survey (PPAS) in primary care and long-term care facilities (LTCF) was completed in April 2020, with 4 995 patients in primary care and 418 patients in LTCF with community-acquired acute respiratory tract infections (CA-ARTI) registered in 21 countries (18 countries contributed to the primary care PPAS, and 5 countries to the LTCF aspect of the PPAS). Analyses of the first PPAS was used to inform the selection of the countries to participate in the PRUDENCE trial. Due to the success of the VALUE-Dx PPAS, the same primary care networks were asked to re-open the PPAS and register patient CA-ARTI contacts during the COVID-19 pandemic (PPAS2).
VSV EBOPLUS	Collection of samples from the paediatric clinical trial ‘Phase 1/2, randomized, controlled open label trial to evaluate the safety and immunogenicity of the rVSVΔG-ZEBOV-GP Ebola virus vaccine candidate in healthy children aged 1 to 12 years and in their adults and/or

Project title	Description of result(s)
	children relatives living in Lambaréné, Gabon'. 120 participants aged 1 to 12 years vaccinated.

Big data solutions to leverage knowledge / implementation of data standards

Project title	Description of result(s)
BigData@Heart	The project has generated a comprehensive and systematic review of contemporary cardiovascular (CV) data sources. This review providing new avenues to improve future real-world research and to achieve better patient outcomes.
BigData@Heart	A paper on *a* registry-based algorithm to predict ejection fraction in patients with heart failure has been produced. The proposed algorithm enables more effective research on heart failure (HF) in the big data setting.
BIOMAP	BIOMAP finalised a mapping exercise on 60 cohorts and developed a glossary for clinical and -omics data, which has been published in the British Journal of Dermatology and has the potential to become a gold standard for new cohorts.
COMBINE	Enhancements to the G42 software tools for pre-clinical drug discovery which will facilitate data analysis within COMBINE and the wider AMR Accelerator and could be made available to external customer groups as part of the commercial activities of Grit42.
COMBINE	A Knowledge Graph database (~50 users) established to link publicly available AMR-related data resources from ChEMBL, PubChem, BindingDB and the SPARC database. External stakeholders can use the demonstration version which contains publicly accessible data sets. COMBINE and other AMR Accelerator groups will be able to integrate their own data into secure instances for bespoke analyses.
ConcePTION	A newer version of the ConcePTION common data model (CDM v.2.2) was released; out of the 21 data sources accessible by the 20 data providers (DAPs) selected, 13 data sources already been converted to the ConcePTION CDM. The DAPs involved in ConcePTION were selected based on their experience and interest in conducting studies relating to medicines safety in pregnancy and breastfeeding, as well as for their expertise in making use of their data source demonstrated by multiple high-quality scientific publications. The data sources and CDM are described in a paper in Clinical Pharmacology & Therapeutics.
DRAGON	DRAGON is developing artificial intelligence (AI) models based on imaging (for example CT scans) to provide a diagnosis and prognosis of COVID-19. To do this, an ISO compliant, secure, flexible and scalable distributed learning network (DistriM) was successfully set up and deployed to six clinical sites throughout Europe. Datasets are uploaded at these sites to its local DRAGON machine and are never transferred over the network. AI models to be trained are downloaded from a remote server at the beginning of the training and then reuploaded to the same server when the training is finished. In this way, data never leaves the data stores but is available to the learning application.
EBiSC2	To improve user experience and FAIRness (i.e. increase findability, accessibility, interoperability, and reusability) of the EBiSC collection, a new cell line catalogue with 10 search filters has been produced, along with the BioSchemas mark-up language introduced in the source code.
EHDEN	In 2021, the EHDEN project held two more open calls for data partners which resulted in an additional 81 partners being identified. As a result, the EHDEN data network now contains 143 data partners from 27 countries with over 510 million patient records. Some of this data has already been used to provide timely evidence in many areas, including on the safety of COVID-19 treatments and vaccines
EHDEN	The EHDEN project performed the largest, most extensive global network study (~126 million people in 8 countries) on background rates of adverse events of special interest (AESI) for COVID-19 vaccines. The study, published in the British Medical Journal, found large variations in the observed rates of AESIs by age group and sex, showing the need for stratification or standardisation before using background rates for safety surveillance.
EQIPD	AD-SOLES (freely available to all): EQIPD has established a freely available online resource curating primary research relating to Alzheimer's disease, available through an R-Shiny dashboard. This will be developed further through funding from ARUK.

Project title	Description of result(s)
ERA4TB	The consortium has put significant efforts into preparing the platform for the management of data generated in the project and legacy data. The core development in this line has been the drug development information management (DDIM) system, which is a platform to collect, organise and disseminate, curated, standardised preclinical and clinical TB data that will allow the data collaboration within ERA4TB and also with other TB projects. The DDIM will be a pillar to achieve a fast drug progression through the pipeline given the seamless flow of data among partners it allows. Additionally, the platform will incorporate legacy data from other TB initiatives. Another related development beyond the state of the art in this line is the implementation of standards for data collection and tabulation to allow for data consistency, aggregation and analysis. This development will facilitate the use of data within the consortium and will contribute to the sustainability of the project beyond its execution time.
eTRANSAFE	In 2021, a new version of the eTRANSAFE preclinical text mining system, PretoxTM 2.0 was developed. The main goal of the system is to assist and help toxicology experts to detect treatment-related findings in animal toxicology reports and present this information in a user-friendly interface via the study report domain software. This system has two main modules; a text mining pipeline that automatically detects and retrieves treatment-related findings from animal toxicological reports using natural language processing (NLP) techniques; and the PretoxTM web application that presents the extracted findings to toxicology experts for validation and curation.
FAIRplus	The FAIRplus FAIR Cookbook was further expanded in 2021 and now includes over 30 recipes on making data FAIR (findable, accessible, interoperable, and reusable). The cookbook includes use cases on omics data, chemical activity datasets, clinical cohorts, and transcriptomics. The consortium hosted a public webinar to showcase the cookbook.
FAIRplus & EHDEN	FAIRplus, in collaboration with EHDEN, published a recipe in the FAIRplus cookbook on making clinical observational data FAIR. The recipe gives advice on adding structured metadata to the back end of web pages to make them findable by search engines such as Google. The standard method to do this, based on Schema.org standards, does not account for medical data, so the consortia created an extension of Schema.org to capture the clinical data-specific metadata.
HYPO-RESOLVE	Completed the building of a large, sustainable database including hypoglycaemia data from 98 clinical trials containing data from 60 194 individuals from different populations of people with type 1 or sulfonylurea- or insulin-treated type 2 diabetes. These include three paediatric trials and several trials using continuous glucose monitoring (CGM). Prior to upload, the data was de-identified to safeguard patients' anonymity, and secure data transfer procedures ensured safe transfer to the Hypo-RESOLVE server.
IDEA-FAST	The IDEA-FAST project aims to use smartphone, wearable and sensor data to identify digital endpoints that provide a reliable, objective and sensitive evaluation of fatigue and sleep. To ensure they gather high quality and interoperable data, the consortium has extended the use of the CDISC study data tabulation model (STDM) data standards that are commonly used to report on clinical trials to the data gathered by the consortium.
ImSAVAR	Creation of version 1.0 of the sample metadata template to collect more than 40 variables, such as unique ID, date of sampling, storage medium, and storage temperature. The template, accessible outside the consortium, is part of the data platform. It will enable interoperability of metadata, sample information and improve FAIRness of data received from EFPIA partners. Confidential data is only meant for the consortium.
PERISCOPE	In addition to the study-specific longitudinal analyses, PERISCOPE developed an analysis framework to analyse the impact of various parameters on clinical/immunological endpoints across multiple cohorts and clinical studies in PERISCOPE. This 'vertical analysis' framework is designed to identify correlations between key immunological biomarkers between the different PERISCOPE studies/cohorts. This can have multiple implications, including the identification of potential redundancy between bioassays. Selecting the most informative bioassays may reduce costs of future clinical trials.
PIONEER	PIONEER data platform launched employing JupyterHub and OMOP-ATLAS and the latest SAS-analytics. This cloud-based platform will provide data access and machine learning analytics capabilities for both academia and industry researchers. At present the PIONEER platform consists of a network of 15 data sets from consortium partners, industry, and associated data partners.
PIONEER	PIONEER welcomed 7 new data providers from 7 different countries in 2021, with a further 7 datasets actively being mapped to OMOP (common data model). Once mapped to OMOP

Project title	Description of result(s)
	and available in the platform, more harmonised data will be available for use by PIONEER researchers to address the most important prostate cancer research questions.
PIONEER & EHDEN	PIONEER collaborated with EHDEN to run a 5-day study-a-thon to investigate the natural history and outcomes of prostate cancer patients managed with 'watchful waiting', a conservative management option for patients with a life expectancy of less than 10 years at time of diagnosis. More than 240 participants including data scientists, clinicians, epidemiologists, patients, and statisticians from 20 different countries analysed prostate cancer patient data from 17 databases across 6 countries. The study-a-thon features in episode 4 of the EHDEN podcast.
PREMIER	The first inventory of active pharmaceutical ingredients (APIs) in the European market has been compiled and is available to all partners to be utilised for scientific purposes. Thanks to this inventory, partners will no longer have to re-do studies and / or invest resources in looking for all the background information on an API.
RADAR-CNS	The RADAR-CNS consortium analysed data from smartphone and wearable devices from 1 062 participants in 5 countries (IT, ES, DK, UK, NL) to monitor behavioural changes during COVID-19. Key results are: • more time using social media apps, particularly around major news events; • lower heart rate; • went to bed later; • slept more; • young people had longer homestay than older people, and fewer daily steps. The consortium also suggested that the RADAR-base data collection platform could be used to passively assess the compliance of lockdown, and could help countries ease out of lockdown. The findings are published in the Journal of Medical Internet Research.
RADAR-CNS	The RADAR-CNS project reported their findings on how health care professionals (HCPs) view the incorporation of remote measurement technologies (RMTs) into everyday clinical practice for the management of central nervous system disorders. Semi-structured interviews were conducted with 26 HCPs who care for patients with epilepsy, depression, or MS. A total of 8 main themes emerged from the analysis: (1) potential clinical value of RMT data; (2) when to use RMT in care pathways; (3) roles of health care staff who may use RMT data; (4) presentation and accessibility of data; (5) obstacles to successful use of RMT; (6) limits to the role of RMT; (7) empowering patients; and (8) considerations around alert-based systems. The findings were reporting in a webinar.
RADAR-CNS	Researchers from the RADAR-CNS project have used a machine learning approach on data collected with wearable devices to detect the presence of severely convulsive seizures in people with epilepsy. Published in the journal JMIR mHealth and uHealth, the study showed that the technique could detect 10 out of 11 seizures correctly with a very low rate of incorrect identifications of just one per five days. Having evaluated the approach in clinical settings, the researchers are now assessing its value in outpatient and community settings. In addition, the team were awarded the Harald Fey Prize for their research looking at the potential of wearable devices to identify and characterise life-threatening seizures in patients who are at risk of sudden unexpected death in epilepsy (SUDEP). The researchers found that accelerometers from wearable devices can indicate post-ictal immobility, the lack of motion following a seizure, which has been associated with SUDEP in patients known to be at high risk.
RADAR-CNS	Researchers from the RADAR-CNS project have developed a new machine learning method to recognise people with COVID-19 from heart rate data provided by wearable physical fitness monitors such as Fitbit. By comparing 19 participants with COVID-19 symptoms to 19 participants without symptoms, researchers showed the method was able to correctly identify all patients with symptoms (100 % sensitivity) and performed very well on identifying people without symptoms (90.6 % specificity), suggesting it would provide a low rate of false alarms.
RADAR-CNS	Researchers from the RADAR-CNS project explored the impact of the COVID-19 lockdown on those with major depressive disorder in a new study published in BMC Psychiatry. The research found changes in depressive symptoms and duration of sleep over the course of the first lockdown in the COVID-19 pandemic. Some of these symptoms varied according to whether participants were experiencing clinically relevant depressive symptoms shortly prior to the pandemic.

Project title	Description of result(s)
RADAR-CNS	A new multi-national study, by the RADAR-CNS project, has shown that data detected by Bluetooth sensors on smartphones can estimate the behaviours and social indicators associated with depression. Depression affects more than 264 million people world-wide. Symptoms of depression often fluctuate in severity and can be difficult to record. This study combined smartphone Bluetooth data with 2 886 questionnaire responses from 316 participants and demonstrated that the Bluetooth data could provide useful insights into supporting people with depression and informing provision of mental health services. The findings were published in the journal JMIR mHealth and uHealth.
RHAPSODY	Plasma lipidomics data were obtained from three type 2 diabetes progression cohorts (2 775 samples); quantitative plasma peptide and protein data from 1 200 samples; polar metabolite data from > 5 000 samples. Polar metabolites and plasma lipidomics data were also generated from 268 plasma samples from pancreas surgery patients (partial pancreatectomy patients) for whom the consortium also obtained clinical information and islet transcriptomic profiles. Plasma lipidomics and islet, liver, fat and muscle transcriptomic data were generated from mouse models of prediabetes. All data are deposited either in the RHAPSODY federated database for sensitive clinical data, or in a central database for non-sensitive data.
VALUE-Dx	VALUE-Dx has successfully framed the concept of 'Lab-Select', a service that uses laboratory testing data from a pan-European network of laboratories to drive decision making. In this context, VALUE-Dx has performed a data interoperability network analysis, and compiled a data interoperability network reference architecture report as well as a data interoperability network proof-of-concept report.
WEB-RADR	The WEB-RADR MedSafety app, which allows for the easy reporting of adverse drug reactions by patients and physicians was rolled out in an additional three countries in 2021: Paraguay, South Africa, Cabo Verde. In addition, an 'adverse events following immunisation (AEFI)' functionality, which can be used to monitor COVID-19 vaccines, was developed in the app.

Education and training for new and existing R&D scientists and stakeholders

Project title	Description of result(s)
C4c	The c4c Academy Learning Platform offers multiple short training courses and an advanced, year-long course in paediatric clinical trials and drug development (started in October 2021) to the c4c members. The c4c Academy has over 1 000 users to date.
CARE	Leveraging Janssen Pharmaceutica NV's broad expertise in antivirals, the project assembled a team of scientists, each with a specific skill set and a variety in years of experience. This team, including post-docs and junior lab technicians, was specifically trained to deploy Janssen's vast resources to search for compounds screening to search for new chemical matter to combat coronavirus infections.
EBiSC2	EBiSC2 is supporting third-party research projects in reaching their sustainability goals by providing best practice guidance and working with them to incorporate, safeguard and distribute newly generated human induced pluripotent stem cells (iPSC) lines from the public EBiSC catalogue. • Publicly available guidance documents and an infographic to provide the iPSC research landscape with clear advice on the benefits and 'how-to' of EBiSC iPSC deposition. • 5 open access publications in 2021 to provide the iPSC research landscape with recommended QC regimes; best practice for iPSC repositories and research projects; and details of generated iPSC line cohorts. • A public webinar entitled 'Pitfalls and best practices for CRISPR/Cas9-based gene editing - 10 things you should think of when designing a good gene editing strategy' was jointly held with Samplix to disseminate new findings to EBiSC customers that purchased cell lines deposited into EBiSC where chromosomal aberrations had been identified in IMI2-ADAPTED. Third-party research impact is highly visible: publications + datasets are clearly linked to relevant cell lines (>100 publications from researchers using EBiSC iPSC lines).
EBOVAC2	A group of 3 scientists and technicians from Centre Muraz in Burkina Faso have been trained to perform vaccine immune response analysis in Paris in Q1 2021 and conducted the analysis of the collected samples and data.

Project title	Description of result(s)
EHDEN	The EHDEN project strengthened their real-world data training academy through the addition of 4 courses, including a module designed by the European Patients Forum to familiarise patients and patient organisations with the basics of health data. The academy currently has 1 400 course enrolees who have completed over 1 800 courses. 93 % of enrolees rated their experience as good to excellent.
EQIPD	E-Learning course: Open access, online training course for researchers world-wide on the principles of research rigour and robustness in animal studies. This online course is for researchers from academia and industry, with a focus on animal studies, but also more broadly applicable. Depending on website traffic, organisers expect approx. 100 researchers per month can receive basic training on the principles underlying the EQIPD quality system.
EQIPD	Around 100 people took part in the third EQIPD summer school for researchers on the principles of research rigour and robustness in animal studies. In 2021, the summer school was held in June (virtually), and the participants were mainly researchers from academia and industry, with a focus on animal studies. Participants received interactive, more in-depth training on the principles underlying the EQIPD quality system.
FAIRplus	In summer 2021, the FAIRplus Fellowship Programme kicked off. For approximately eight months, the programme will guide its fellows through a series of modules on the findable, accessible, interoperable, and reusable (FAIR) principles for data management in the life sciences. The 18 participants come from academia and industry, including AstraZeneca, Barcelona Supercomputing Center, BenevolentAI, GSK, University of Luxembourg, University of Greifswald, Janssen Pharmaceuticals, Bitac and the University of Aberdeen.
GetReal Initiative	A new updated edition of the foundational course 'Real World Evidence in Medicine Development', started in September 2021 (the course, which has been run since 2017, was updated to include in particular the latest information on tools and literature). In total, 230 people have already attended this course to get understanding of the current techniques, opportunities and challenges for the use of real-world evidence in medicine development. In addition, two new courses were developed as part the GetReal Academy and making use of the Elevate Health platform. • 'Structured Benefit–Risk Assessment of Medicinal Products': this self-paced online course is already available and open to anyone who wishes to extend their knowledge in structured benefit risk assessment with a specific focus on multi-criteria decision analysis. • 'Methodology, Statistics and Operation of Pragmatic Trials': this self-paced course will be soon open for registration.
H2O	8 free educational videos (1 kick-off, 1 patient empowerment, 1 request for interest, 2 PROs, 1 Why join, 1 H2O impact, 1 project overview), seminar recordings, 7 factsheets (1 general, 1 for each of the following stakeholders: patients, HCP, regulators, health authorities, researchers, industry), 2 patients' leaflets (project information and benefits tailored to patient stakeholders) and the 3 operational plans (governance and sustainability models) have been produced.
HARMONY	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 the common data model vocabulary, format, approaches to data modelling in various blood cancers, model complexity and data availability, introduction to data analytics using Apache Zeppelin platform-based notebook, and harmonisation of quality assurance processes by validating results of previous studies.
IDEA-FAST & Mobilise-D	IDEA-FAST has collaborated with the Mobilise-D project to create the Digital Health Catalyst. The aim of the catalyst is to foster the next generation of digital health researchers and professionals. With a focus on early career researchers, it offers a programme of activities which provide exposure to a rich scientific environment, training, publishing assistance, networking, and more.
NEURONET	NEURONET published the regulatory and health technology assessment (HTA) engagement decision tool in the NEURONET Knowledge Base. The tool outlines key processes and procedures for engaging with regulatory, HTA bodies, and payers. The tool will help IMI projects identify relevant procedures, based on the project's stage of research and asset developed.
PERISCOPE	Following validation of the whole-blood based assay for measuring pertussis-specific cellular responses in infants, knowledge transfer (for example via a workshop and SOPs) to

Project title	Description of result(s)
	consortium partners was initiated and the assay was implemented in all infant vaccination studies (Africa, UK, Finland).
PIONEER	PIONEER has trained 8 EAU Guidelines Associates in the theory of OMOP mapping via the EHDEN Academy. 5 members of the PIONEER consortium have also taken an additional training course in OMOP mapping using the GMV Antari modelling software for OMOP conversion. Finally, the project produced internal training material on the development and maintenance of the R packages and Shiny apps.
RTCure	2 extensive workshops with a total of 25 participants aimed at educating PhD students, R&D scientists, and patients in how to interpret graphs and statistics were arranged in Autumn 2021.
TransQST	Kidney QST model webinar was provided to consortium members as well as to the other IMI consortium partners (eTRANSAFE & TransBioLine) to explain the applications and potential context of use of the model.
TransQST	Webinar on cell turnover model for predicting GI toxicity presented to IMI2 TransQST consortium and IMI consortium partners (eTRANSAFE & TransBioLine).

Impact on regulatory framework

Project title	Description of result(s)
AIMS-2-TRIALS	Received an EMA Letter of support for the VABS-II Adaptive Behaviour Composite (VABS-II-ABC) score as measure of adaptive social functioning in people with autism without intellectual disability to be used as an anchor for a biomarker in research.
Big Data for Better Outcomes (BD4BO) programme	The IMI BD4BO projects of IMI (PIONEER, HARMONY Alliance, BigData@Heart, ROADMAP and EHDEN) developed a set of recommendations to inform EU decision makers to respond to the public consultation on the European Health Data Space (EHDS). These recommendations should help in shaping the regulatory framework.
DRIVE	The EMA Vaccine Working party assessed and provided comments on the DRIVE's influenza vaccine effectiveness (IVE) results report 2019/2020. DRIVE prepared a rebuttal document in response to EMA's comments.
DRIVE	DRIVE has demonstrated the added value of joint public-private European platforms and their potential to be applied to other vaccines post-marketing evaluation, notably against COVID-19. Back in November 2020, several DRIVE partners (namely FISABIO, P95, THL, Sanofi-Pasteur and GSK) started developing COVIDRIVE, a public-private partnership for brand-specific COVID-19 vaccines effectiveness evaluation in the EU, based on DRIVE assets (study network, vaccine effectiveness methods, study platform governance, IT infrastructure for data collection and pooled analysis). This platform proposal was proactively presented to EMA in December 2020 who welcomed this initiative and then proposed to COVID-19 Marketing authorisations holders at a Vaccine Europe meeting (Task Force for COVID-19 vaccines, epidemiology and pharmacovigilance). COVIDRIVE was launched in September 2021.
GetReal Initiative	As mentioned in the work plan 2021 and continuing in 2022, the EMA's Committee for Medicinal Products for Human Use (CHMP) will further explore the feasibility of using a more explicit approach to describe value judgments in the current regulatory benefit/risk assessment framework and the ADDIS tool will be used by regulators as an educational tool.
H2O	Discussions with different regulatory bodies at national (Spain, Germany, The Netherlands and Austria) and pan-European levels have taken place to stress the need and impact of value-based healthcare and discuss how the incorporation of patient-reported outcomes into general outcome measurement schemes in real-life settings in healthcare can contribute to advance in this direction.
HYPO-RESOLVE	The consortium completed interaction with the EMA to obtain scientific qualification advice for the patient reported outcome (PRO) measuring the impact of hypoglycaemia in diabetic patients. The feedback from EMA was overall positive and endorsed the approach of the consortium to develop the PRO, with some recommendations to improve some aspects of the future work of the project. The PRO will be an important tool to recognise, evaluate, and reduce the burden of hypoglycaemia as part of the treatment of type 1 and type 2 diabetes.

Project title	Description of result(s)
INNODIA	The project has received a letter of support from the EMA for the adaptation of the INNODIA Master Protocol in Type 1 Diabetes (T1D) for studies in prevention. The approach taken by the consortium using standardised recruitment, centralised data collection and standardised data evaluation provides a very valuable opportunity to track T1D from the appearance of auto-antibodies, through dysglycaemia and to the full presentation with symptomatic disease. The protocol will strongly support academic researchers and companies in planning and conducting future trials in T1D.
ITCC-P4	Publication of the white paper International consensus on minimum preclinical testing requirements for the development of innovative therapies for children and adolescents with cancer that provides recommendations based on the experience of the US NCI funded Preclinical Testing Consortium and ITCC-P4 for the use of cell-based and mouse models for paediatric solid malignancies, as well as guidance on the scope and content of preclinical proof-of-concept data packages to inform clinical development dependent on clinical urgency. These recommendations, which resulted from the multistakeholder meeting held in 2018 with representation from major EU and US paediatric research centres, PPTC leadership, FDA leadership, patient advocacy and concerned EU citizens, can serve as a minimal guidance necessary to jumpstart preclinical paediatric research globally. They will serve as the basis for a guidance document to be discussed with the EMA to improve prioritisation and effectiveness of drug development for children and adolescents with cancer.
Mobilise-D	The EMA issued a second letter of support for Mobilise-D's digital mobility outcomes (DMOs) as monitoring biomarkers of mobility performance in regulatory drug trials. The second letter outlines EMA's endorsement on the clinical concept to validate disease-specific and disease-independent DMOs as monitoring biomarkers, on the observational study to validate DMOs in four diseases (Parkinson's disease, chronic obstructive lung disease, multiple sclerosis, and proximal femoral fracture), and on the clinical concept to validate DMOs as surrogate endpoint, predictive of clinical outcome. This is another significant achievement supporting the approach used by Mobilise-D to develop validated and accepted DMOs.
PharmaLedger	The PharmaLedger blockchain use case on Electronic Product Information (ePI) was presented at the Danish Medicines Agency and during an Innovation Task Force meeting at the European Medicines Agency. This use case, which aims to simplify the generation, update and delivery of the medicine package leaflets, has the potential to reduce the manufacture of billions of paper leaflets per year.
PREFER	The EMA released the draft qualification opinion on a proposed research framework for patient preference studies (e.g. purpose, objectives, how to design and conduct the studies and how to interpret the results) and a points to consider document on considerations for selecting the methods to do the patients preference study. In this draft opinion, the EMA endorses the proposed research framework and points to consider document 'as a comprehensive reference document for planning and conducting patient preference studies (PPS)'. This was the first EMA-EUnetHTA (i.e. regulator and health technology assessment bodies) joint procedure. Further to the closure of the 1-month public consultation, the EMA is now finalising the qualification opinion.
RADAR-AD	Published a review outlining the qualification opinions (QOs) and advices (QAs) and scientific advices (SAs) of the Committee for Medicinal Products for Human Use (CHMP) on the use of novel remote monitoring technologies (RMTs) in clinical trials. This work summarises the types of devices that are intended to be used in clinical trials for supporting/submitting applications for obtaining marketing authorisation (registration trials) and outlines the main recommendations of the CHMP.
RHAPSODY	RHAPSODY developed interactions with both the EMA and MHRA to seek advice about the use of RHAPSODY biomarkers in (i) predicting T2D development and progression; and (ii) modifying disease drug treatments. Health economists performed cost-effectiveness assessments to evaluate the potential interest for EU and US health care systems of using 12 of the RHAPSODY biomarkers to stratify or target preventive and therapeutic treatments of T2D. They showed that using the biomarker ENPP7 to drive treatment decisions would be cost effective in the UK setting.
RTCure	An extensive white paper with tentative guidelines for studies aimed at prevention of rheumatoid arthritis (RA) has been developed by several partners and the document has been presented and evaluated by the Swedish Medical Products Agency (MPA) in May 2021. This paper and the feedback from the regulators can be used in the further development of guidelines for trials aimed at prevention of RA.
RTCure	The consortium defined at-risk patient populations eligible for rheumatoid arthritis (RA) prevention trials. These are included in a Regulatory Briefing document used for discussions

Project title	Description of result(s)
	with the national regulatory agencies in the UK and Sweden around the unmet clinical need and potential trials in the risk for RA population.
TransBioLine	The project aims to develop novel safety biomarkers that will reliably indicate injury of the different target organs for drug development purposes. Fruitful interaction with regulatory authorities (EMA and FDA) have been made leading to the acceptance of four organ work package Letters of Intent into the FDA Biomarker Qualification Program: • Drug-induced vascular (DIVI) injury biomarkers measured in the blood by immunoassays and mass spectrometry • Drug-induced serum-based CNS injury biomarker panel (DINI) • Urine and serum biomarker of drug induced kidney injury as assessed by multiple assays (DIKI) • Drug-induced liver injury biomarker panel (DILI). If successful, regulatory qualification of biomarker sets may have a very strong impact on drug development and potentially clinical (diagnostic) applications.
TransQST	Engagement with regulatory bodies: Discussion with regulatory bodies (EMA, FDA and NC3Rs) during 8th TransQST General Assembly Meeting in November 2021 on the potential use of modelling approaches to support liver, kidney, gastro-intestinal and cardiac safety assessment of novel drugs.
Trials@Home	In 2021, the Trials@Home consortium met with the EMA's Innovation Task Force (ITF) for an early dialogue with European experts on scientific and regulatory topics relevant to decentralised clinical trials (DCTs). The meeting objectives were to explore the regulators' expectations of data, regardless of where and how it is collected (e.g., at home or in the clinic), and to discuss the methodology for the Trials@Home RADIAL trial. More than 40 regulators from more than 15 National Competent Authorities across Europe attended, which clearly demonstrated great interest in the topic of DCTs.

Implementation of project results inside industry

Project title	Description of result(s)
COMBACTE-CDI	Contribution to the testing and implementation of new bio-informatic tool BIOMERIEUX EPISEQ® CS that allows users to transform large next-generation sequencing datasets into microbiological insights without bioinformatics competencies or hardware investment. Leverage the use a multiplex PCR syndromic assay developed by bioMérieux (BIOFIRE® FILMARRAY® gastrointestinal panel) to assess the presence of other pathogens in stools of diarrheic syndromes than C. diff.
EBiSC2	Implementing human induced pluripotent stem cells (iPSC) protocols and cells lines in portfolio R&D activities. Key example to illustrate how the new tools and processes generated by EBiSC2 have been implemented by industry participants - human neuronal co-culture platform, as described in Stem Cell Research. • To accelerate the generation of mature, human astrocytes, a public partner generated a genetically modified iPSC line. • Trialling of iPSC line and associated differentiation and neuronal co-culture protocol by EFPIA partners resulted in significant improvements in the development of a functionally mature astrocytic identity. • EBiSC makes industry standards and tools available to the whole scientific community and boosts a collaborative spirit in other research projects. In addition, the iPSC line and associated differentiation and neuronal co-culture protocol is incorporated into upscaling workstreams for EBiSC2 public and EFPIA partners to jointly assess feasibility towards developing astrocytes as a standard EBiSC cell product.
EBOVAC projects	In early 2021, a single-dose COVID-19 vaccine developed by the Janssen Pharmaceutical Companies of Johnson & Johnson received conditional marketing authorisation by the European Medicines Agency (EMA) and Emergency Use Authorization from the U.S. Food and Drug Administration

Project title	Description of result(s)
	This vaccine leverages the company's unique and proprietary AdVac® technology. Through the EBOVAC projects, IMI funded Phase 1, 2 and 3 clinical studies that generated data on the safety of the AdVac® vaccine platform, providing evidence for the regulatory decisions.
EBOVAC1	The Janssen 2 dose vaccine regimen was WHO Pre-Qualified on 27 April 2021. It was subsequently deployed to vaccinate frontline workers (FLWs) in Guinea and Sierra Leone in response to the February 2021 Ebola outbreak in the sub-prefecture of Gouécké, Nzérékoré Region of Guinea. 17 787 FLWs have received the vaccine regimen in the deployment to date. The vaccine regimen has also received temporary authorisation for deployment in the Democratic Republic of the Congo (in support of a proposed campaign in Mbandaka region).
PERISCOPE	The industry partners have implemented the stream-lined cellular immunity assay against pertussis antigens using small volumes of whole blood rather than isolated lymphocytes. Serology assays to measure pertussis responses in preclinical infection models have been implemented by industry partners and are now up and running.
TransQST	Kidney quantitative systems toxicology (QST) model: The improved version of the proof-of-concept QST model of drug-induced kidney injury established by ABBVIE, SIMCYP & Leiden University is currently under evaluation by ABBVIE and GSK for potential internal use & further development. Two historical compounds were explored to date.
TransQST	GI QST model of oncotherapeutics-induced diarrhoea: ABBVIE is assessing the application of the QST oncotherapeutics-induced gastrointestinal (GI) injury for clinical translation of preclinical GI safety (*in vivo*) prior to clinical trials for study design. The toxicity effects from a new therapeutic modality are being investigated.
TransQST	TXG-MAPr: ABBVIE reached an agreement to in-license the TXG-MAPr software developed by Leiden University. Now ABBVIE implemented the Docker version of rat liver TXG-MAPr behind the company's firewall. The implementation of TXG-MAPr for primary human hepatocytes (PHH) and rat kidney is foreseen and the applicability of the software for safety/toxicity assessment will subsequently be evaluated.
TransQST	Liver QST model: A minimal mechanistic model for liver injury was developed by ABBVIE for the data integration and prediction for preclinical toxicity studies. The concept of minimal cell injury model implemented in the proof-of-concept kidney QST model was adapted for this use case. One historical compound was investigated where emerging applications including predicting long-term injury and *in silico* identification of NOAEL were demonstrated.
TransQST	Multiscale quantitative systems toxicology oncotherapeutics-induced gastrointestinal injury model. AZ is assessing the application of the multiscale QST oncotherapeutics-induced gastrointestinal (GI) injury model for clinical translation of preclinical GI safety (*in vivo* and organoids) prior to clinical trials for study design and risk assessment.
TransQST	Implementation and scaling of the cardiac safety simulation. The CAPSim application was built as a proof-of-concept for industrial implementation and scaling at Sanofi. Its web frontend embeds input configurations including compound information, automatic parameter retrieval from database and estimation by QSAR, asynchronous parallel execution of simulations in the background and collection and graphical presentation of all results. Implemented in the CAPSim application, early compound triage and rational experimental design are both effectively facilitated. Two use cases in particular have proven effective for programme acceleration. On the one hand, *in silico* simulation allows the project to study entirely 'virtual' substances before any resources are spent for lab work, and effectively narrows down the list of potential candidates for synthesis. On the other hand, model-driven selection of most-promising testing candidates reduces the need for experimental studies. This way, *in silico* simulation is embedded in pharmaceutical research programs at an appropriate scale, seeking to optimise novel drug candidates.
VSV EBOPLUS	The project is providing highly relevant information for the pharmaceutical industry, analysing the immune and molecular signatures of immune responses, elicited by the rVSV-ZEBOV Ebola vaccine 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. The detailed analyses of immune and molecular signatures of immune responses elicited by the rVSV-ZEBOV Ebola vaccine in humans conducted within the project provide relevant information on VSV-ZEBOV Ebola vaccine immunogenicity and support its development by the industrial partner.

Accessibility of resources/outputs beyond consortium

Project title	Description of result(s)
AIMS-2-TRIALS	Published the updated Longitudinal European Autism Project LEAP wave-3 common protocol via the Open Science Framework. This study adds a third timepoint (up to 7 years later) to the assessments included in the original LEAP study, significantly increasing the data evidence necessary to ascertain the prognostic value of candidate biomarkers in predicting individual developmental trajectories and stability and/ or change in core and associated features of autism over time. Furthermore, it also adds digital measures obtained via active and passive devices.
AIMS-2-TRIALS	Published standardised methodological protocols for conducting 'normative modelling' to assess how each autistic individual in a given sample diverges from age (and/ or sex) expected norms. The methodologies, described in Translational Psychiatry, are critical tools to aid the discovery and validation of autism stratification biomarkers.
Beat-DKD	Published the protocol of the iBEAt study. iBEAt is the largest prospective multi-centre observational imaging cohort study of diabetes kidney disease (DKD) to date, recruiting 500 patients with type 2 diabetes (T2D). iBEAt will provide invaluable insights into the progression and heterogeneity of DKD and aims to contribute to a more personalised approach to the management of DKD in patients with type 2 diabetes.
BIGPICTURE	The tools wsidicom and wsidicomizer allow researchers and developers to access whole slide images stored in DICOM format and convert other images to DICOM. The tools are used within the consortium for example in the online viewer Cytomine. Additionally, the tools are publicly available as open source projects.
COMBACTE-CDI	First large well characterised C. diff strain collection including whole genome sequencing from humans, food and animals. This collection is a useful resource that will shortly be made publicly available to researchers.
COMBINE	Accelerator portfolio pipeline overview developed, maintained and publicly available. This will make the global AMR community aware of and able to track progress made by AMR Accelerator projects. It will facilitate accuracy and completeness of any broad analysis of activity in the AMR space.
COMBINE	The consortium has developed an experimental protocol for a standardised mouse pneumonia model for PK/PD studies on gram-negative bacteria. This will be shared with the scientific community as a publication (manuscript in preparation). The COMBINE project will now determine reproducibility of results from lab-to-lab using the standard protocol and use this protocol to assess preclinical PK/PD of benchmark small molecule antibiotics and improve preclinical-to-clinical translation.
COMBINE	Enhancements to the G42 software tools for pre-clinical drug discovery which will facilitate data analysis within COMBINE and the wider AMR Accelerator and could be made available to external customer groups as part of the commercial activities of Grit42.
COMBINE	A Knowledge Graph database (~50 users) established to link publicly available AMR-related data resources from ChEMBL, PubChem, BindingDB and the SPARC database. External stakeholders can use the demonstration version which contains publicly accessible data sets. COMBINE and other AMR Accelerator groups will be able to integrate their own data into secure instances for bespoke analyses.
ConcePTION	ConcePTION tools including common data models and common analytics used in major EU-projects related to COVID-19 disease, pregnancy or vaccines, some of them funded by EMA. • ACCESS project • Early Covid-19 Vaccine Monitor/COVID-19 vaccine monitor • CONSIGN • VAC4EU studies to monitor COVID-19 vaccines safety.
ConcePTION	Glossary openly accessible that has been developed in collaboration with two other European projects to ensure a common understanding of terminology
DRIVE	DRIVE has developed a sample size tool that has been implemented in the DRIVE website for free open use by scientific community. This web application allows to perform sample size calculations for cohort and test negative design studies on brand-specific and overall vaccine efficacy. The project's open data strategy is described in a document on the project website.
EBiSC2	To make human induced pluripotent stem cell (iPSC) research sustainable long-term, the EBiSC Bank was established as single access point with on-demand offering from the EBiSC Portfolio for research use by academic and commercial organisations against a fee: disease-

Project title	Description of result(s)

	relevant and quality-controlled iPSC lines & comprehensive data (total >900 iPSC cells to date from donors affected by >30 genetic diseases including a cohort of 45 iPSC lines derived from Huntington's disease (HD) gene-expansion carriers (HDGECs) and associated controls);
	The cell catalogue was enriched through on-demand generation of novel iPSC lines to meet long-term economic and scientific sustainability goals and evolving requirements from industry and academia, for example:
	• gene edited disease and isogenic control lines:
	  ○ novel gene edited iPSC lines generated with formal EBiSC deposition (for external distribution) ongoing;
	  ○ additional cell line cohorts generated by external research projects identified, deposition ongoing;
	• iPSC-derived cells like early neurons (iNGN2 neurons).
	Additional protocols can be exploited by external users through use of EBiSC2 service provision activities, in addition to EBiSC2 iPSC reprogramming, gene editing, banking, quality control and biosample collection for specific disease/genetic variants.
	Quotes for iPSC services were provided (e.g., reprogramming, GE, banking, quality control), allowing EBiSC2 to establish implementation processes which are easy to manage and deliver.

EQIPD	The defined framework for the EQIPD quality system (QS) is freely available and is presented in a video. The Guarantors of EQIPD, that were part of EQIPD consortium, are also likely to offer assessment against the EQIPD QS for a fee.
EQIPD	EQIPD Quality System (QS): This quality system allows self- and external- assessment of performance in terms of preclinical research in academic and commercial labs, including approaches to data handling and minimising risks of bias. 5 labs have undergone external assessment. EQIPD established a legal entity to oversee this system in the future and issued a request for proposals to identify an implementing partner. This system is available as an open source tool. QS has been described in an open-access publication in eLife.
EQIPD	ASySD (freely available to all): EQIPD developed a tool for the automatic de-duplication of systematic review search results, described in a preprint. The tool has been used in several other systematic review projects including the SPRINT H2020 project.
ESCulab	The ESCulab project has published an article in Nature Reviews Drug Discovery, which highlights the progress towards the clinic from public and private collaborators and presents some of the successes achieved so far for academic, SMEs and pharmaceutical partners that have made use of the ELF initiative.
eTRANSAFE	Toxicogenomic data gene co-expression network analysis tool: TXG-MAPr is an open source app for DILI (drug-induced liver injury), DIKI (drug-induced kidney injury) and human primary hepatocytes analysis that was developed by eTRANSAFE in collaboration with the EUToxRisk and TransQST projects. The interactive tool allows users to analyse dose- and time-response curves, compound correlation plots and functional annotation of the weighted correlation network analysis (WGCNA) modules to derive mechanistic information of the selected toxicity. Work is already ongoing with the project EFPIA partners, several of which have shown interest in the application of the TXG-MAPr web tools for analysing their own data sets. The application of the tools in this context would improve their uptake and enhance their ultimate impact.
eTRANSAFE	Updating and improving the OmniPath molecular biology database: OmniPath is a database of molecular biology prior knowledge. It combines data from over 100 resources and builds 5 integrated databases: signalling network (interactions), enzyme-PTM relationships, protein complexes, protein annotations (function, localization, tissue, disease, structure, etc), and intercellular communication roles (e.g. ligand, receptor). During 2021, the eTRANSAFE project updated and improved the database, which is publicly available.
EUbOPEN	• First chemogenomics data set published • Protocols published • >100 protein structures deposited in the PDB for public access • Chemical probes data published • Chemical probes made accessible without any restriction on use for free • >600 proteins of >300 targets purified, plasmids deposited at Addgene • Bioimages in archive.

Project title	Description of result(s)
	By this EUbOPEN is paving the way through the objective of developing high quality chemical tool compounds for 1 000 human proteins, which represent one third of the druggable genome. Researchers in academia and industry alike will therefore be able to use the tools to study diseases, and identify proteins that play a key role in disease development and so could be targeted by drugs. The tools will also help scientists to design drugs capable of blocking specific proteins involved in diseases.
EUbOPEN	36 chemical probes from EUbOPEN, EFPIA and partners collaborating with EUbOPEN approved by the independent scientific committee and made available to the research community.
FAIRplus	The FAIRplus FAIR Cookbook was further expanded in 2021 and now includes over 30 publicly available recipes on making data FAIR (findable, accessible, interoperable, and reusable). The cookbook includes use cases on omics data, chemical activity datasets, clinical cohorts, and transcriptomics.
GetReal Initiative	Launch of the GetReal Institute, an independent, member-led, not-for-profit organisation to ensure access, updates and further development of (new) tools, methods and best practices in the generation and use of real-world evidence for better health care decision-making. Membership to join the Institute is open to organisations of key stakeholders including decision makers, public and private researchers, patients and clinicians, data custodians, and technology developers.
GetReal Initiative	Release of the GetReal Trial Tool (open access) that offers guidance to evaluate the options and implications of design choices made in a pragmatic trial. (GetReal trial tool is an upgraded version of the PragMagic tool developed in GetReal to better fit the needs of academic and industry scientists). Over 500 users have registered to access the tool.
GetReal Initiative	Release of an improved version of the Aggregate Data Drug Information System (ADDIS) tool, in particular the interface multiple criteria decision analysis, that was developed within GetReal. The use of the tool is currently focused on structured benefit-risk assessment, preference elicitation, and shared (clinical) decision-making. The tool is available in various environments: publicly available (including all analyses options); and a protected version (including all analyses options, management and survey tooling for shared clinical decision-making).
HARMONY	HARMONY has signed in 2021 Associated Membership agreements with the National University of Ireland – Blood Cancer Network Ireland; the Latin-American Myelodysplastic Syndromes Group (GLAM); the Technical University of Dresden – University Hospital Carl Gustav Carus; The Polish Adult Leukemia Group; Humanitas Research Hospital; Cardiff University – National Cancer Research Institute; Fondazione per la Ricerca Ospedale di Bergamo; Co-operative study group for childhood acute lymphoblastic leukaemia; the Austrian Group of Medical Tumour Therapy; and Maria Skłodowska-Curie National Research Institute of Oncology. Data access (for free) shall only be requested in relation to an approved research question when the Associated Member participates in the analysis.
HYPO-RESOLVE	Developed and published in Scientific Reports an algorithm to determine the optimal duration of continuous glucose monitoring (CGM) data required to reliably estimate time in hypoglycaemia. This formula will be helpful in the design of those clinical trials where minimal CGM monitoring duration is crucial in cost-effectiveness terms.
HYPO-RESOLVE	Developed and published in the Journal of Diabetes Science and Technology a simulation model of the behaviour of people with type 1 diabetes (T1D), realistically simulating the carb-counting error, that can be used to perform realistic *in-silico* clinical trials, which are significantly faster and cheaper that classical experimental trials.
IMI-PainCare	The SME MRC Systems GmbH used IMI-PainCare results to develop two devices: EPS-10 multi-pin HFS electrode and MRI-compatible Pinprick stimulators with contact trigger. Both devices are being used in clinical trials in the project. These products became available on the open market in 2021, having previously been deployed within the project only.
ImSAVAR	The consortium developed an initial version of immune related adverse outcome pathways (irAOPs) for skin rash, which has been represented using MINERVA. MINERVA is a free web-based knowledge management tool. It is integrated with standard representation of pathways to enable users to visualise and obtain detailed representations of biological mechanisms.

Project title	Description of result(s)
MELLODDY	The MELLODDY project, which is applying machine learning algorithms to drug discovery databases, has publicly released the raw ChEMBL files that they have used for the initial development of the algorithm. They have also written a short blog on how this data was used in the project.
MELLODDY	The MELLODDY project publicly released the ChemFold software to facilitate machine learning on drug discovery data. The software provides a realistic split of chemical structures (compounds) between training, validation, and test sets such that the performance on the test set is meaningful to reliably infer future performance. The following methods are included: • random split • sphere exclusion clustering based split • locality sensitive hashing (LSH) based split • scaffold trees The project published a paper on the subject in the Journal of Cheminformatics.
MELLODDY	MELLODDY publicly released their data standardisation framework for federated machine learning on pharmaceutical data, MELLODY-TUNER. The innovation consists of a Python software library for pre-processing and standardizing pharmaceutical data so that these data can be used for federated machine learning pharma partners.
MELLODDY	The MELLODDY SparseChem software package provides fast and accurate machine learning models for biochemical applications. It is especially suited to very high-dimensional models with sparse inputs, e.g., millions of features and millions of compounds. The software is publicly available in GitHub and includes examples using ChEMBL data.
NEURONET	NEURONET publicly published the outputs of the IMI neurodegenerative portfolio via the NEURONET Knowledge Base (KB). To date, KB represents the assets, deliverables, publications and tools of 21 projects in the portfolio. The most popular KB module, the Asset Map, represents 90 project assets. Since its launch, KB has received just over 16, 00 views and over 2 000 users.
RHAPSODY	The RHAPSODY project has assembled a federated database with fully harmonised data (CDISC SDTM format) from 6 prediabetes cohorts, 4 T2D progression cohorts, 1 gastric bypass cohort and 1 clinical trial cohort, from 5 different EU countries and totalling > 68 000 individuals. This federated database contains multi-omics data and genetic data in addition to biochemical and clinical data. The database is being sustained through the European Platform for Diabetes and Complications (EPDC).
RHAPSODY	A new software package, dsSwissKnife has been developed to allow non-disclosive remote federated analysis on sensitive data. The tool has been made open access. Functionalities include implementations for a kmeans clustering algorithm, principal component analysis, as well as a number of functions from specific packages (such as imputation, random forests, synthetic data generation).
TransQST	COSMOS (Causal Oriented Search of Multi-Omic Space): Computational tool developed by Universitätsklinikum Heidelberg that facilitates the integration of multiple omics data (proteomics, phosphoproteomics, transcriptomics and metabolomics) using networks. The tool was published on Bioconductor. Paper accepted at Molecular Systems Biology.
TransQST	The DisGeNET database is made available under the Attribution-NonCommercial-ShareAlike 4.0 International License. The DisGeNET Cytoscape App is available through the Cytoscape App Store, with +23K downloads from the Cytoscape App store. The app is described in a paper in the Computational and Structural Biology Journal.
TransQST	Application of COSMOS (Causal Oriented Search of Multi-Omic Space) for 5-FU toxicity study: The project developed a pipeline to analyse the toxicity of 5-FU treatment in small intestine and colon samples using COSMOS. The multi-omics (metabolomics and gene expression) integration revealed mechanistic, molecular pathways that are responding to the different doses of treatment. The paper is published in Toxicogenomics and Omics Technologies, and the code is publicly available for everyone on GitHub.
TransQST	Development of an open source, high performance computing version of CARNIVAL (CAusal Reasoning pipeline for Network identification using Integer VALue programming). CARNIVAL allows to infer the activity of signalling pathways from expression data, which can be utilised

Project title	Description of result(s)
	to understand or design interventions of toxic perturbations. The original algorithm was based on a commercial optimisation algorithm (IBM CPLEX). UKHD have been working on the development on an alternative, free and open-source version which extends its usability for industrial partners and for general, non-academic users outside of the consortium, further it is capable of using computational clusters.

Miscellaneous

Project title	Description of result(s)
AMYPAD	Published an article outlining the differences in the way Alzheimer's disease is understood by a lay audience compared to in a research context. A greater appreciation of these differences may improve guidelines for Alzheimer biomarker disclosure to patients by identifying research-related terms that may cause misunderstandings.
DECISION	DECISION developed and evaluated the first design of their rapid COVID-19 diagnostic device using a next-generation nucleic acid amplification technology called pulse-controlled amplification (PCA). PCA offers similar performance to the well-known COVID-19 PCR tests, but can provide a result in less than 15 minutes. Based on this first evaluation, a second electronics design is under development to optimize temperature distribution and other variables.
eTRANSAFE	Building on the work carried out in 2020, the eTRANSAFE consortium assembled a multi-disciplinary cross-industry and cross-academic team of statisticians, toxicologists and data-scientists from academia and industry to implement their virtual control groups (VCGs). VCGs are where historical animal control group data is used to replace the control arm of future toxicity studies which could reduce the number of animals used in research by 25 %. The team are using a stepwise approach, which includes quality-checking of all data, evaluation of the VCGs against real control groups before approaching regulatory authorities in order to discuss whether VCGs are an acceptable method to replace control-group-animals in toxicity studies.
Gravitate Health	Gravitate Health aims to guide patients to understandable, trustworthy, up-to-date health information that meets their needs and literacy levels. To help in the development of their software, the consortium has developed several patient 'personas' which are fictional but realistic descriptions of typical health data users based on real-world data. Applying the principles of human-centred design and user experience best practices, the project sourced data from interviews carried out in Norway, Portugal, Italy, Spain, and Ireland, and then validated the personas and user journeys via crowdsourcing. From a smoker with IBS to a child with a feeding tube and the sibling of someone with Down's Syndrome, the personas represent a diverse group of people whose circumstances represent those of a wide swathe of the population.
RAPID COVID	The consortium has successfully developed (CE marked) two diagnostic panels which can detect the causative pathogens in patients who present with COVID-like symptoms, and differentiate SARS-CoV-2 alongside 17 common causes of upper-respiratory tract infections and 11 common causes of pneumonia. This gives increased information to clinicians to support treatment decisions and improve patient outcomes, while contributing to control of SARS COV-2 spread. The first version for high throughput liquid handler has been delivered by PrimaDiag. A software analysis prototype has been completed by BioSistemika. The kits are currently being tested against gold standards in two countries: Spain and France.
ROADMAP	ROADMAP published their findings on public involvement in dementia research. Throughout the project, in-person consultations were held with people with dementia and caregivers. As a result of this input, significant improvements were made to the accessibility and acceptability of the project surveys. In addition, the public involvement promoted better understanding of concepts around disease progression and how researchers might approach measuring and interpreting findings. The people with dementia and caregivers effectively expressed difficult concepts through real-world examples.

Annex 3: Publications from projects

Hot publications in 2021

Hot publications are those that received enough citations to place in the top 0.1 % of papers in their research field.

- Pfister, Dominik et al. (2021) NASH limits anti-tumour surveillance in immunotherapy-treated HCC, NATURE 592: N/A
- Simon, David et al. (2021) SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases, ANNALS OF THE RHEUMATIC DISEASES 80: 1312
- Haberman, Rebecca H. et al. (2021) Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease, ANNALS OF THE RHEUMATIC DISEASES 80: 1339
- Attwood, Misty M. et al. (2021) Trends in kinase drug discovery: targets, indications and inhibitor design, NATURE REVIEWS DRUG DISCOVERY 20: 839

2021 publications featured in the top 10 journals

- Wu, Qin et al. (2021) Protein arginine methylation: from enigmatic functions to therapeutic targeting, NATURE REVIEWS DRUG DISCOVERY 20: 509
- Attwood, Misty M. et al. (2021) Trends in kinase drug discovery: targets, indications and inhibitor design, NATURE REVIEWS DRUG DISCOVERY 20: 839
- Karwath, Andreas et al. (2021) Redefining beta-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis, LANCET 398: 1427
- Hofbauer, Lorenz C. et al. (2021) Novel approaches to target the microenvironment of bone metastasis, NATURE REVIEWS CLINICAL ONCOLOGY 18: 488
- Heilbronner, Simon et al. (2021) The microbiome-shaping roles of bacteriocins, NATURE REVIEWS MICROBIOLOGY 19: 726
- Prajapati, Jigneshkumar Dahyabhai et al. (2021) How to Enter a Bacterium: Bacterial Porins and the Permeation of Antibiotics, CHEMICAL REVIEWS 121: 5158

Highly cited publications in 2021

Highly cited papers have received enough citations to place in the top 1 % of papers in their research field.

- Pfister, Dominik et al. (2021) NASH limits anti-tumour surveillance in immunotherapy-treated HCC, NATURE 592: N/A
- Stebbing, Justin et al. (2021) JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality, SCIENCE ADVANCES 7: N/A
- Lee, Matthew M. Y. et al. (2021) Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF), CIRCULATION 143: 516
- Lumley, Sheila F. et al. (2021) The Duration, Dynamics, and Determinants of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibody Responses in Individual Healthcare Workers, CLINICAL INFECTIOUS DISEASES 73: E699
- Stefan, Norbert et al. (2021) Global pandemics interconnected - obesity, impaired metabolic health and COVID-19, NATURE REVIEWS ENDOCRINOLOGY 17: 135
- Fenwick, Craig et al. (2021) Changes in SARS-CoV-2 Spike versus Nucleoprotein Antibody Responses Impact the Estimates of Infections in Population-Based Seroprevalence Studies, JOURNAL OF VIROLOGY 95: N/A
- Alix-Panabieres, Catherine et al. (2021) Liquid Biopsy: From Discovery to Clinical Application, CANCER DISCOVERY 11: 858

- Simon, David et al. (2021) SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases, ANNALS OF THE RHEUMATIC DISEASES 80: 1312
- Pollard, Andrew J. et al. (2021) Safety and immunogenicity of a two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial, LANCET INFECTIOUS DISEASES 21: 493
- Haberman, Rebecca H. et al. (2021) Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease, ANNALS OF THE RHEUMATIC DISEASES 80: 1339
- Blomberg, Bjorn et al. (2021) Long COVID in a prospective cohort of home-isolated patients, NATURE MEDICINE 27: 1607
- Kasinath, Vignesh et al. (2021) JARID2 and AEBP2 regulate PRC2 in the presence of H2AK119ub1 and other histone modifications, SCIENCE 371: 362
- Peng, Han et al. (2021) Accurate brain age prediction with lightweight deep neural networks, MEDICAL IMAGE ANALYSIS 68: N/A
- Zheng, Linli et al. (2021) The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis, AGEING RESEARCH REVIEWS 66: N/A
- Shi, Yang et al. (2021) Cryo-EM structures of tau filaments from Alzheimer's disease with PET ligand APN-1607, ACTA NEUROPATHOLOGICA 141: 697
- Fusar-Poli, Paolol et al. (2021) Preventive psychiatry: a blueprint for improving the mental health of young people, WORLD PSYCHIATRY 20: 200
- Hoepel, Willianne et al. (2021) High titers and low fucosylation of early human anti-SARS-CoV-2 IgG promote inflammation by alveolar macrophages, SCIENCE TRANSLATIONAL MEDICINE 13: N/A
- Laporte, Manon et al. (2021) The SARS-CoV-2 and other human coronavirus spike proteins are fine-tuned towards temperature and proteases of the human airways, PLOS PATHOGENS 17: N/A
- Wang, Chunyan et al. (2021) A conserved immunogenic and vulnerable site on the coronavirus spike protein delineated by cross-reactive monoclonal antibodies, NATURE COMMUNICATIONS 12: N/A
- Zavridou, Martha et al. (2021) Prognostic Significance of Gene Expression and DNA Methylation Markers in Circulating Tumor Cells and Paired Plasma Derived Exosomes in Metastatic Castration Resistant Prostate Cancer, CANCERS 13: N/A
- Schuller, Marion et al. (2021) Fragment binding to the Nsp3 macrodomain of SARS-CoV-2 identified through crystallographic screening and computational docking, SCIENCE ADVANCES 7: N/A
- Jordan, Elizabeth et al. (2021) Evidence-Based Assessment of Genes in Dilated Cardiomyopathy, CIRCULATION 144: N/A
- Shi, Yang et al. (2021) Structure-based classification of tauopathies, NATURE 598: 359
- Forstenpointner, Julia et al. (2021) No pain, still gain (of function): the relation between sensory profiles and the presence or absence of self-reported pain in a large multicenter cohort of patients with neuropathy, PAIN 162: 718
- Wu, Yinzhe et al. (2021) Fast and Automated Segmentation for the Three-Directional Multi-Slice Cine Myocardial Velocity Mapping, DIAGNOSTICS 11: N/A
- Wissfeld, Jannis et al. (2021) Deletion of Alzheimer's disease-associated CD33 results in an inflammatory human microglia phenotype, GLIA 69: 1393
- Markus, Aniek F. et al. (2021) The role of explainability in creating trustworthy artificial intelligence for health care: A comprehensive survey of the terminology, design choices, and evaluation strategies, JOURNAL OF BIOMEDICAL INFORMATICS 113: N/A
- Sun, Luanluan et al. (2021) Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses, PLOS MEDICINE 18: N/A
- Lugo-Marin, Jorge et al. (2021) COVID-19 pandemic effects in people with Autism Spectrum Disorder and their caregivers: Evaluation of social distancing and lockdown impact on mental health and general status, RESEARCH IN AUTISM SPECTRUM DISORDERS 83: N/A
- Ni, Xiaomin et al. (2021) Structural Insights into Plasticity and Discovery of Remdesivir Metabolite GS-441524 Binding in SARS-CoV-2 Macrodomain, ACS MEDICINAL CHEMISTRY LETTERS 12: 603
- Roman-Urrestarazu, Andres et al. (2021) Association of Race/Ethnicity and Social Disadvantage With Autism Prevalence in 7 Million School Children in England, JAMA PEDIATRICS 175: N/A

Annex 4: 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 5 patents/trademarks awarded from the beginning of IMI2 until 31 December 2021.

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’.

PEVIA – 2 patent applications on ‘mélanges d’epitopes t cd8 immunogènes du virus Ebola’ and ‘peptides immunogènes issus de la nucléoprotéine du virus Ebola’.

EBiSC2 – 2 trademark applications for the EBiSC trademark.

GRAVITATE-HEALTH – 1 trademark awarded on “G-lens”, a digital health information tool.

Annex 5: 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 same materiality criteria are applicable to the FP7 and H2020 programmes.

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 (FP7 and H2020). 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, as defined in the IMI ex-post audit strategy approved by the Governing Board on 14 December 2010 and the H2020 Ex-Post Audit Strategy (2016-2025), 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 IMI contributions on completion of the audits but does not take into account the corrections and follow-up undertaken by IMI.

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[60]:

$$\frac{\sum_{i=1}^{n} \mathrm{err}_i * \mathrm{SI}_i}{\mathrm{P}}$$

- n = total sample size;
- 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);
- SI_i = sampling interval used for selecting transactions from the sample;
- P = total accepted IMI 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[61]:

$$\mathbf{ResER\% = \frac{(RepER\% * (P-A) - (RepERsys\% * E)}{P}}$$

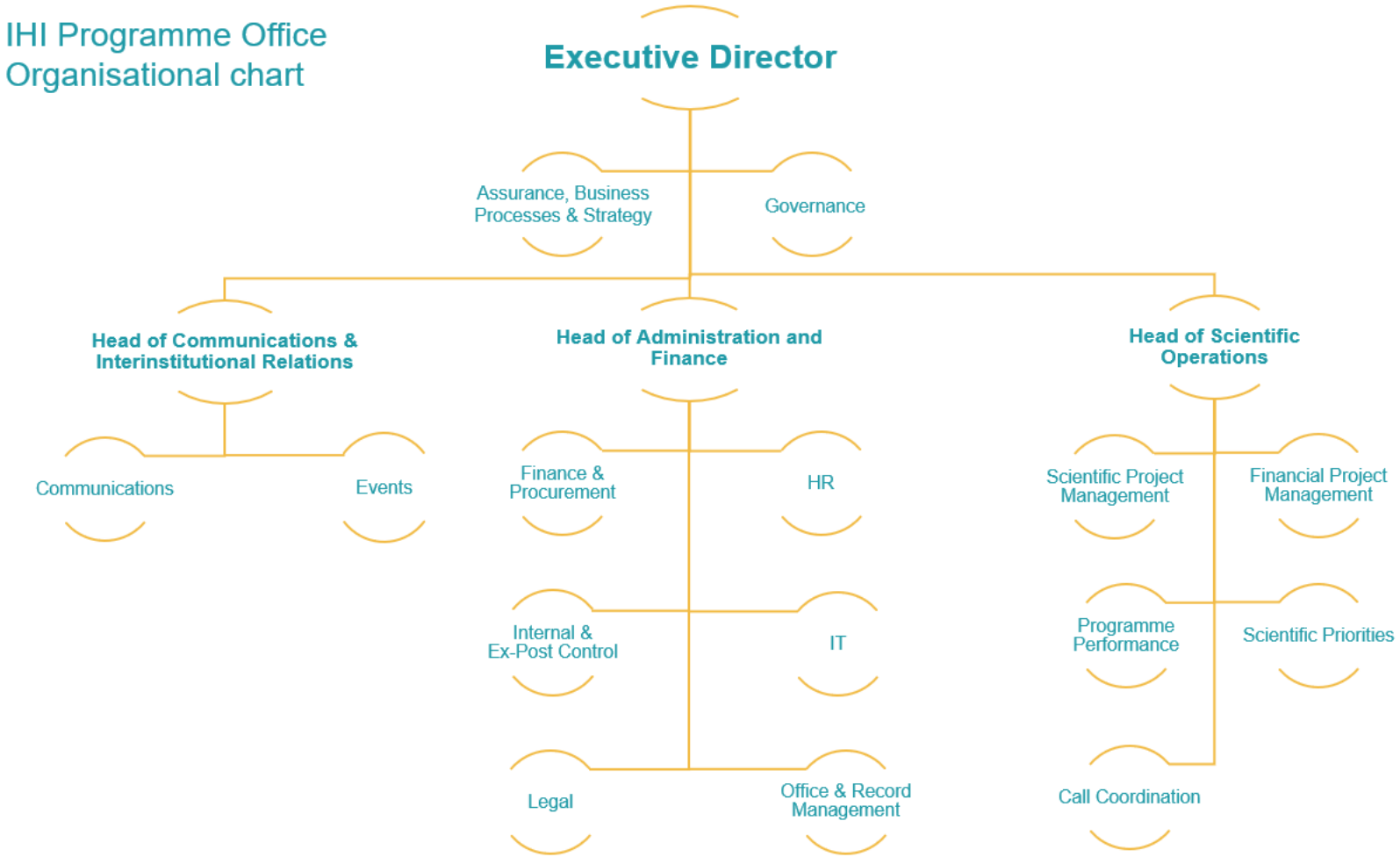
Where:

- **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;
- **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.

60 Based on the Horizon 2020 Ex-post Audit Strategy (2016 – 2025).
61 Idem.

Annex 6: Organisational chart



Annex 7: Staff establishment plan

Grade	Year 2020			Year 2021												
	Establishment plan 2020			Evolution in posts						Organisational evolution			Establishment plan 2021			Posts filled on 31/12/21
				Promotion / career advancement			Turnover (departures / arrivals)			New posts (per grade)			Requested budget			
	Perm.	TA	Total	Perm.	TA - LT	TA - ST	Perm.	TA - LT	TA - ST	Perm.	TA - LT	TA - ST	Perm.	TA	Total	TA
AD16																
AD15																
AD14		1	1											**1**	**1**	1
AD13																
AD12		2	2											**2**	**2**	1
AD11		2	2											**2**	**2**	2
AD10		1	1											**1**	**1**	2
AD9		7	7											**7**	**7**	5
AD8		6	6											**6**	**6**	4
AD7		2	2											**2**	**2**	4
AD6		8	8		**+3**									**11**	**11**	6
AD5		4	4		**-3**									**1**	**1**	6
Total AD		33	33											33	33	**31**
AST11																
AST10																
AST9																

Grade	Year 2020			Year 2021												
	Establishment plan 2020			Evolution in posts						Organisational evolution			Establishment plan 2021			Posts filled on 31/12/21
				Promotion / career advancement			Turnover (departures / arrivals)			New posts (per grade)			Requested budget			
	Perm.	TA	Total	Perm.	TA - LT	TA - ST	Perm.	TA - LT	TA - ST	Perm.	TA - LT	TA - ST	Perm.	TA	Total	TA
AST8		1	1											**1**	**1**	1
AST7																
AST6																
AST5																
AST4		4	4											4	4	3
AST3																1
AST2		1	1											1	1	0
AST1																
Total AST		6	6											**6**	**6**	**5**
SC6																
SC5																
SC4																
SC3																
SC 2																
SC1																
Total SC																
Overall total		**39**	**39**											**39**	**39**	**36**

- Perm. = permanent staff
- TA = temporary agent
- LT = long-term contract
- ST = short-term contract

Contract agents

Grade	2020	2021	Posts filled on 31/12/2021
CA FG IV	3	3	3
CA FG III	11	11	9
CA FG II	1	1	1
CA FG I			
Total CA	**15**	**15**	**13**

Notes:

- CA = contract agent
- FG = function group

Seconded national experts (SNEs)

SNEs	2020	2021	Posts filled on 31/12/2021
Total	**2**	**2**	**1**

Annex 8: Annual Accounts

The annual accounts for 2021 are provided in a separate document, which is officially handed over to the budgetary authorities, the European Court of Auditors, and the external auditors.

Annex 9: List of projects

(Grant agreements signed as of 31 December 2021)

IMI1 projects

Project acronym	Full project title	Website	Subject area
ABIRISK	Anti-biopharmaceutical immunization: prediction and analysis of clinical relevance to minimize the risk	www.abirisk.eu	drug safety
ADVANCE	Accelerated development of vaccine benefit-risk collaboration in Europe	vac4eu.org	vaccines
AETIONOMY	Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy	www.aetionomy.eu	Alzheimer's disease and Parkinson's disease
APPROACH	Applied public-private research enabling osteoarthritis clinical headway	www.approachproject.eu	osteoarthritis
BioVacSafe	Biomarkers for enhanced vaccine safety	www.biovacsafe.eu	vaccines
BTCure	Be the cure		rheumatoid arthritis
CANCER-ID	Cancer treatment and monitoring through identification of circulating tumour cells and tumour related nucleic acids in blood	www.cancer-id.eu	cancer
CHEM21	Chemical manufacturing methods for the 21st century pharmaceutical industries		green chemistry
COMBACTE-CARE	Combatting bacterial resistance in Europe - carbapenem resistance	www.combacte.com/about/about-combacte-care-detail/	antimicrobial resistance
COMBACTE-MAGNET	Combatting bacterial resistance in Europe - molecules against Gram negative infections	www.combacte.com/about/about-combacte-magnet-detail/	antimicrobial resistance
COMBACTE-NET	Combatting bacterial resistance in Europe	www.combacte.com/about/about-combacte-net-detail/	antimicrobial resistance
COMPACT	Collaboration on the optimisation of macromolecular pharmaceutical access to cellular targets		drug delivery
DDMoRe	Drug disease model resources		knowledge management
DIRECT	Diabetes research on patient stratification		diabetes
DRIVE-AB	Driving re-investment in R&D and responsible antibiotic use	drive-ab.eu	antimicrobial resistance
EBiSC	European bank for induced pluripotent stem cells	www.ebisc.org	stem cells
EHR4CR	Electronic health record systems for clinical research		knowledge management
ELF	European Lead Factory	www.europeanleadfactory.eu	drug discovery

Project acronym	Full project title	Website	Subject area
EMIF	European medical information framework	www.emif.eu	knowledge management, Alzheimer's disease, metabolic syndromes
EMTRAIN	European medicines research training network	www.emtrain.eu	education and training
ENABLE	European Gram negative antibacterial engine	www.nd4bb-enable.eu	antimicrobial resistance
EPAD	European prevention of Alzheimer's dementia consortium	ep-ad.org	Alzheimer's disease
eTOX	Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the *in silico* prediction of toxicities	www.e-tox.net	knowledge management, drug safety
eTRIKS	Delivering European translational information & knowledge management services	www.etriks.org	knowledge management
Eu2P	European programme in pharmacovigilance and pharmacoepidemiology	www.eu2p.org	education and training
EU-AIMS	European autism interventions - a multicentre study for developing new medications	www.eu-aims.eu	autism
EUPATI	European patients' academy on therapeutic innovation	www.eupati.eu	education and training
EUROPAIN	Understanding chronic pain and improving its treatment		chronic pain
FLUCOP	Standardization and development of assays for assessment of influenza vaccines correlates of protection	www.flucop.eu	vaccines
GetReal	Incorporating real-life clinical data into drug development	www.getreal-institute.org	relative effectiveness
iABC	Inhaled antibiotics in bronchiectasis and cystic fibrosis	www.qub.ac.uk/sites/iABC	antimicrobial resistance
IMIDIA	Improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes		diabetes
iPiE	Intelligent assessment of pharmaceutical in the environment		environmental issues
K4DD	Kinetics for drug discovery	www.k4dd.eu	drug discovery
MARCAR	Biomarkers and molecular tumor classification for non-genotoxic carcinogenesis		safety, cancer
MIP-DILI	Mechanism-based integrated systems for the prediction of drug-induced liver injury		drug safety
NEWMEDS	Novel methods leading to new medications in depression and schizophrenia		schizophrenia, depression

Project acronym	Full project title	Website	Subject area
OncoTrack	Methods for systematic next generation oncology biomarker development	www.oncotrack.eu	cancer
Open PHACTS	The open pharmacological concepts triple store	www.openphactsfoundation.org	knowledge management
OrBiTo	Oral biopharmaceutics tools		drug delivery
PHARMA-COG	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in the early clinical development	web.archive.org/web/20211027032259/https://www.alzheimer-europe.org/Research/PharmaCog	Alzheimer's disease
PharmaTrain	Pharmaceutical medicine training programme	www.pharmatrain.eu	education and training
PRECISESADS	Molecular reclassification to find clinically useful biomarkers for systemic autoimmune diseases		rheumatoid arthritis and lupus
PREDECT	New models for preclinical evaluation of drug efficacy in common solid tumours		cancer
PreDiCT-TB	Model-based preclinical development of anti-tuberculosis drug combinations		tuberculosis
PROactive	Physical activity as a crucial patient reported outcome in COPD		chronic obstructive pulmonary disease (COPD)
PROTECT	Pharmacoepidemiological research on outcomes of therapeutics by a European consortium		pharmacovigilance
QUIC-CONCEPT	Quantitative imaging in cancer: connecting cellular processes with therapy		cancer
RAPP-ID	Development of rapid point-of-care test platforms for infectious diseases		infectious diseases
SafeSciMET	European modular education and training programme in safety sciences for medicines	www.safescimet.eu	education and training
SAFE-T	Safer and faster evidence-based translation		drug safety
SPRINTT	Sarcopenia and physical frailty in older people: multi-component treatment strategies	www.mysprintt.eu	geriatrics
StemBANCC	Stem cells for biological assays of novel drugs and predictive toxicology		stem cells
SUMMIT	Surrogate markers for vascular micro- and macrovascular hard endpoints for innovative diabetes tools	www.imi-summit.eu	diabetes
TRANSLOCATION	Molecular basis of the outer membrane permeability	www.translocation.eu	antimicrobial resistance

Project acronym	Full project title	Website	Subject area
U-BIOPRED	Unbiased biomarkers for the prediction of respiratory disease outcomes		asthma
ULTRA-DD	Unrestricted leveraging of targets for research advancement and drug discovery	www.ultra-dd.org	drug development
WEB-RADR	Recognising adverse drug reactions	web-radr.eu	pharmacovigilance
ZAPI	Zoonotic anticipation and preparedness initiative		infectious diseases

IMI2 projects

Project acronym	Full project title	Website	Subject area
3TR	Identification of the molecular mechanisms of non-response to treatments, relapses and remission in autoimmune, inflammatory, and allergic conditions	3tr-imi.eu	autoimmune diseases
AB-Direct	Antibiotic distribution and recovery in tissue	amr-accelerator.eu/project/ab-direct	antimicrobial resistance
ADAPTED	Alzheimer's disease apolipoprotein pathology for treatment elucidation and development	www.imi-adapted.eu	Alzheimer’s disease
ADAPT-SMART	Accelerated development of appropriate patient therapies: a sustainable, multi stakeholder approach from research to treatment-outcomes	adaptsmart.eu	MAPPs
AIMS-2-TRIALS	Autism Innovative Medicine Studies – 2 – Trials	www.aims-2-trials.eu	autism
AMYPAD	Amyloid imaging to prevent Alzheimer’s disease	www.amypad.eu	Alzheimer’s disease
ARDAT	Accelerating research & development for advanced therapies	ardat.org	advanced therapies
BEAMER	Behavioral and adherence model for improving quality, health outcomes and cost-effectiveness of healthcare	beamerproject.eu	Treatment adherence
BEAT-DKD	Biomarker enterprise to attack DKD	www.beat-dkd.eu	diabetes
BigData@Heart	Big data @ heart	www.bigdata-heart.eu	big data, cardiovascular disease
BIGPICTURE	Central repository for digital pathology	www.bigpicture.eu	artificial intelligence
BIOMAP	Biomarkers in atopic dermatitis and psoriasis	biomap-imi.eu	skin diseases

Project acronym	Full project title	Website	Subject area
C4C	conect4children - Collaborative network for European clinical trials for children	conect4children.org	Paediatric clinical trials
CARDIATEAM	Cardiomyopathy in type 2 diabetes mellitus	cardiateam.eu	diabetes
CARE	Corona accelerated R&D in Europe	www.imi-care.eu	coronaviruses
COMBACTE-CDI	Combatting bacterial resistance in Europe - clostridium difficile infections	www.combacte.com/about/combacte-cdi-understanding-of-the-epidemiology-and-clinical-impact-of-clostridium-difficile-infection/	antimicrobial resistance
COMBINE	Collaboration for prevention and treatment of MDR bacterial infections	amr-accelerator.eu/project/combine	antimicrobial resistance
ConcePTION	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation	www.imi-conception.eu	medicines safety
COVID-RED	COVID-19 infections - remote early detection	www.covid-red.eu	coronaviruses
DECISION	A minituarized disposable molecular diagnostics platform for combatting coronavirus infections		coronaviruses
DO>IT	Big data for better outcomes, policy innovation and healthcare system transformation	bd4bo.eu	big data
DRAGON	Rapid and secure AI imaging based diagnosis, stratification, follow-up, and preparedness for coronavirus pandemics	europeanlung.org/dragon	coronaviruses
DRIVE	Development of robust and innovative vaccine effectiveness	www.drive-eu.org	vaccines
EBISC2	EBiSC2 – A sustainable European bank for induced pluripotent stem cells	ebisc.org	stem cells
EBODAC	Communication strategy and tools for optimizing the impact of Ebola vaccination deployment (Compliance with vaccine regimens)	www.ebovac.org/ebodac	Ebola and related diseases
EbolaMoDRAD	Ebola virus: modern approaches for developing bedside rapid diagnostics	www.ebolamodrad.eu	Ebola and related diseases
EBOMAN	Manufacturing and development for rapid access Ebola vaccine	www.ebovac.org/eboman	Ebola and related diseases
EBOVAC1	Development of a prophylactic Ebola vaccine using an heterologous prime-boost regimen	www.ebovac.org/the-trials/	Ebola and related diseases

Project acronym	Full project title	Website	Subject area
EBOVAC2	Development of a prophylactic Ebola vaccine using an heterologous prime-boost regimen: Phase II	www.ebovac2.com	Ebola and related diseases
EBOVAC3	Bringing a prophylactic Ebola vaccine to licensure	www.ebovac.org/ebovac-3	Ebola and related diseases
EFOEUPATI	Ensuring the future of EUPATI beyond 2020	www.eupati.eu	education and training
EHDEN	Electronic health data in a European network	www.ehden.eu	big data
EPND	European Platform for Neurodegenerative Diseases	epnd.org	neurodegenerative diseases
EQIPD	European quality in preclinical data	quality-preclinical-data.eu	data quality, neurodegenerative diseases
ERA4TB	European regimen accelerator for tuberculosis	era4tb.org	antimicrobial resistance
ESCulab	European screening centre; unique library for attractive biology	www.europeanleadfactory.eu	drug discovery
eTRANSAFE	Enhancing translational safety assessment through integrative knowledge management	etransafe.eu	safety
EUbOPEN	EUbOPEN: Enabling and unlocking biology in the OPEN	www.eubopen.org	drug discovery
EU-PEARL	EU patient-centric clinical trial platform	www.eu-pearl.eu	clinical trial design
FACILITATE	Framework for clinical trial participants data reutilization for a fully transparent and ethical ecosystem	www.facilitate-project.eu	health data
FAIRplus	FAIRplus	fairplus-project.eu	knowledge management
FILODIAG	Ultra-fast molecular filovirus diagnostics	www.filodiag.eu	Ebola and related diseases
GetReal Initiative	The GetReal Initiative	www.getreal-institute.org	relative effectiveness
GNA NOW	Novel Gram-negative antibiotic now	amr-accelerator.eu/project/gna-now/	antimicrobial resistance
GRAVITATE-HEALTH	Gravitate–Health: Empowering and equipping Europeans with health information for active personal health management and adherence to treatment	www.gravitatehealth.eu	digital health
H2O	H2O Health outcomes observatory	health-outcomes-observatory.eu	digital health
HARMONY	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology	www.harmony-alliance.eu	big data, cancer

Project acronym	Full project title	Website	Subject area
HARMONY PLUS	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology – PLUS	www.harmony-alliance.eu/harmony-plus/story	big data, cancer
HIPPOCRATES	Health initiatives in psoriasis and psoriatic arthritis consortium European states	www.hippocrates-imi.eu	autoimmune disease
Hypo-RESOLVE	Hypoglycaemia – redefining solutions for better lives	hypo-resolve.eu	diabetes
iConsensus	Integrated control and sensing platform for biopharmaceutical cultivation process high-throughput development and production	www.iconsensus.eu	manufacturing technologies
IDEA-FAST	Identifying digital endpoints to assess fatigue, sleep and activities in daily living in neurodegenerative disorders and immune-mediated inflammatory diseases	ideafast.eu	digital health
IM2PACT	Investigating mechanisms and models predictive of accessibility of therapeutics (IM2PACT) into the brain	im2pact.org	drug delivery
IMI-PainCare	Improving the care of patients suffering from acute or chronic pain	www.imi-paincare.eu	pain
IMMUcan	Integrated immunoprofiling of large adaptive cancer patients cohorts	immucan.eu	cancer
Immune-Image	Specific imaging of immune cell dynamics using novel tracer strategies	www.immune-image.eu	imaging
ImmUniverse	Better control and treatment of immune-mediated diseases by exploring the universe of microenvironment imposed tissue signatures and their correlates in liquid biopsies	www.immuniverse.eu	autoimmune diseases
Impentri	Development of Impentri, an intravenous imatinib formulation for COVID-19 acute respiratory distress syndrome (ARDS)	impentri.exvastat.com	coronaviruses
IMPRiND	Inhibiting misfolded protein propagation in neurodegenerative diseases	www.imprind.org	neurodegenerative disease
imSAVAR	Immune safety avatar: nonclinical mimicking of the immune system effects of immunomodulatory therapies	imsavar.eu	autoimmune diseases, cancer
Inno4Vac	Innovations to accelerate vaccine development and manufacture	www.inno4vac.eu	vaccines
INNODIA	Translational approaches to disease modifying therapy of type I diabetes: an innovative approach towards understanding and arresting type I diabetes	innodia.eu	diabetes

Project acronym	Full project title	Website	Subject area
INNODIA HARVEST	Translational approaches to disease modifying therapy of type 1 diabetes - HARVESTing the fruits of INNODIA	www.innodia.eu/harvest	diabetes
ITCC-P4	ITCC pediatric preclinical POC platform	www.itccp4.eu	paediatrics, cancer
KRONO	Evaluation of a production ready portable, point-of-need platform (instrument and reagents), direct from nasal swab test for the molecular diagnostic detection of COVID-19 infection		coronaviruses
LITMUS	Liver investigation: testing marker utility in steatohepatitis	www.litmus-project.eu	liver disease
MACUSTAR	Intermediate AMD: Development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention	www.macustar.eu	eye disease
MAD-COV 2	Modern approaches for developing antivirals against SARS-CoV 2	mad-cov2.eu	coronaviruses
MELLODDY	Machine learning ledger orchestration for drug discovery	www.melloddy.eu	machine learning
MOBILISE-D	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement	mobilise-d.eu	digital health
MOFINA	Mobile filovirus nucleic acid test		Ebola and related diseases
MOPEAD	Models of patient engagement for Alzheimer's disease		Alzheimer's disease
NECESSITY	New clinical endpoints in primary Sjögren's syndrome: an interventional trial based on stratifying patients	www.necessity-h2020.eu	Sjögren's syndrome
NeuroDeRisk	Neurotoxicity de-risking in preclinical drug discovery	neuroderisk.eu	safety
NEURONET	Efficiently networking European neurodegeneration research	imi-neuronet.org	neurodegenerative disease
NGN-PET	Modelling neuron-glia networks into a drug discovery platform for pain efficacious treatments		pain
OPTIMA	Optimal treatment for patients with solid tumours in Europe through artificial intelligence	www.optima-oncology.eu	cancer
PARADIGM	Patients active in research and dialogues for an improved generation of medicines: advancing meaningful patient engagement in the life cycle of medicines for better health outcomes	imi-paradigm.eu	patient involvement in R&D

Project acronym	Full project title	Website	Subject area
PD-MIND	Parkinson disease with mild cognition impairment treated with nicotinic agonist drug	www.pd-mind.org	Parkinson's disease
PD-MitoQUANT	PD-MitoQUANT – A quantitative approach towards the characterisation of mitochondrial dysfunction in Parkinson's disease	www.pdmitoquant.eu	Parkinson's disease
PERISCOPE	Pertussis correlates of protection Europe	www.periscope-project.eu	vaccines
PERSIST-SEQ	Building a reproducible single-cell experimental workflow to capture tumour drug persistence	persist-seq.org	cancer
PEVIA	Pan Ebola vaccine innovative approach		Ebola and related diseases
PHAGO	Inflammation and AD: modulating microglia function – focussing on TREM2 and CD33	www.phago.eu	Alzheimer's disease
PharmaLedger	PharmaLedger	pharmaledger.eu	blockchain
PIONEER	Prostate cancer diagnosis and treatment enhancement through the power of big data in Europe	prostate-pioneer.eu	big data, cancer
PREFER	Patient preferences in benefit risk assessments during the drug life cycle	www.imi-prefer.eu	patient involvement in R&D
PREMIER	Prioritisation and risk evaluation of medicines in the environment	imi-premier.eu	environmental issues
PRIMAVERA	Predicting the impact of monoclonal antibodies & vaccines on antimicrobial resistance	www.primavera-amr.eu	antimicrobial resistance
PRISM	Psychiatric ratings using intermediate stratified markers: providing quantitative biological measures to facilitate the discovery and development of new treatments for social and cognitive deficits in AD, SZ and MD	prism-project.eu	neurological disorders
PRISM 2	Psychiatric ratings using intermediate stratified markers 2	prism2-project.eu	neurological disorders
PROMISE	Preparing for RSV immunisation and surveillance in Europe	imi-promise.eu	respiratory disease
PROTECT-trial	Proton versus photon therapy for esophageal cancer - a trimodality strategy	protecttrial.eu	cancer
RADAR-AD	Remote assessment of disease and relapse – Alzheimer's disease	www.radar-ad.org	Alzheimer's disease
RADAR-CNS	Remote assessment of disease and relapse in central nervous system disorders	www.radar-cns.org	neurological disorders
RAPID-COVID	Robust automation and point of care identification of COVID	www.imi-rapidcovid.com	coronaviruses

Project acronym	Full project title	Website	Subject area
RealHOPE	Real world handling of protein drugs - exploration, evaluation and education	realhope.se	biologicals
RESCEU	Respiratory syncytial virus consortium in Europe	resc-eu.org	respiratory disease
RESOLUTE	Research empowerment on solute carriers	re-solute.eu	drug development
REsolution	Add medical genetic solutions to RESOLUTE	re-solute.eu/resolution	drug development
RespiriNTM	Progress novel assets (one FIH start) for non-tubercular mycobacteria that may act synergistically with bedaquiline and cytochrome bc drugs	respiritbntm.eu	antimicrobial resistance
RespiriTB	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	respiritbntm.eu	antimicrobial resistance
RHAPSODY	Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification	www.imi-rhapsody.eu	diabetes
ROADMAP	Real world outcomes across the AD spectrum for better care: multi-modal data access platform	roadmap-alzheimer.org	big data, Alzheimer's disease
RTCure	Rheuma tolerance for cure	www.rtcure.com	rheumatoid arthritis
Screen4Care	Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies	www.screen4care.eu	rare diseases
SISAQOL-IMI	Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials	www.sisaqol-imi.org	cancer
SOPHIA	Stratification of obese phenotypes to optimize future obesity therapy	imisophia.eu	obesity
STOPFOP	Saracatinib trial to prevent FOP	www.stopfop.com	rare / orphan diseases
T2EVOLVE	Accelerating development and improving access to CAR and TCR-engineered T cell therapy	t2evolve.eu	advanced therapies, cancer
TransBioLine	Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease	transbioline.com	safety
TransQST	Translational quantitative systems toxicology to improve the understanding of the safety of medicines	transqst.org	safety

Project acronym	Full project title	Website	Subject area
Trials@Home	Center of excellence – remote decentralised clinical trials	trialsathome.com	digital health
TRIC-TB	Boosting Ethionamide efficacy and lowering the dose with a small molecule transcriptional modulators, to overcoming MDR-TB infections and define a new place for Ethionamide in 1st-line TB treatments	amr-accelerator.eu/project/tric-tb	antimicrobial resistance
TRISTAN	Imaging biomarkers (IBs) for safer drugs: validation of translational imaging methods in drug safety assessment	www.imi-tristan.eu	safety
UNITE4TB	Academia and industry united innovation and treatment for tuberculosis	www.unite4tb.org	antimicrobial resistance
VAC2VAC	Vaccine lot to vaccine lot comparison by consistency testing	www.vac2vac.eu	vaccines
VALUE-Dx	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use	value-dx.eu	diagnostics
VHFMoDRAD	Viral haemorrhagic fever: modern approaches for developing bedside rapid diagnostics	vhfmodrad.eu	Ebola and related diseases
VITAL	Vaccines and infectious diseases in the ageing population	vital-imi.eu	vaccines
VSV-EBOPLUS	Systems analysis of adult and pediatric responses to the VSV-ZEBOV Ebola vaccine	vsv-eboplus.eu	Ebola and related diseases
VSV-EBOVAC	Vaccine safety and immunogenicity signatures of human responses to VSV-ZEBOV	www.vsv-ebovac.eu	Ebola and related diseases
WEB-RADR 2	WEB-RADR 2	web-radr.eu/web-radr2	pharmacovigilance

Annex 10: List of acronyms

Acronym	Meaning
3Rs	Replacement, reduction and refinement
AAR	Annual Activity Report
ABAC	Accrual Based Accounting System
ABC-CT	Autism Biomarker Consortium for Clinical Trials
ACE	Angiotensin converting enzyme
ACPA	Antibodies to citrullinated protein antigens
AD	Alzheimer's disease
AD	Atopic dermatitis
ADDIS	Aggregate Data Drug Information System
ADME	API uptake, distribution, metabolism and excretion
AE	Adverse event
AESI	Adverse event of special interest
AFS	Anti-fraud strategy
AI	Artificial intelligence
ALHN	Autism Learning Health Network
AlloHSCT	Allogenic hematopoietic stem cell transplant
ALS	Amyotrophic lateral sclerosis
ALTO	Arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept Long-Term Outcome
AML	Acute myeloid leukaemia
AMR	Antimicrobial resistance
AP	Associated Partner
aP	Acellular pertussis
API	Active pharmaceutical ingredient
API	Application programming interface
APIPPRA	Arthritis Prevention In the Pre-clinical Phase of RA with Abatacept
ARDS	Acute respiratory distress syndrome
ARES	Advanced Records System
ASD	Autism spectrum disorder
ATCC	American Type Culture Collection
ATG	Antithymocyte globulin
ATM-AVI	Aztreonam-avibactam
Autism CRC	Cooperative Research Centre for Living with Autism
AWP	Annual Work Plan
BBB	Blood-brain barrier
BCEC	Brain capillary endothelial-like cells
BD4BO	Big Data for Better Outcomes
BMGF	Bill and Melinda Gates Foundation
BMI	Body mass index
BSL	Biosafety level

Acronym	Meaning
CA	Commitment appropriations
CA	Contract agent
CAAR	Consolidated Annual Activity Report
CA-ARTI	Community-acquired acute respiratory tract infection
CAFS	Commission Anti-Fraud Strategy
CARB-X	Combating Antibiotic-Resistant Bacteria
CAS	Common Audit Service
CCI	Customer-centric index
CDA	Confidential disclosure agreement
CDER	Center for Drug Evaluation and Research
CDI	*Clostridioides difficile* infection
CDISC	Clinical Data Interchange Standards Consortium
CDM	Common data model
CE	Conformité Européenne
CEPS	Centre for European Policy Studies
CERT-EU	Computer Emergency Response Team
CGM	Continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human Use
CIA	Colalgen induced arthritis
CMS	Content management system
CNS	Central nervous system
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
CONT	European Parliament Budgetary Control Committee
COPD	Chronic obstructive pulmonary disease
CORDA	Common Research Data Warehouse
COS	Core outcome set
COVID-19	Coronavirus disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
C-Path	Critical Path Institute
CRA	Clinical Research Associates
CRS	Common representative sample
CRS	Cytokine release syndrome
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CT	Computed tomography
CTA	Clinical trials agreement
CTN	Clinical trials network
CV	Cardiovascular
DAP	Data provider
DAS	Declaration of Assurance
DCT	Decentralised clinical trial

Acronym	Meaning
DDIM	Drug Development Information Management
DG	Directorate-General
DG BUDGET	European Commission Directorate-General for Budget
DG DIGIT	European Commission Directorate-General for Informatics
DG HR	European Commission Directorate-General for Human Resources and Security
DG RTD	European Commission Directorate-General for Research and Innovation
DIA	Drug Information Association
DIKI	Drug-induced kidney injury
DILI	Drug-induced liver injury
DINI	Drug-induced CNS (central nervous system) injury -
DIVI	Drug-induced vascular injury
DKD	Diabetic kidney disease
DMO	Digital mobility outcome
DoA	Description of action
DOI	Digital object identifiers
DoW	Description of work
DPF	Diagnostic and prognostic factors
DPIA	Data protection impact analysis
DPMS	Diagnostic and patient management study
DRC	Democratic Republic of the Congo
DTAP	Diphtheria, tetanus and acellular pertussis
DW	Data warehouse
EC	European Commission
ECA	European Court of Auditors
ECRAID	European Clinical Research Alliance on Infectious Diseases
ED	Executive Director
EDCTP3	European & Developing Countries Clinical Trials Partnership 3
EDES	Early Detection and Exclusion System
EDPS	European Data Protection Supervisor
EEG	Electroencephalogram
EFGCP	European Forum for Good Clinical Practice
EFNA	European Federation of Neurological Associations
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EHDS	European Health Data Space
EJP RD	European Joint Programme on Rare Diseases
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENSO	Exploring New Scientific Opportunities
EORTC	European Organisation for Research and Treatment of Cancer
EPDC	European Platform for Diabetes and Complications
EPF	European Patient Forum

Acronym	Meaning
ePI	Electronic product information
EPSO	European Personnel Selection Office
ERM	Enterprise risk management
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EUnetHTA	European Network for Health Technology Assessment
EuropaBio	European Association for Bioindustries
EURORDIS	Rare Diseases Europe
FAIR	Fraud and irregularity in research
FAIR	Findable, accessible, interoperable, reusable
FC	Financial contribution
FC	Flow cytometry
FDA	US Food and Drug Administration
FG	Function group
FIH	First in human
FLW	Frontline worker
FNIH	Foundation for the National Institutes of Health
FOP	Fibrodysplasia ossificans progressiva
FP	Full proposal
FP7	Seventh Framework Programme
FTE	Full time equivalent
FTIH	First time in human
FWC	Framework contract
GA	Grant Agreement
GAMIAN-Europe	Global Alliance of Mental Illness Advocacy Networks-Europe
GAP	Grant Agreement preparation
GB	Governing Board
GCGH	Grand Challenges in Global Health
GDPR	General Data Protection Regulation
GI	Gastrointestinal
H2020	Horizon 2020
HCP	Healthcare professional
HDGEC	Huntington’s disease gene-expansion carrier
HERA	Health Emergency Preparedness and Response Authority
HES	Higher or secondary education establishment
HF	Heart failure
hiPSC	Human induced pluripotent stem cell
hPSCreg	Human pluripotent stem cell registry
HIV	Human immunodeficiency virus
HR	Human resources
HTA	Health technology assessment
HTS	High throughput screening

Acronym	Meaning
IA	Innovation Action
IaaS	Infrastructure as a Service
iAMD	Intermediate age-related macular degeneration
IAS	Internal Audit Service of the European Commission
IAVI	International AIDS Vaccine Initiative
IBD	Inflammatory bowel disease
IBV	Infectious bronchitis virus
IC	Internal control
ICF	Internal control framework
ICMR	Indian Council of Medical Research
ICU	Intensive care unit
IDG	Illuminating the Druggable Genome
IHI JU	Innovative Health Initiative Joint Undertakings
IKC	In-kind contribution
IMI1 JU	Innovative Medicines Initiative 1 Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMU	Inertial measurement unit
IoT	Internet of things
iPSC	Induced pluripotent stem cell
irAE	Immune related adverse event
irAOP	Immune related adverse outcome pathway
IRP	Integrated research platform
IT	Information technology
ITF	Innovation Task Force
ITRE	European Parliament Committee on Industry, Research and Energy
IVE	Influenza vaccine effectiveness
JAMA	Journal of the American Medical Association
JDRF	Juvenile Diabetes Research Funding and Advocacy
JIF	Journal impact factor
JTI	Joint Technology Initiative
JUs	Joint Undertakings
KB	Knowledge base
KIM-1	Kidney injury molecule 1
KPI	Key performance indicator
LEAP	Longitudinal European Autism Project
LT	Long-term contract
LTCF	Long term care facilities
mAB	Monoclonal antibody
MC	Mass cytometry
MCI	Mild cognitive impairment
MDD	Major depressive disorder
MHRA	Medicines and Healthcare products Regulatory Agency

Acronym	Meaning
miRNA	Micro RNA
MISP	Malware information sharing platform
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MS	Multiple sclerosis
MSCA	Marie Skłodowska-Curie Actions
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NBDC	Nearby Bluetooth device count
NC3Rs	National Centre for the Replacement, Refinement and Reduction of Animals in Research
NF	Neurofibromatosis
NH	National hub
NIH	National Institutes of Health
NLM	Natural language processing
NSCLC	Non-small-cell lung cancer
OECD	Organisation for Economic Cooperation and Development
OLAF	European Anti-Fraud Office
OMERACT	Outcome Measures in Rheumatology
OMOP	Observational Medical Outcomes Partnership
OpenDSU	Open data sharing units
OTH	Other type of organisation
OVA	Ovalbumin
PA	Payment appropriations
PBK	Physiologically-based pharmacokinetic
PBP	Penicillin-binding protein
PC	Parent cohort
PCA	Pulse-controlled amplification
PCR	Polymerase chain reaction
PD	Parkinson’s disease
PD-1	Programmed cell death protein 1
PDX	Patient derived xenografts
PEOF	Patient Engagement Open Forum
PET	Positron emission tomography
PHH	Primary human hepatocytes
PIBD	Paediatric inflammatory bowel disease
PIP	Preschool Brain Imaging and Behaviour Project
PiR	Partner in Research
PK/PD	Pharmacokinetic/pharmacodynamic
PLoS	Public Library of Science
PMO	Paymaster Office
PNHS	Prognostic and natural history study

Acronym	Meaning
PoC	Point of care
PoC	Proof of concept
PoN	Point of need
POND	Province of Ontario Neurodevelopmental Network
PPAS	Point prevalence audit survey
PPP	Public-private partnership
PPS	Patient preference study
PPTC	Pediatric Preclinical Testing Consortium
PRC	Private for-profit entity
PRD	Partially-responsive depression
PRO	Patient reported outcome
PROM	Patient reported outcome measure
pSS	primary Sjögren's Syndrome
PUB	Public body
QA	Qualification advice
QC	Quality control
QES	Qualified electronic signature
QO	Qualification opinion
QoL	Quality of life
qPCR	quantitative polymerase chain reaction
QSAR	Quantitative structure activity relationship
QST	Quantitative systems toxicology
R&D	Research and development
R&I	Research and innovation
RA	Rheumatoid arthritis
RADIAL	Remote And Decentralised Innovative Approaches to Clinical Trials
RAE	Risk assessment exercise
RAFS	Common Research Family Anti-Fraud Strategy
REC	Research organisation
RepER	Representative error rate
ResER	Residual error rate
RIA	Research and Innovation Action
RMIC	Risk management and internal control
RMT	Remote monitoring technology
RSV	Respiratory syncytial virus
RTO	Research and Technology Organisation
RWE	Real world evidence
S&D	Socialists and Democrats
SA	Scientific advice
SaaS	Software as a service
SAE	Serious adverse event
SA-PJI	*Staphylococcus aureus* prosthesis joint infection

Acronym	Meaning
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBA	Single Basic Act
SBC	Session border controller
SC	Scientific Committee
SEP	Staff establishment plan
SEP	Selection and evaluation phase
SEP	H2020 IT tool for submission and evaluation of proposals
SEP DS	SEP Data Store
SFARI	Simons Foundation Autism Research Initiative
SGG	Strategic Governing Group
SGLT2	Sodium-glucose cotransporter-2
SIP	Security Implementation Plan
SIP	Science and Innovation Panel
SLA	Service level agreement
SLC	Solute carrier
SLE	Systemic lupus erythematosus
SME	Small and medium-sized enterprise
SNE	Seconded national expert
SO	Scientific officer
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
ST	Short-term contract
STDM	Study data tabulation model
SUDEP	Sudden unexpected death in epilepsy
SWP	Standard Working Party
SyGMa	H2020 IT tool for grant management
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary agent
TAR	Target actionability review
TB	Tuberculosis
TBE	Tick-borne encephalitis
THL	Terveyden ja hyvinvoinnin laitos
TNF	Tumour necrosis factor
TolDC	Tolerogenic dendritic cell
TRD	Treatment-resistant depression
TREM2	Triggering receptor expressed on myeloid cells 2
TRL	Technology readiness level

Acronym	Meaning
TTG	Time to grant
TTI	Time to inform
TTP	Time to pay
TTS	Time to sign
UFM	Unaffected family members
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe
VAP	Ventilator-associated pneumonia
VCG	Virtual control group
VoC	Variant of concern
WDC	World Dementia Council
WHO	World Health Organisation
WP	Work package
wP	Whole cell pertussis

Annex 11: Analysis and assessment of the Consolidated Annual Activity Report 2021 (CAAR 2021) by the IHI JU Governing Board

Legal Basis

Article 23 of the IHI JU Financial Rules[62] states that *"The authorising officer shall report annually to the governing board on the performance of his or her duties for year N-1 in the form of a consolidated annual activity report"*.

Article 23 of the IMI2 JU Financial Rules further specifies that *"No later than 1 July each year, the governing board shall send the consolidated annual activity report together with its assessment of it to the Court of Auditors, the Commission, the European Parliament and the Council"*.

Analysis

Key objectives for 2021 are set out in the **Annual Work Plan** (AWP 2021) and include: 1) a smooth transition to IHI; 2) completion of the execution of Strategic Research Agenda priorities; 3) sound budget implementation; 4) demonstration of EU added-value of IMI2 JU; 5) involvement of industry from related sectors other than the pharmaceutical industry; 6) internationalisation of IMI2 JU, and; 7) dissemination of IMI project outcomes. **IMI2 JU operated from 1 January to 29 November 2021**.

The Governing Board recognises **the progress made by the JU** towards achieving these objectives and notes in particular that, in 2021, fifteen final IMI2 projects were launched thereby completing the significant project portfolio comprising 123 projects. Many of these projects will run for several more years, being managed by the IHI Programme Office. Of particular note is that more than half of these IMI2 projects involve **patient organisations** and **healthcare professionals' associations** as consortium partners, members of advisory or stakeholder groups. Several IMI projects have actively recruited and supported **SMEs** outside of the projects.

In 2021, IMI projects continued to deliver **impactful results** in key areas such as diabetes, dementia, paediatric medicines and COVID-19, generating new tools, methodologies, processes, services, training materials, etc.

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[63] range from the discovery of an **antibody** against SARS-CoV-2 and the repurposing of existing medicines for use as **COVID-19** treatments to the discovery of a **genetic link** with the likelihood of developing a severe disease to the better understanding of **Parkinson's**, **Alzheimer's**, **diabetes**, **autism**, and childhood **cancer** (to name a few). Other key achievements include harnessing the power of **big data** to assess **vaccine safety**, regulators' endorsement of a research framework for **patient preference studies** and the development of a pan European clinical trial and laboratory network on **antimicrobial resistance** (AMR) to fast-track potential new anti-microbials.

- By the end of 2021, IMI2 projects had registered 20 completed regulatory procedures, 7 patent/trademark/registered design applications and 5 patents/trademarks awarded.

- **Communication activities** were effective, focussing on developing political support for and raising awareness of IMI among all target groups, by emphasising project results and impact, namely:

    - News articles, videos and success stories were published.
    - Social media and the newsletter were used to promote editorial content.
    - Press coverage showed reference to IMI in 6,302 articles worldwide.
    - Due to the on-going COVID-19 pandemic, the traditional Stakeholder Forum was turned into a series of virtual events called the IMI Impact Series that attracted a significant audience.

[62] The IMI2 JU Financial Rules were re-adopted by the IHI Governing Board as the IHI JU Financial Rules on 16 December 2021 (decision IHI-GB-DEC-2021-03).
[63] IMI website: https://www.imi.europa.eu/projects-results/success-stories-projects

- “Project factsheets” and “news and events” remained among the most visited sections of the IMI website. The most popular news story was about the vaccine project ZAPI. The IMI website will be archived in 2022, but will remain accessible to the public.

- The Governing Board notes with satisfaction that in its report on the financial year 2020, 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. The auditors indicated that audits of randomly selected IMI payments to Horizon 2020 beneficiaries showed only one case with an error above 1% of the audited costs related to the declared direct costs.

- In 2021, the **Internal Audit Service** performed an audit on Horizon 2020 grant implementation in IMI2 JU. The objective of this audit was to assess the adequacy of the design and the efficiency and effectiveness of the internal control system in place in for the implementation of grant agreements under Horizon 2020 programme. The Governing Board notes that according to the final audit report, the overriding strength of the JU is the commitment and dedication of the Project Officers and Financial Officers, and their line managers, who oversee the implementation of grant agreements.

- In relation to the use of **human resources**, the Governing Board is of the opinion that activities carried out by JU staff in 2021 were in line with the assigned objectives.

- The CAAR 2021 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 2021, the Governing Board is of the view that the key objectives set up for 2021 have been met in compliance with legality, regularity and sound financial management.

The Governing Board recognises the setting up of IHI and notes in particular that:

- **European partnerships** are a key approach in **Horizon Europe** whereby the EU set up **joint undertakings** to complement existing policy frameworks by addressing global challenges and EU priorities that require critical mass and a long-term vision that is agreed and committed to by the respective sectors.

- The European Commission published its proposal for establishing joint undertakings under Horizon Europe, including IHI, on 23 February 2021.

- Upon the conclusion of the legislative process and adoption of Council Regulation 2021/2085 establishing nine Joint Undertakings under Horizon Europe, the **IHI JU started to exist on 30 November 2021** and took over the rights and obligations of IMI2 JU.

- The Governing Board acknowledges the important role IHI JU is expected to play in contributing to important EU health policies and initiatives such as fighting cancer (**Europe’s Beating Cancer Plan**), increasing industrial competitiveness (**Industrial Strategy**), ensuring access to innovative and affordable medicines (**Pharmaceutical Strategy** for Europe) and harnessing the potential of health data (**European Health Data Space**).

- The **total budget for IHI is EUR 2.4 billion**, half of which comes from Horizon Europe and the other half from IHI industry partners and other organisations that decide to support the objectives of IHI as Contributing Partners. The Innovative Health Initiative (IHI JU) has a stronger focus on **cross-sectoral projects** involving not only the pharmaceutical sector but also biotechnology, medical technologies, vaccines and digital health.

- The **Governing Board** of the IHI JU held its constitutive meeting on 16 December 2021 and adopted all decisions necessary to allow the JU to become operational. A **new IHI website** was launched successfully on 15 December 2021 bringing 3 446 visits and 10 006 page views. A new IHI logo and corporate identity were created, combining a new look with reference to the brand of its predecessor, and infographics and promotional materials were disseminated. The change from the IMI2 programme to IHI programme was a significant milestone and the Governing Board recognises the role of the **Programme Office** in organising and facilitating this transition.

- Given that the Council Regulation establishing IHI only came into force at the end of 2021, no IHI calls for proposals were launched in 2021.

Assessment

The declaration of the Executive Director and the Consolidated AAR 2021 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 2021.

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 implementation of the IMI2 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**.

The Governing Board notes the **smooth transition** of IMI2 JU to **IHI JU** and **business continuity**.

Therefore, the IHI JU Governing Board hereby adopts this analysis and assessment of the Consolidated AAR 2021 of the authorizing officer. This analysis and assessment will be included in the Consolidated AAR 2021.

Brussels, June 2022

For the Innovative Health Initiative Joint Undertaking,

signed
Irene Norstedt, Chairperson of the Governing Board

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