

The right prevention and treatment for the right patient at the right time

Outline Strategic Research Agenda for a
biomedical research public private partnership
under Horizon 2020

08 July 2013

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Executive summary

The Strategic Research Agenda (SRA)

The SRA has been written to reflect a summary of the major challenges currently facing the European healthcare system, the pharmaceutical industry and the regulatory framework. It is intended to provide a framework which will underpin the development of specific projects or research programmes which will be prioritised for funding as described below.

The current healthcare ecosystem is not sustainable

The current and future healthcare challenge in Europe, and indeed globally, is driven by the increasing inability of governments to afford world-class care for populations that are living longer, often with chronic disease, associated with lifestyle changes that increase risk for cardio-respiratory, neuropsychiatric, metabolic disease, musculoskeletal and other conditions. The costs of care continue to increase steadily as new more expensive treatments are introduced and adherence with prescribed treatment regimens remains low.

This comes at a time when the pharmaceutical industry, which lies at the heart of the healthcare ecosystem, is also under increasing pressure. The ageing population brings the demand for a new generation of medicines at a time when patent cliffs are reducing revenue with reduced investment available for future innovations as a result. Cuts in healthcare spending driven by austerity measures put additional pressure on companies to provide evidence to support the effectiveness of their drugs on health care outcomes (often hampered by lack of adherence to prescribed treatment regimens), and lead to price cuts on existing and new medicines. The increasing involvement of patients in the decisions regarding their healthcare options and decentralization of healthcare provision are also driving the need for innovative approaches to delivery and monitoring adherence to prescription paradigms new medicines.

Now is the time for change

Despite the tough economic environment, the availability of the complete sequence of the human genome, the growing body of ‘-omic’ data sets and epigenetic markers in health and disease, the availability of for instance patients’ electronic medical records, next generation genetics for target identification and sophisticated bioinformatics techniques offers the opportunity to revolutionise the current medicines development process. Increased participation of citizens and patients early in the R&D process also offers the opportunity to better understand the needs of each individual, the behaviours that drive poor lifestyle choices and non-adherence to prescription regimens therefore offering the opportunity to create not just medicines, but integrated treatment programmes tailored to maximise outcomes. For the pharmaceutical industry the knowledge and tools generated to support precision medicine will not only lead to more tailored treatment paradigms and programmes but will also fundamentally improve efficiency of drug discovery focusing on human biology as well as early development using innovative biomarkers to obtain proof of mechanism. For healthcare providers, the availability of clinical, imaging and molecular biomarkers predictive of response and side effects, as well as better delivery and monitoring devices offers the potential to improve the quality of care. For payers, these tools have the potential to reduce costs in the long term by providing more cost-effective treatments with less adverse events. For patients, the focus on precision medicine will lead to the availability of tailored integrated treatment programmes aim to maximise the benefit gained from preventative or therapeutic interventions and minimise the risk.

IMI will drive a new and integrated approach to R&D

While offering enormous opportunity, no one sector or institution can realise the potential that these scientific advances offer if working in silo. Only by engaging all key stakeholders, can **the vision of IMI2 to deliver the right treatment to the right patient at the right time for priority diseases be**

realised. All sectors within the healthcare ecosystem will need to work together to build the environment and infrastructure that allows the full value of this innovation to be realised. The new biomedical PPP proposed between the pharmaceutical industry and the EU (represented by the European Commission) will be uniquely positioned to provide the transparent platform required to facilitate engagement and coordinated co-operation between all key stakeholders in the provision of healthcare today i.e. healthcare practitioners, regulators, patients and payers to ensure new scientific advances are translated into innovative, effective products, strategies, interventions and services.

Defining the research priorities

Meeting the increasing demands of healthcare in Europe is undermined by misalignment of preclinical predictions with clinical realities, late stage failures in drug development and misalignment of innovators with expectations of regulators and payers. The resulting low productivity impedes the delivery of improved healthcare solutions to patients. The Strategic Research Agenda (SRA) for IMI2 outlines the major challenges currently facing the European healthcare system, the pharmaceutical industry and the regulatory framework and provides an outline of the research required to address each of these in turn. To successfully realise the ambitious goals of IMI2 all of these areas will need to be addressed. This cannot be achieved by this PPP alone. Scientific advances continue to be made across the globe, these must be fully leveraged and collaboration with other large international public private partnerships will be key to ensure research remains cutting edge and public funds are used in the most efficient way. The decisions regarding prioritisation of new efforts to be funded under IMI2 will be based on the following criteria

- 1) EU research priorities as highlighted under H2020 and the priority of the healthcare challenges for Europe as outlined in the WHO priority medicines report.
- 2) The need for true PPP. Efforts will be focussed on those areas where multi-stakeholder engagement is paramount for success. New research programmes initiated will not only address the scientific and technological challenges but will also be designed to address the associated regulatory and healthcare delivery challenges.
- 3) The level of activity ongoing in other initiatives both within Europe and across the globe. The new PPP will actively seek collaboration with other ongoing initiatives and funding bodies which will be paramount to ensuring maximum synergy and avoiding duplication of effort.

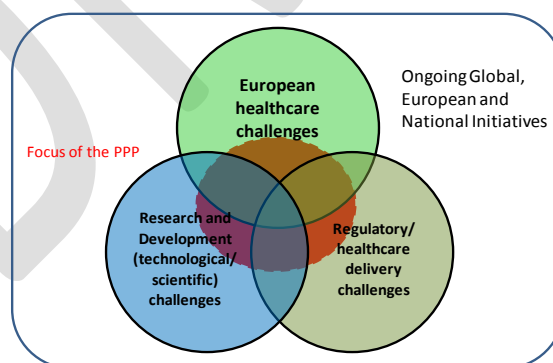


Fig 1. The PPP will provide the unique opportunity to facilitate engagement of all key stakeholders involved in the provision of healthcare to address key challenges and ensure new scientific advances are translated into effective new medicines addressing priority healthcare challenges in Europe and across the globe.

Establishing Europe as a world leader in medicines development

The new generation biomedical research PPP will focus on research and innovation that address key elements of the EU research priorities as outlined under H2020 and support the aim of the European health policy, Health 2020 which is “to improve the health and well-being of populations, reduce health inequalities, and ensure sustainable people-centred health systems”.

Furthermore, PPP offers the potential to position Europe as a world leader in medicines development and at the same time will contribute to maintaining or reinvigorating industrial research and activity in areas of high societal interest especially those that currently suffer from disinvestment and to create a world class, integrated R&D framework that will attract investment and in turn strengthen the competitiveness of the European-based industries, creating new market opportunities increasing employment and economic growth.

Addressing the major bottlenecks from discovery to delivery

Four major areas have been identified where an integrated approach will have significant impact on increasing the probability of success and reducing the overall cost of new medicines.

1) Target identification and biomarker research (efficacy and safety).

Failure of efficacy to translate from pre-clinical models to the clinical setting combined with the emergence of adverse events not predicted from the pre-clinical models remain at the core of late stage attrition. The PPP will focus on gaining a better understanding of disease mechanisms to facilitate target identification and also use this knowledge for the identification of biomarkers predictive of efficacy as well as biomarkers that may serve as surrogate markers in clinical trials. In parallel efforts will be made to better understand the molecular mechanisms underlying adverse events and identify new methodologies to support the assessment of PK/PD responses at an organ level. The new PPP offers a unique opportunity for scientists, regulators and health technology assessment agencies to work together to ensure that efforts to develop biomarkers are tailored to their intended purpose whether for internal decision making, regulatory submissions or demonstration of effectiveness. This will increase the quality of the biomarkers identified, reduce duplication of effort where biomarker development is applicable to the disease indication and/or drug classes, while facilitating the uptake of these scientific advancements.

2) Driving the adoption of innovative clinical trial design

Efficacy and safety. Clinical trials account for a large proportion of the overall development costs of any new medicine. Bayesian statistical methods are being used increasingly in clinical research to minimise the number of patients included in a randomised clinical trial (RCT) and decrease the chance of maintaining a patient in an unfavourable treatment arm. The drive towards precision medicine is taking this concept even further, driving the need for the development of new patient focussed clinical outcome measures and new clinical trial paradigms to support the evaluation of benefit/risk in small numbers of stratified patient populations and the development of infrastructures for collection and sharing of trial data, together with methods for meta-analysis of trial data to investigate outcomes across multiple trials in different locations.

Relative effectiveness. For many years healthcare systems were able to fund new medicines based on regulatory approval, however, health technology assessment (HTA) agencies and other healthcare decision makers now assess the expected future value of a medicine when used in “real world” clinical practice. Currently, data packages which aim to minimise uncertainty for regulatory authorities on safety and efficacy may leave significant uncertainty in the assessments of real world effectiveness/risk of new medicines and thus slow the speed and level of patient access. The advent of digital media and the use of Smartphone’s and Tablets offer the opportunity to develop new methods for collecting real world effectiveness/risk data utilising more patient reported outcomes, however with it brings the challenge of managing the collection, validation and analysis of data, cost-effectiveness of data collection, privacy laws and data security.

Addressing these challenges requires an integrated approach exploring the development of novel biomarkers and patient focussed clinical endpoints, innovative trial designs, patient centred benefit/risk and effectiveness/risk assessment and alternative regulatory pathways to ensure that

future development strategies address the needs of all decision makers from the outset. The level of integration required to achieve this ambitious goal would not be possible without the PPP framework being proposed.

3) Innovative Medicines

Preventative medicine. The ageing population and increased incidence of chronic disease is driving the need for investment in the discovery and development of preventative medicines. Given the current strain on the healthcare system it is essential to incentivise this research for diseases with high impact on society such as Alzheimer's disease and osteoarthritis. To be successful cooperation is essential between the drug developer, regulatory authorities and HTA agencies to define new clinical trial designs for determining efficacy and safety profiles and methods for collecting relative effectiveness data. In addition the means of valuing innovation and providing incentives will need to be reconsidered given that current patent protection only lasts for 20 years, for prevention medication this will not provide sufficient time for companies to recoup their development cost.

Medicines for areas of high public health concern. There is also a need to stimulate research and investment in areas where there is high public health concern, but where companies have largely withdrawn from drug discovery such as antibiotic resistance and stroke. The PPP will therefore aim to jointly develop novel therapeutic agents to tackle areas where low return on investment or lack of other market incentives prohibits the development of new effective medicines.

4) Patient tailored adherence programmes

One of the biggest challenges facing the pharmaceutical industry and healthcare providers alike is the issue of patients failing to adhere to prescribe dosing regimens which compromises the effectiveness of prescribed medications. This is a problem which is only set to become more prevalent as the trend for healthcare to be pushed outside the hospital setting increases and the age of the population increases. Effective adherence programmes will require an integrated approach which provides a range of services from clinical support and education to patients, the development of new drug delivery systems to the development of robust, portable monitoring devices. Including patients, healthcare providers, the regulatory authorities and HTA agencies in the design of such programmes will be key to their success to ensure they are optimally tailored for the end user while fulfilling regulatory requirements.

Disease areas of focus

11 priority disease areas (Antimicrobial resistance, Osteoarthritis, Cardiovascular diseases, Diabetes, Neurodegenerative diseases, Psychiatric diseases, Respiratory diseases, Autoimmune diseases, Ageing-associated diseases/conditions, Cancer, Orphan Disease) have been highlighted in the SRA as being of high priority for both the European healthcare system and the pharmaceutical industry. Each of these areas poses different challenges when considering the discovery, development and delivery of innovative effective medicines. In each of these diseases research conducted under IMI2 will be tailored to deliver the tools and capabilities required to address those challenges that pose the biggest barriers to effective healthcare solutions (an outline of the most significant challenges can be found in Appendix 1 of the SRA).

Focus on Vaccines

Vaccination is one of the most valuable and cost effective public health measures to prevent and control the spread of viral/bacterial infectious diseases responsible for high mortality and morbidity. Reduced childhood mortality, increased longevity and changing birth rates are dramatically altering demographics in Europe and around the world. With these changes comes the need to extend the vision of vaccination from early life and childhood alone to the whole life span and from prevention to prevention and treatment. The PPP will address the changing risks and immunological

characteristics of this life span which requires innovative solutions to understand and measure the immune system maturation, and tackle emerging/unmet medical needs.

Enabling Technologies

Knowledge management (KM) solutions and services are critical in the efficient execution of modern, multicentre biomedical studies, especially exploratory early clinical/translational research studies. The increasing volume (terabytes/patient), diversity (Clinical, GWAS/RNASeq, eHR, 'omic, Cytometry, Imaging, pharmacology, pharmacovigilance etc) and velocity (e.g. real time telemetric monitoring of patients, social media feeds, etc) of biomedical data is creating significant 'big data' challenges (and opportunities) for healthcare R&D. Provision of such services will be a critical component for delivering Scientific Excellence and the most innovative healthcare solutions.

Implementation

Success in a continuously changing environment like medicines development depends on operational excellence in all phases of the value chain from early research up to the regulatory process and the market. Well trained networks of professionals who are familiar not only with the most recent changes in their specific area but the overall context of medicines research and development are a prerequisite to ensure the successful implementation of the advances made during the lifetime of the PPP.

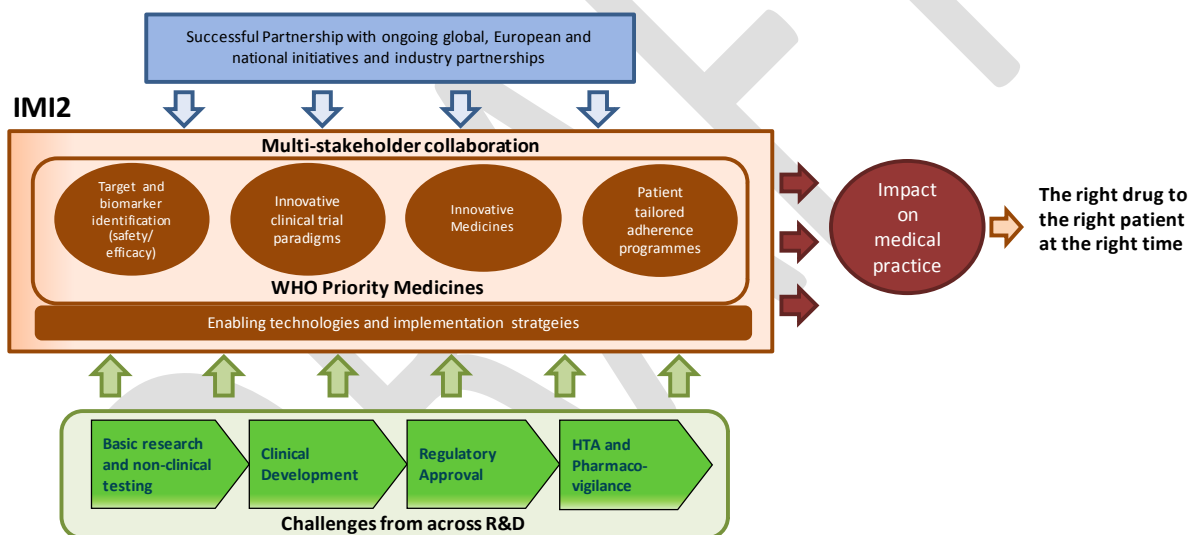


Fig 2. The new biomedical PPP being proposed will partner with ongoing initiatives (and funding bodies) to create cross disciplinary, international research teams with the aim of delivering integrated and effective healthcare solutions for priority diseases. The PPP will not only focus on the technical and scientific advances required, but will also support the implementation of these advances through the development of appropriate training materials and networks.

Impact of IMI2

IMI2 will deliver tools, methods and prevention and treatment options (directly or indirectly) that will progress the vision of personalised medicine and prevention. Through providing the framework required to support collaboration between scientists, regulators, HTAs, patients and healthcare providers, IMI2 will ensure that research is translated into implementable solutions to current healthcare challenges. Solutions that are not purely focussed on the development of new medicines, but that provide a holistic personalised healthcare package as well as maintain people healthy and productive throughout their lifetime. Reclassification of diseases based on their root cause and not symptoms will help addressing unmet needs even in areas where a range of options exist but patients do not respond, because their symptoms are misleading therapy choices. New biomarkers and methods to support the stratification of patients to those that are predicted to respond to new

medicines, to monitor response and reliably predict the safety of new medicines, will rationalise the way clinical trials are conducted and increase the safety of new medicines. This in turn will impact medical practice with potential for more rational use of healthcare budgets and resources. IMI2 will make an invaluable contribution to maintaining or reinvigorating industrial research and activity in areas of high societal interest that currently suffer from disinvestment. Better suited formulations and dosages will improve patient compliance essential in acute infections or long term chronic conditions where disease control is essential for a normal and productive life. Finally, presence of all stakeholders in the IMI2 framework will facilitate exploitation of results in the regulatory and clinical practice and evolution of the research, development, licensing and healthcare delivery systems apace with science and opportunities it creates.

DRAFT

1. Introduction and Background

1.1. The Strategic Research Agenda (SRA)

This current document provides an outline proposal for the SRA which will underpin a new biomedical research public-private partnership (PPP) to be funded under H2020 (IMI2). The general framework that is proposed is adopted from the EU H2020 specific programme and the vision created as a result of discussions held at the EU Copenhagen Research Forum 2012. EFPIA, together with Vaccines Europe and input from 52 organisations (individual scientists, research institutes, academic hospital centres, learned societies, research funding organisations (incl. ppps), EU (funded) initiatives, umbrella organisations, governmental organisations and regulatory agencies gathered between June 2012 and April 2013) have developed the specific objectives and activities outlined below. It is envisaged that public consultation will continue throughout 2013 with finalisation of the agenda due by the end of 2013.

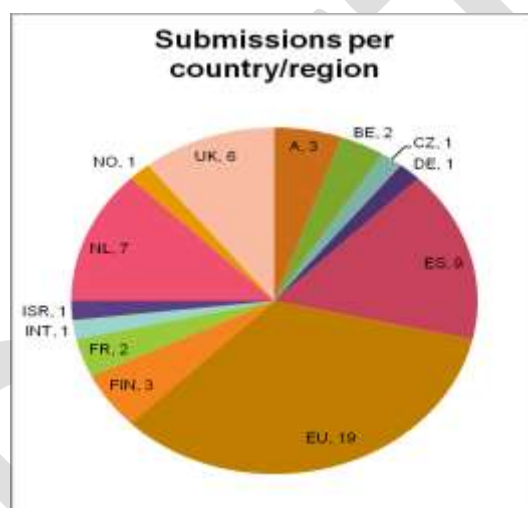


Fig. 3 Regional representation of input received from 52 independent organisations across Europe.

The SRA for IMI2 outlines the major challenges currently facing the European healthcare system, the pharmaceutical industry and the regulatory framework together with an outline of the research required to address each of these in turn. The SRA is not intended to define specific projects that will be conducted during the lifetime of IMI2, these will be created after the overarching strategy is adopted. Learning from the IMI experience, it is important that the SRA sets a balance between focus and clear strategic direction which will allow delivery of tangible results and sufficient degree of openness and flexibility which will make it possible to incorporate any sector or technology as well as cutting edge scientific advances as they are made.

To successfully realise the ambitious goals of IMI2 all of the areas outlined in the SRA will need to be addressed, however to ensure the most efficient use of the available funding, to maximise success and maintain competitiveness for Europe, IMI2 will need to partner with ongoing national, European and international initiatives. The decisions regarding prioritisation of new efforts to be funded under IMI2 will be based on the following criteria:

- 1) EU research priorities as highlighted under H2020 and the priority of the healthcare challenges for Europe as outlined in the WHO priority medicines report.
- 2) The need for true PPP. Efforts will be focussed on those areas where multi-stakeholder engagement is paramount for success. New research programmes initiated will not only

address the scientific and technological challenges but will also be designed to address the associated regulatory and healthcare delivery challenges, required to facilitate translation of the results into meaningful healthcare solutions.

- 3) The level of activity ongoing in other initiatives both within Europe and across the globe. The new PPP will actively seek collaboration with other ongoing initiatives and funding bodies which will be paramount to ensuring maximum synergy and avoid duplication of effort.

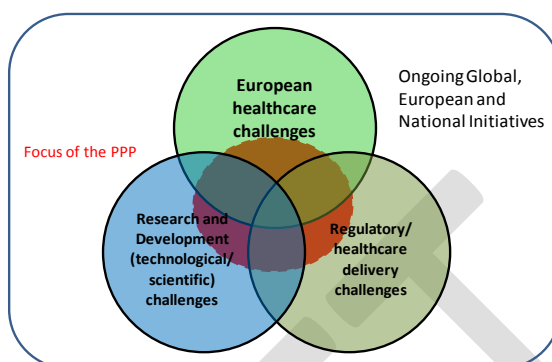


Fig 4. IMI2 will provide the unique opportunity to facilitate engagement of all key stakeholders involved in the provision of healthcare to address key challenges and ensure new scientific advances are translated into effective new medicines and vaccines addressing priority healthcare challenges in Europe and across the globe.

1.2. The aim and vision of IMI2 – The right prevention and treatment, to the right patients at the right time

The aim of the European health policy, Health 2020 is “to improve the health and well-being of populations, reduce health inequalities, and ensure sustainable people-centred health systems”¹. A sustainable healthcare system is a holistic one in which the patients are responsible for their wellness and quality of life; physicians, therapists, nutritionists, community carers, and all other actors in the value chain are motivated to this goal; delivery of care takes into account patient beliefs, values and both rational and irrational behaviors; the care is affordable to both public and private payers and promotes health; sustainable businesses can thrive; and the education, prevention and management of chronic conditions are aligned to achieve this goal.

The aim of IMI2 is to enable an appropriate European-level research and innovation response that will make a crucial contribution to delivering better health and wellbeing for all, and positioning Europe as a leader in the rapidly expanding global markets for health and wellbeing innovations.

Delivering innovative solutions can only be achieved through combining the expertise of large and mid-size pharmaceutical and biotech companies (and associated contract research organizations), academia, patient organizations, regulators, health technology agencies (HTA) and health authorities – all having a shared desire to change and improve the current healthcare ecosystem. In broad terms by implementing the proposed SRA, IMI2 aims to provide the framework required to initiate collaborative projects able to drive major and fundamental new innovations to remove barriers to the delivery of effective and efficient healthcare to citizens/patients.

Specifically IMI2 will:

- Create cross disciplinary research to improve the efficiency of the entire medicines development process from discovery all the way through to patient access, thus improving access, quality and cost for more sustainable health systems;
- Conduct collaborative research focussing directly on generating innovative preventative and therapeutic treatment options addressing priority healthcare challenges for Europe (i.e. where the burden of disease is the highest, not just of primary care but on the entire social security and labour system);
- Provide a transparent platform facilitating engagement of all key stakeholders in the provision of healthcare i.e. healthcare practitioners, regulators, HTA agencies, patients and payers to ensure new scientific advances are translated into effective healthcare solutions;
- Provide training and infrastructure needs to support effective implementation of the research outcomes;
- Drive widespread translation of the resulting and existing knowledge into innovative, effective products, strategies, interventions and services through long term and coordinated co-operation between all players in the healthcare ecosystem;
- Create an integrated R&D framework that will attract investment and in turn strengthen the competitiveness of the European-based industries, creating new market opportunities increasing employment and economic growth.

The PPP will also support implementation of EU policies amongst others in the field of Active and healthy ageing, Mental health, Antimicrobial resistance, Pharmacovigilance/patient safety and Good clinical practice.

Successful delivery of this vision will rely on:

- The ability to work in a cross-sector and multidisciplinary way with all sectors and/or companies which could contribute to IMI2 project objectives including those that may not normally participate in biomedical research such as information technology and imaging sectors
- Collaboration with academic scientists from all areas of science, including emerging and non life sciences and technologies
- Collaboration with regulators, HTA agencies, health authorities and payers whose decision making depends on robust scientific data and who will ultimately drive the necessary change to harvest the potential of stratified cost effective prevention and therapies
- Significant involvement of the patient community to facilitate both the shaping and execution of the research projects
- The establishment of large scale innovative collaborative partnerships and the of pan-European networks of excellence to create specialised clusters able to attract world leading scientists and reinvigorate fields of research which currently suffer from disinvestment globally.

1.3. Building on the strengths of Europe

The impact that biomedical research has on society, means that it is poised to become the dominant science of the 21st century. However the full potential for biomedical research will only be realised if new advances are aligned and integrated with the needs of society and translated into cost-effective healthcare solutionsⁱⁱ. The new biomedical PPP being proposed is well positioned to provide the

infrastructure required to realise this opportunity, utilising the strengths that Europe offers as well as creating an excellent opportunity for synergistic international collaboration.

There is now overwhelming evidence that investment in biomedical research yields economic returns through improved health gains and through commercial exploitation of research outputsⁱⁱⁱ. Although growth in biomedical research has slowed, the United States of America (US) remains dominant in the field of health and life sciences. The US therefore remains an attractive destination for researchers resulting in the 'brain drain' from Europe. This is exacerbated further by the rapidly expanding science base of emerging economies such as Brazil, China and India. It is therefore essential that Europe continues to drive innovation in order to remain competitive in biomedical research.

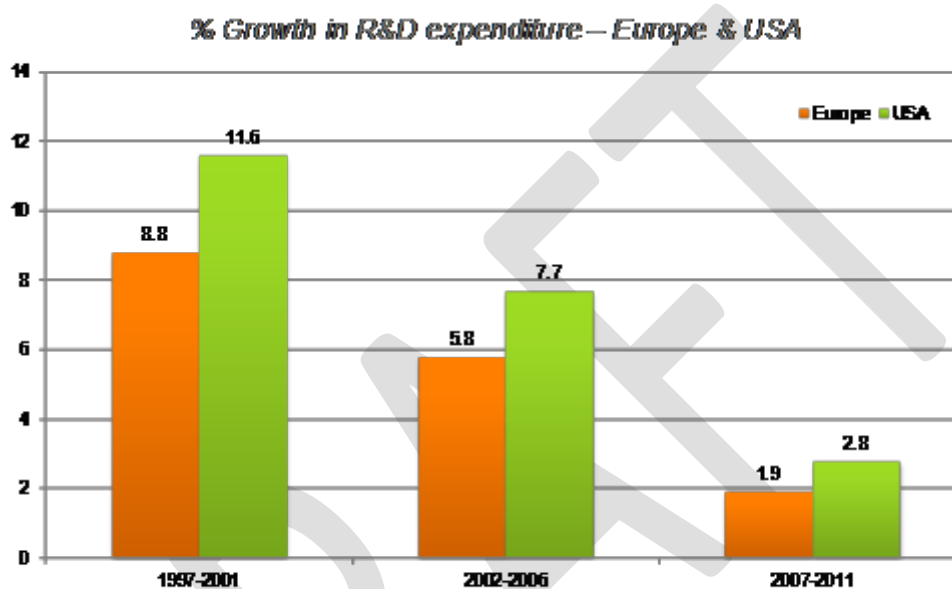


Fig 5: Growth in R&D has slowed in both Europe and the US. Source: EFPIA/PhRMA

To remain competitive it is essential that Europe continues to build on its strengths while realising the opportunity that globalisation brings for synergistic international collaboration. Europe has unique strengths in its values, creativity and diversity and it offers excellent opportunities with motivated world-leading researchers, higher education institutions and governmental research organisations^{iv}. When it comes to health, Europe has a number of unique characteristics. The fact that the organisation of healthcare and its delivery is the responsibility of each Member State, leads to diversity in population, disease demographics and healthcare practices. While this can cause challenges, this is also a unique feature and one which can also bring its advantages. The existence of national and European level funding opportunities also leads to a rich diversity of expertise and excellence in biomedical research. Collaboration across member states provides a unique opportunity to leverage core expertise, learn and adopt best practice. Indeed the EU complements national policies through actions which impact on cross-border health or patient mobility.

Large research infrastructures are another cornerstone to European competitiveness in the field of biomedical research. As IMI has demonstrated, large research clusters can foster collaboration on a pan-European and indeed global scale and provide large research communities with the required access to expertise, innovative methods and technologies to deliver sustainable solutions to healthcare challenges. Europe has a number of major scientific clusters which facilitate the scientific integration of Europe and strengthen its international outreach and attractiveness. ESFRI has called for the construction of thirteen pan-European research infrastructures. Several of these are

strategically important for biomedical research: BBMRI for biobanking and biomolecular resources, ECRIN for clinical research, EATRIS for translational research, ERINHA for high safety level laboratory, Euro-bioimaging for biomedical imaging infrastructure, Openscreen for screening platforms for chemical biology, and ELIXIR which underpins biological information and data storage for biomedical research. Many of these are also now engaged in the legal framework for a European Research Infrastructure Consortium (ERIC) to facilitate the joint establishment and operation of research infrastructures of European interest. Cooperation between these frameworks and with the newly proposed PPP will strengthen Europe's impact in the area of biomedical research and further enhance attractiveness for global cooperation and collaboration and ensure efficient use of available research funding. Research infrastructures can also strengthen European position by encouraging mobility and improving education and training.

1.4.Learning from the Innovative Medicines Initiative (IMI)

The proposed new biomedical research PPP builds on the success of IMI, which was a first of its kind PPP aiming at both accelerating medicines development and improving competitiveness of the sector in Europe.

IMI pioneered large scale open collaborations between academia, industry, regulators and patient groups, providing a neutral platform and creating collaborative frameworks that recognised the needs of both public and private partners. Early projects running under the IMI framework focussed on development of tools and methodologies which address industry bottlenecks which will:

- Result in the development of new biological markers and health outcome measures that will improve internal decision making allowing failures to be detected much earlier in clinical development
- Improve our ability to gather patient data, quantify and communicate the benefit/risk of medicines and vaccines
- Improve our ability to predict safety of new medicines, e.g. antibodies and vaccines
- Enhance our ability to translate pre-clinical pharmacology to the clinical setting

The results achieved mid-way through the projects term are of high quality and will have significant impact on medicines R&D. For example, in the fields of Alzheimer's disease (PharmaCog), chronic pain (EUROPAIN), psychiatric disorders (NEWMEDS), autism (EU-AIMS), diabetes (SUMMIT/IMIDIA) and asthma (UBIOPRED), innovative animal models have been developed and standardised to improve the translation of pre-clinical data to the clinical setting. Unprecedented levels of data sharing between public and private partners has resulted in the launch of a new in silico tox prediction software, which when fully validated will significantly improve our ability to predict the safety of new medicines (eTOX) and therefore play a direct role in reducing attrition rates. Advances in clinical trial design in schizophrenia will reduce trial duration which is estimated to save on average €2.8Million per clinical trial conducted (NEWMEDS) leading to significant reductions in development costs. Recently the PROTECT consortium released the Drug Consumption Databases in Europe which is a comprehensive and structured source of information on drug consumption in Europe in addition to the PROTECT ADR database which is a downloadable Excel file listing in MedDRA PT or LLT all adverse drug reactions listed in section 4.8 of the Summary of Product Characteristics. SUMMIT has developed an innovative ultrasound/radiofrequency based methodology for the assessment of vascular plaque pathology which will significantly enhance investigators ability to assess response to treatment therefore improving our ability to demonstrate proof of mechanism much earlier in the drug development process. This will have a direct impact on the ability of drug developers to focus efforts on promising new treatments while terminating those destined to fail much earlier in the process.

As the potential of large scale open collaboration has been realised by public and private partners, the IMI SRA has steadily evolved from developing tools and methodologies which address industry bottlenecks only to programmes which address research and development bottlenecks in areas which span across the full value chain from development to patient access. This transition has resulted in projects that will:

- Create a European research community to support the discovery and development of novel antibiotic agents tackling resistant pathogens
- Lead to the generation of new trial designs driving change in the regulatory framework and subsequently significantly reducing the duration and cost of clinical development
- Drive the development of a new regulatory approved framework and optimised study designs for the collection of real world data
- Identify biomarkers and develop tools which allow a better evaluation of the benefit/risk profile drugs and vaccines

The second half of the IMI term has therefore provided a bridge into the Horizon 2020 vision to tackle societal challenges in the area of health and wellbeing. The launch of the €400M New Drugs for Bad Bugs (ND4BB) Initiative, aimed at tackling the growing health threat that antibiotic resistance poses, has demonstrated the level of action that can be initiated when research is focussed on areas that are of priority for academic scientists, pharmaceutical R&D, regulatory and HTA agencies and healthcare providers alike. The success of ND4BB is driven by the societal need for action and the willingness of all stakeholders to work together to agree the priority areas of focus and jointly creating a strategy for the implementation of research which will result in tangible benefits to pharmaceutical R&D, patients and healthcare providers. ND4BB has been an excellent pilot and has positioned Europe at the core of the global fight against antibiotic resistance. By adopting a similar approach, IMI2 will continue to build Europe as a global leader in the delivery of healthcare solutions for medicines of priority to society.

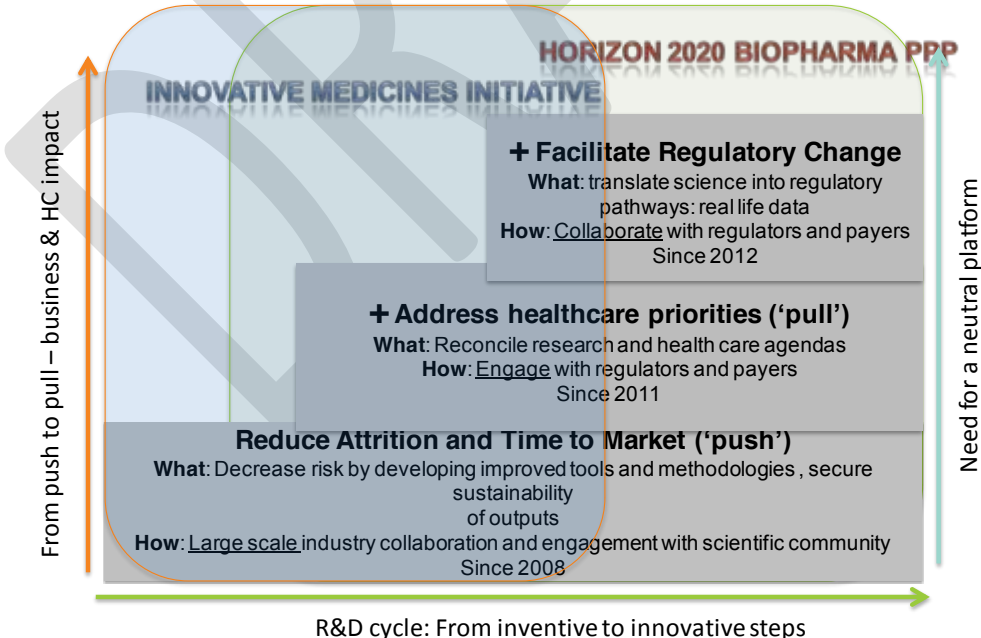


Fig 6: Transition from IMI to IMI2

2. Establishing the Research Priorities for IMI2

2.1.Challenges facing the healthcare ecosystem of today

Describing the full extent of the healthcare challenges facing Europe and indeed the world is outside the scope of this document and have been eloquently documented in the European Health Report^v, and WHO Priority Medicines Report^{vi}. However a summary of the key challenges most relevant to the vision of IMI2 can be found described below.

The Ageing Population[ageing or aging?]

The population in the European Region is ageing rapidly and it is predicted that the number of people aged 65+ will almost double over the next 50 years, from 85 million in 2008 to 151 million in 2060^{vii}. Advanced age is often accompanied by chronic disease, deterioration in vision, hearing, musculoskeletal function, bone strength, immunity and nerve function as well as late-onset depression and dementia that negatively impact an individual's quality of life and increase demand on the healthcare system. While there are regional variations, in general older individuals utilise more healthcare resources than younger individuals with the level of healthcare spending on patients aged 80 or over being as much as twice those aged 50-64 as is the case in Sweden and Spain^{viii}. In the current economic climate, healthcare systems are under unsustainable pressure, with the number of adults per working person increasing, countries are struggling to finance their healthcare needs. In response, countries are driving up the retirement age, however, productivity lost due to the impact of an elderly workforce many of which suffer from chronic diseases leads to additional societal costs.

Increase in the incidence of chronic disease

In addition to ageing, poor dietary habits and lack of physical activity, are also contributing to the burden of chronic disease, with approximately 50% of the European population considered to be overweight or obese^{ix}. For example: 50% of the burden of cardiovascular disease has been attributed to high blood pressure as a consequence of such lifestyle factors; increased levels of obesity in children is driving the incidence of Type 2 diabetes mellitus in juveniles, with some predicting that within the next 10 years, type 2 diabetes (which normally onsets in adulthood) will be the most commonly diagnosed form of diabetes in children^x and a combination of ageing and increase in related factors such as obesity is also driving the incidence of osteoarthritis and the incidence of dementia. The increased incidence of chronic disease coupled with the extended years that patients may live with chronic diseases place incredible pressure on the healthcare system. There is therefore a need to investigate opportunities to develop new prevention strategies, not only from a medicines development perspective, but also from the perspective of driving lifestyle changes. To date, there is no scaled solution for the maintenance of wellness of those suffering from chronic conditions, which is economically sustainable.

Change in demographics and epidemiology

In addition to natural and man-made disasters, social, economic and political disruptions, migration is an additional factor that is affecting demographics. Urbanisation and greater mobility have contributed to the introduction of new pathogens such as H5N1 avian flu virus demonstrating the impact a flu pandemic could cause. Climate and environmental change are also driving shifts in the geographical distribution of diseases. It is anticipated that global warming will drive an increase in chronic inflammatory diseases, respiratory illnesses like asthma and bronchitis while increased mobility is predicted to increase the incidence of neglected and poverty related diseases (such as HIV and Tuberculosis (TB)) which to date have been largely associated with developing countries. TB accounts for the second most infectious disease burden in Europe, and although new incidence reports are decreasing, there are reported increases of at least 10% in Belgium, Cyprus and Hungary between 2009 and 2010^{xi}. Antibacterial resistance is of particular concern and is the focus of many

European Initiatives including the New Drugs for Bad Bugs Initiative (funded by IMI) launched in 2012. Increased hospital stays, additional discharge costs to facilities, extra medical care needed, and productivity loss has set the societal cost of AMR in excess of €1.5Billion per year. Due to the small commercial market associated with treatment of these diseases, investment in research and new treatment for these diseases is small.

Prescription adherence

Studies have shown that on average only approximately one-third of patients actually adhere to prescribed dosing regimens, one-third partially adhere, with the remaining third being completely non-compliant^{xii}. This lack of compliance (consuming medication at irregular intervals or failing to complete a course) compromises the effectiveness of prescribed medications. The problem is not confined to patients with relatively minor illnesses, but also to those suffering from life threatening conditions. A staggering 50% of renal transplant patients are thought to be non-compliant even though they depend on immunosuppressive medications to survive^{xiii}. More than 20% to 30% of patients are reported to have omitted doses or failed to complete their full course of antibiotics. This improper use of antibiotics together with inappropriate prescribing is driving the emergence of antibiotic resistant bacteria which is now a major public health concern. Lack of adherence puts tremendous strain on healthcare systems through wasted medications, re-testing and acute medical care that would otherwise not be required, and on social systems through avoidable reduction in productivity.

Patient and citizen needs and involvement in the healthcare ecosystem

In past decades, patient and citizens had little or no participation in setting healthcare priorities. Today the situation is very different, the benefit of patient and citizen involvement is widely accepted by all stakeholders and is supported by legal and regulatory requirements. Recently, the Council of Europe declared that the public should be involved in decisions affecting healthcare,^{xiv} a position that is supported by government reports, legislation and by patient and citizen groups. As healthcare progresses towards precision medicine, patient input will be essential to the development of new outcome measures and integrated treatment paradigms that move away from a medicine only approach, to one of a personalised care package. To realise its full potential the concept of precision medicines relies on patients and citizens being suitably educated regarding the health options available to them, as well as a more open dialogue between patient and healthcare providers.

2.2.The role of Research & Development in addressing healthcare challenges

R&D productivity: decreasing the cost of innovation

In parallel to the increased healthcare demand, the number of late stage failures continues to drive the cost of developing new vaccines and treatment modalities. Of 5,000 compounds that enter pre-clinical testing, only five, on average, are tested in human trials and only one of these five receives approval for therapeutic use. This high attrition rate continues to be driven by a number of factors which prevent drug developers accurately predicting efficacy and safety of new medicines early in the development process. Furthermore, increasing regulatory demand and also increasing demand from payers to demonstrate effectiveness over existing treatments to support reimbursement, is adding further complexity and costs to the development process which in turn contributes to attrition^{xv}. Increases in productivity are essential at all points in the drug discovery and development process from target identification and selection, through clinical development, manufacture and supply in order to deliver cost effective medicines.

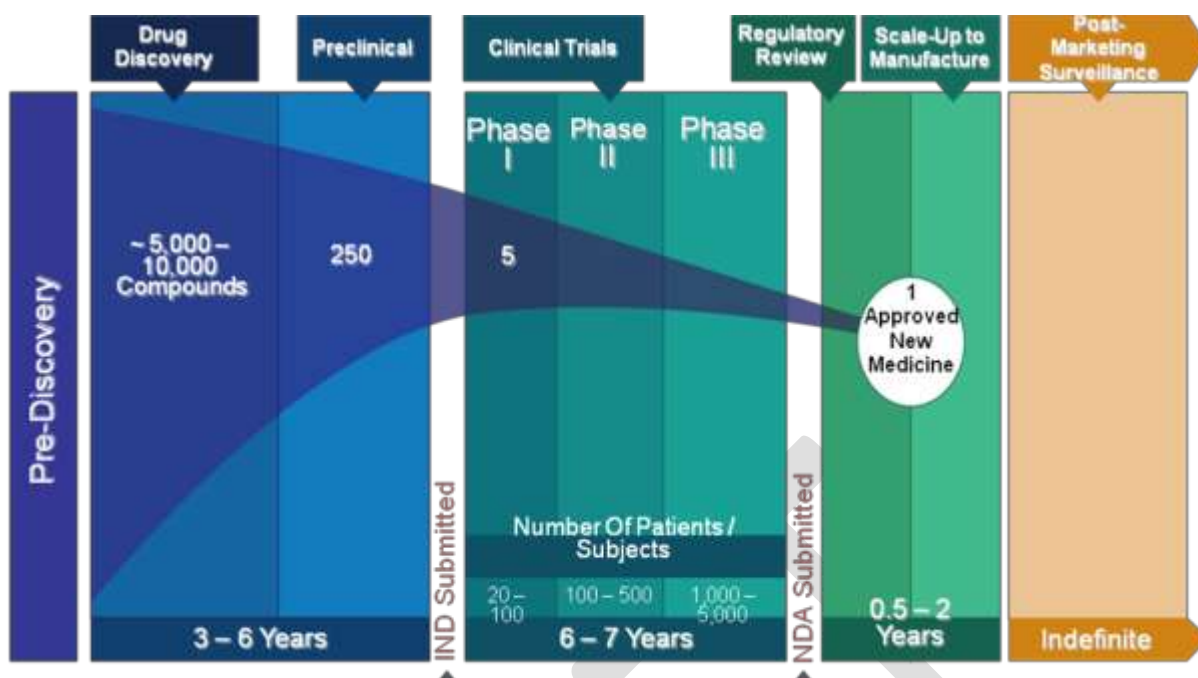


Fig 7: With the cost of developing a drug estimated at \$1.2 Billion, attrition rates in pharmaceutical R&D are unsustainable. Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; CBO, *Research and Development in the Pharmaceutical Industry*, 2006

Addressing the needs of the society

It is essential that the pharmaceutical industry remains focussed on developing medicines that meet the demands of society and healthcare providers. Prioritisation therefore has to be given to the prevention (primary and secondary) and treatment of chronic diseases, more personalised treatment programmes and new medicines and vaccines for diseases with high societal burden, but where pharmaceutical investment is low. For the drug developer the development of precision medicines requires significant advances in the understanding of the complex mechanisms underlying disease in order to develop the biomarkers required to support diagnosis, patient stratification, monitor disease progression and to predict drug efficacy and safety. The approach also drives the need for new clinical trial designs, regulatory and HTA frameworks that support the assessment of efficacy/risk and effectiveness/risk of new medicines using small numbers of stratified patients. Development of novel endpoints that more comprehensively capture the true value of a medicine to patients is essential, not only to inform drug developers with regards to innovative treatment approaches, but also to better inform payers about the added value to society of any new medicine. Primary prevention is the ultimate goal in medicines development, and will rely not only on the development of better diagnostic and prognostic markers, but also new clinical endpoints and trial designs, regulatory and HTA framework. Success in this area will be achieved in the shorter term by focussing efforts on better understanding the behaviours that prevent those at high risk from disease adhering to recommended lifestyle changes and prescribed medication in order to develop more patient oriented approaches to improve compliance.

Lack of adherence to prescriptions

For industry, non-compliance of patients is estimated to be responsible for at least one-third of attrition. This is a problem which is only set to become more prevalent as the trend for healthcare to be pushed outside the hospital setting increases. Furthermore, decline in memory, polypharmacy and poor ability to swallow tablets makes adhering to prescribe dosing regimens a particular challenge for the elderly.

Adherence programmes can take many different forms, from providing clinical support and education about their medication to patients with serious illnesses, to the development of robust, portable electronic monitoring devices and wireless networks across which data they collect can be sent. With advances in information technology, reminders to patients can be sent via e-mail and voice calls wherever they are. In some cases it is also possible to include the monitoring device in the tablet itself, which then allows clinicians to record specific biological variables therefore better understanding the medicine. In turn this will lead to a change in the way that industry develops new medicines, it is feasible that such advances in technology could allow the conduct of ‘controlled’ clinical trials in a real-world setting. Furthermore both the drugs themselves and the compliance programmes that are used to support them will need to be tested and approved by the regulatory authorities. This will also have significant impact on the supply chains which will have to manage the development and delivery of these new systems to multiples customers across the globe. By placing the patient at the core of this research, will directly benefit the patient, social and healthcare sectors and the industry.

2.3. Regulatory, health technology assessment and healthcare delivery challenges

Creating the environment to drive innovation

The regulatory and HTA systems are key factors in the development of new medicines and thus in innovation. Both regulators and HTA agencies play an essential role in balancing societal expectations of new medicines addressing unmet medical needs and ensuring a favourable benefit/risk and effectiveness/risk profile for these medicines and value for payers.

The drive towards a more precision/stratified medicines approach requires a parallel shift in the regulatory and HTA framework in order to facilitate the evaluation of benefit/risk and effectiveness/risk in small numbers of stratified patient populations and the development of infrastructures for the collection and sharing of trial data, together with methods for meta-analysis of trial data to investigate outcomes across multiple (stratified) trials in different locations. Methodologies currently utilised by regulators and HTA agencies are not always sufficiently flexible to support evaluation of precision medicine approaches leading to different recommendations being reached across different countries. This can be driven by many reasons including different requests for evidence, different interpretation of evidence generated or the impact of different economic models. There is therefore a need to generate consensus around the continuum of evidence generation across Europe.

The concept of precision medicine doesn’t only rely on the development of new treatment modalities, but also on the development of a wide range of supporting services that patients and citizens need to effectively manage their health. This in turn has an impact on the regulatory and HTA framework, as no longer will it just be the drug that requires approval and value assessment, but rather the entire treatment programme.

In the case of priority diseases where healthcare burden is high, it has been suggested that there may be a particular benefit in providing earlier patient access to some medicines before full marketing authorization. For example, the EMA have suggested investigation of a “staggered” approval approach to assessing the benefit/risk profile for a broader population, for which earlier access may be granted to a “better-defined or more restricted population of good responders” before full market authorization. To this end a progressive early access model is currently under discussions. The Medicines Adaptive Pathways to Patients (MAPP) model aims to provide a comprehensive, alternative authorization pathway for certain categories of products; for example, for products intended to treat a clearly defined group of patients based on the high unmet need.

However, this proposal for MAPP would fail if reimbursement systems do not reflect the need for targeted patient access. So, it is important that the proposals be advocated and harmonized as a comprehensive package. Achieving this objective will require collaboration among the EU Commission, the EMA and reimbursement bodies to ensure transparency of the intent and application of the regulatory process, and to promote the use and reimbursement of medicines approved through a progressive regulatory process.

Changes in healthcare delivery structure

Changes in the way healthcare will be delivered in the future will also have a direct impact on the future of R&D. The primary care sector is expanding and becoming more regimented as general practitioners perform minor surgeries and healthcare payers increasingly mandate the treatment protocols they must follow^{xvi}. The move from individual prescribing to treatment protocols demands better understanding of disease diagnosis and progression as well as the ability to demonstrate the cost effectiveness of new medicines to ensure doctors continue to have a range of alternative treatments to choose from, ensuring patient care remains individualised.

In contrast, secondary care is reducing as hospital focus on specialist care while leaving other healthcare providers to provide care at home. In addition, increased availability of over the counter products is leading to an increase in self medication. Not only does this result in the need for patients to have more comprehensive information about the medicines they take in order for them to make more informed decisions about their treatment options, this also presents further challenges with respect to the collection of real world data pertaining to effectiveness and the benefit/risk of medicines.

Health inequalities are now well recognised as key factors determining the outcomes and distribution of health burden, with factors such as poor diet, exposure to tobacco smoke, alcohol and lack of exercise posing risks in addition to other genetic or biological factors. This demands the need for increased research in health systems, social sciences and health economics alongside more traditional R&D^{xvii} as well as the need to educate healthcare practitioners, patients and citizens on how to better manage their own health and treatment options.

3. Research Objectives of IMI2

3.1. Four major axes of research

As described above IMI2 will focus on addressing scientific challenges where multi-stakeholder input is essential for success. These efforts can be captured under 4 major topics as outlined below.

3.1.1. Axis 1: Target validation and biomarker research (efficacy and safety)

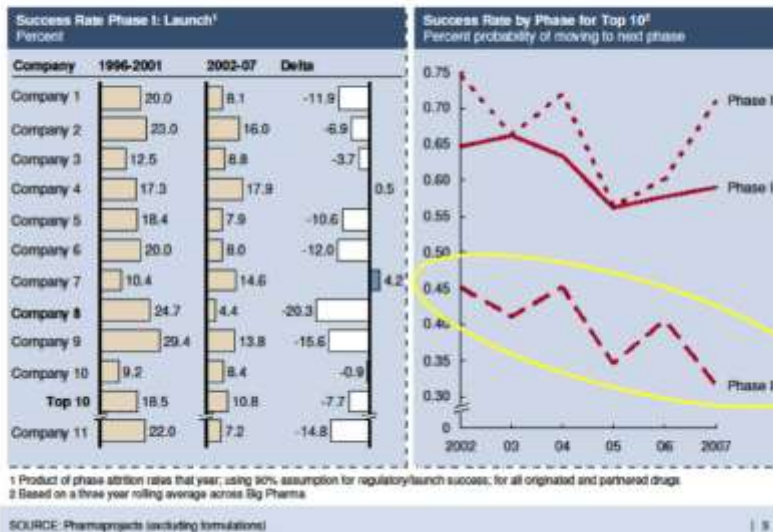
The challenge to be addressed

Failure of efficacy to translate from pre-clinical models to the clinical setting combined with the emergence of adverse events not predicted from the pre-clinical models remain the most frequent cause of failures in the late stages of clinical development. The development of the capabilities, biomarkers and tools required to better inform drug and vaccine developers and identify failures earlier is essential in order to significantly improve the overall productivity of R&D. Not only will this improve the efficiency of medicines development as a whole, but it will open the opportunity to drive the concept of precision medicine, which aims to provide the right treatment for the right patient with maximum benefit and safety. For healthcare providers, the availability of clinical, imaging and molecular biomarkers predictive of response and side effects offers the potential to

improve the quality of care. For payers, these tools have the potential to reduce costs in the long term by providing more cost-effective treatments with less adverse events. For patients, these tools will ensure that they receive the therapeutic approach that will provide greatest benefit and prevent them being offered medicines that have little chance of providing benefit or being denied access to approved medicines due to misclassification to a different disease.

Attrition: High attrition at phase 2 and increasing

Overview of Attrition across the Industry



N Singh & J. Gobburu, Presentation: Attrition and Pharmacometrics, January 25, 2011

Fig 8: Attrition rates continue to increase at Phase II. Better endpoints for assessing clinical pharmacology and therapeutic benefit are required to better inform drug developers and identify failures earlier.

Objectives

The concept of precision medicine aims to provide the tools and knowledge required to determine the right treatment for the patient at the right time resulting in maximum benefit for the patient. The development of such tools will only be achieved through developing a better understanding of the mechanisms underlying disease, the occurrence of adverse events and the complex interplay of factors driving patient's individual responses to drug and vaccines both with respect to efficacy and the emergence of adverse events.

IMI2 will leverage the availability of the complete sequence of the human genome and the growing body of '-omic' data sets and epigenetic markers in health and disease, the availability of for instance patients' electronic medical records, next generation genetics for target identification and sophisticated bioinformatics to:

- Identify new or alternative therapeutic concepts (targets) for treatment and prevention of disease and generate the research tools (e.g. chemical probes and recombinant antibodies) required to further characterise the biology of novel genes/proteins and validate new therapeutic concepts pre-clinical and clinically.
- Identify and validate biological markers, tools and assays (biochemical, imaging and functional) to support disease reclassification and patient stratification approaches, monitor disease progression, provide proof of pharmacological response, predict and monitor the efficacy and safety of drugs and vaccines as well as biomarkers that may serve as surrogate markers in clinical trials

- Better understand the types of biomarkers, outcomes and composite endpoints that regulators and HTAs could accept and what level of validation is needed for their utilisation in order to direct discovery efforts. Initiating formal consultation procedures as appropriate.
- Enhance understanding of the immunological mechanisms and host–pathogen and host–vaccine interactions to enable improvements in the design of both preventive and therapeutic vaccines.
- Improve the profiling of immune responses to infection and to vaccination in different age groups, identifying novel correlates of protection against infectious diseases and possibly other non-infectious conditions
- Better understanding of the molecular determinants of inter-individual variability to drug and vaccine efficacy and safety thus reducing the underlying biological variability of trial patient populations to enable reliable measures of treatment effect.
- Understand the molecular mechanisms underlying drug toxicity in humans to drive mechanism-based drug and vaccine safety assessment and early prediction of clinical and non-clinical drug and vaccine response to improve the predictability of translating pre-clinical findings to the clinical setting.
- Develop non-invasive measures (such as imaging technology) of drug exposures at the organ level to deliver a better understanding of the PK/PD relationship of a drug or vaccine and therefore more accurately predicting the therapeutic index of a drug (that is the difference between the level of drug required to provide a beneficial effect and an unwanted effect).
- To develop a platform pre-clinical assays utilising normal and disease tissue, stem cell technology, genetic manipulation and cloning to create more predictive in vitro, ex vivo and in vivo models of the relationship between drug exposure, pharmacological response, inter-individual variability with respect to efficacy and safety to improve translation from pre-clinical testing to the clinic
- Development of systems models and strategies combining technology, biology (omics) and computational methods, with information retrieved from historical compounds tested in preclinical models or in patients for evaluation/prediction of drug safety and efficacy

3.1.2. Axis 2: Adoption of innovative clinical trial paradigms

The Challenge to be addressed

In an attempt to decrease clinical development times and cost, a number of innovative adaptive designs (as, for example, discussed at the EMA/EFPIA 2nd Workshop on Adaptive Design in Confirmatory Trials, April 2009 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2009/11/event_detail_000007.jsp&mid=WC0b01ac058004d5c3) have been introduced. Bayesian statistical methods are being used increasingly in clinical research to minimise the number of patients included in a randomised clinical trial (RCT) and decrease the chance of maintaining a patient in an unfavourable treatment arm. Accumulating results can be assessed at any time, including continually, with the possibility of modifying the design of the trial; for example, by slowing (or stopping) or expanding accrual, unbalancing randomization to favour better performing therapies, dropping or adding treatment arms, and changing the trial population to focus on patient subsets that are responding better to the experimental therapies. While paved with good intent, many designs focus primarily on obtaining efficacy but which prevents challenges when balancing the need to collect sufficient data regarding potential adverse events. Trial design and analysis can become complex and bias (e.g. changes of the patient population over time; changes in molecular strain characteristics) can be introduced. More efforts are therefore required to further refine the concept of adaptive trial design.

Even with these advances, data packages which aim to minimise uncertainty for regulatory authorities on safety and efficacy may leave significant uncertainty in the assessments of real world effectiveness/risk of new medicines and vaccines and thus slow the speed and level of patient access. For many years healthcare systems were able to fund new medicines and vaccines based on regulatory approval, however, HTA agencies and other healthcare decision makers now assess the expected future value of a medicine when used in “real world” clinical practice. With the increasing emphasis on “value”, defined as the relationship of outcomes to cost, there is a need for better ways to measure outcomes (benefit and risk) that are clinically meaningful but standardized across countries and clinical setting. The advent of digital media and the use of Smartphone’s and Tablets offer the opportunity to develop new methods for collecting real world benefit/risk data utilising more patient reported outcomes, however with it brings the challenge of managing the collection, validation and analysis of data, cost-effectiveness of data collection, privacy laws and data security.

At the same time as the demand for demonstration of value is increasing, drug development is progressing further toward precision medicine approaches. This is driving the need for the development of new patient focussed clinical outcome measures and new clinical trial paradigms to support the evaluation of benefit/risk in small stratified patient populations and the development of infrastructures for collection and sharing of trial data, together with methods for meta-analysis of trial data to investigate outcomes across multiple (stratified) trials in different locations. The move towards generating more preventative approaches to the management of disease has also prompted discussion between drug developers and the regulatory agencies to build on this concept creating a framework which would support progressive patient access to medicines with significant benefit to patients and to society as a whole. The Medicines Adaptive Pathways to Patients (MAPP) model is a concept which encompasses innovative approaches in drug development, regulatory marketing authorisation processes and HTA/payer access decision making and will require the establishment of a new approach and new tools to more rapidly and more efficiently bring medicines to patients.

Collaboration with other global, European and national initiatives

There has been substantial work, via the EMA and various think-tanks (e.g., Centre for Innovation in Regulatory Science (CIRS)) to define a better, more structured and more patient-responsive approach to defining benefit/risk. WEBAE and other ongoing initiatives are focussed on the development of the IT infrastructure and methodologies and regulatory framework required to allow access to social media sites to allow access to self reported medical insights such as adverse events associated with medicines, vaccines or devices. The public private partnership should build on this work and work already conducted by the EMA, The Centre for Innovation in Regulatory Science (CIRS), Pharmacoepidemiological Research on Outcomes of Therapeutics by the European Consortium (IMI PROTECT) and Pharmaceutical Benefit-risk assessment (PhRMA BRAT) to define and agree standards for the future application of the benefit/risk assessment (i.e. how it is to be used and by whom). Collaboration is also anticipated with the IMI Get Real project which is focussed on improving the collection of real world data.

Core Objectives:

- Establish a framework (with clearly defined rules, ethical standards and data privacy measures) to support the interaction of key stakeholders (especially patient groups) involved in the clinical development of new medicines and vaccines. Principles will be applied across all axes of research.
- Develop innovative clinical endpoints which more closely reflect value to the patient and HTAs (e.g. patient reported outcome measures) and better understand the types of composite endpoints that regulators and payers could accept and what level of validation is needed for their utilisation initiating formal consultation as required.
- Develop a better understanding of the

- Increase the role of the patient in research by including patient reported outcomes, improve the methodologies available for communicating the benefit/risk of new medicines and vaccines thus creating a ‘community’ approach to pharmacovigilance and understanding patient preferences, real-life use and effectiveness, the efficiency of risk mitigation strategies and caregiver experience through direct questioning in trials, and through observed comment in social media, diaries and other less direct ways.
- Validated, quantitative methodologies for assessing patient and healthcare professional’s preferences in benefit/risk assessments pre- and post market authorisation. Establish agreement on how best to integrate patient preferences with regulatory benefit/risk criteria and effectiveness/risk assessment and clinical judgement across different countries.
- Utilise innovative endpoints, trial designs, simulation and analytical approaches to devise new clinical trial paradigms both pre-and post-marketing which permit the assessment of outcomes (good and bad) in small patient populations balancing the needs for regulation (efficacy/safety) and HTA agencies (effectiveness/safety) as well as the risk and cost for pharmaceutical companies.
- Establish validated systems to support the cost-effective collection of high quality benefit/risk and effectiveness/risk data via digital media and understand how this can be integrated in to pharmacovigilance framework.
- Continue to build on efforts already underway in EHR4CR and Transcelerate, to harness the use of electronic healthcare record (EHR) systems to improve the design and conduct of randomised clinical trials, pragmatic and adaptive and extend these efforts to support the conduct of efficient and high quality observational research on medicines and full care pathways after medicines are authorized and used in clinical practice.
- Gain agreement on the pre-approval data required for conditional marketing authorisation (MA) vs. ‘full’ MA, qualitative vs. quantitative assessment methodology, and the need for active comparator clinical trials; post-approval data required to maintain the benefit/risk assessment; alignment on data required for regulatory benefit/risk and HTA needs; and communication of benefit/risk within medicine labels.
- Create the framework required to successfully implement “Medicines Adaptive Pathways for Patients” (MAPP) to provide a basis for effective and safe introduction of new treatments for selected populations. Work proactively with payers early in the life-cycle to agree how a product should be reimbursed when utilising the MAPP framework.
- To build on efforts currently ongoing in GetReal to create a framework to allow the identification of and overcome the operational difficulties associated with generating evidence of relative effectiveness before launch and provide roof of concept for new regulatory pathways to inform discussion on regulatory guidance

3.1.3. Axis 3: Innovative Medicines

The challenge to be addressed

The ageing population and increased incidence of chronic disease is driving the need for investment in developing new therapeutic strategies which integrate early detection and prevention. In addition there are a number of diseases which, although they place enormous burden on the healthcare systems of today, (such as stroke and antibiotic resistance) pharmaceutical companies have largely withdrawn from either due to high risk of failure or due to the lack of return on investment. The global economic impact of such diseases may be dire if effective preventive and therapeutic measures are not implemented to help decrease the burden of this disease.

The enormity of such a task must not be underestimated, in many cases those diseases that still lack effective treatments such as Alzheimer’s disease and stroke are littered with clinical failures

demonstrating the fundamental lack of understanding of the mechanisms underlying disease and tools required to predict efficacy and safety of new therapeutic approaches. Primary prevention remains the holy grail of drug discovery and development and will require significant investment to enable the scientific and technological advances required to make this an achievable goal. Medicine and vaccine development approaches must therefore also combine programmes which allow patients to understand their individual risk of disease and how they can reduce their risk through lifestyle choices and improved adherence to prescribed medication provided to manage known risk factors of disease such as hypertension and diabetes. There is the need for the development of new diagnostic and prognostic tools to identify those at risk and determine what type and level of primary and secondary intervention required. Furthermore any new medicine aimed at primary prevention must not only demonstrate the ability to significantly delay or prevent the onset disease but must also be well tolerated so as not to increase burden through the occurrence of adverse events.

Core Objectives:

- Where burden of disease is high, conduct the research required to determine interventions that would provide the biggest improvement to patient health outcomes from both a patient and healthcare provider perspective, establish the potential economic benefit of intervention and impact on healthcare delivery
- Better understand the barriers to investment of pharmaceutical companies where burden of disease is high and return is low and develop creative approaches to incentivise research in these disease areas.
- Conduct the basic research and develop the tools required to support the development of innovative preventative medicines for disease of high societal impact
- Where co-investment is justified based on societal and healthcare need, and there are sufficient validated tools available, jointly develop novel therapeutic agents and disease prevention strategies
- Conduct research required to support the establishment of the necessary regulatory pathways and frameworks and payer framework to support the authorisation of new preventative medicines (driven under axis 2)
- Provide improved access to information and support allowing individuals to make more informed decisions on the management of their own health and treatment options better understand individual behaviours which are shown to lead to health problems, and have potential opportunities for earlier, non-medical interventions.
- Integrate the needs of HTA agencies into the early R&D process, thus ensuring that at the time of the initial assessments of a new medicine, the public sector review bodies have the data that support their robust evidence-based decision making and R&D focus efforts on medicines that demonstrate sufficient value to warrant reimbursement.

3.1.4. Axis 4 : Patient tailored adherence programmes

The challenge to be addressed

While offering the potential to revolutionise healthcare, the concept of precision medicine is not only about developing the knowledge and tools required to target therapies to those most likely to respond from a scientific perspective, but rather to create tailored treatment programmes designed to maximise beneficial health outcomes^{xviii} and reduce the incidence of non adherence with prescribed medicines. To achieve this it will be essential to better understand individual patient behaviours, societal, lifestyle and environmental factors that influence the engagement of patients with their treatment pathways, an area which to date has received little attention.

Equally, efforts are required to develop the new technologies in pharmaceutical processing, manufacturing, and supply that can underpin and enable provision of robust quality medicinal

products and vaccines to individual patients who require them^{xix}. Although the strategic technology demands of the precision healthcare field are uncertain, complex dosing regimens will require advances in formulation technology to enable accurate and precise administration of the most appropriate dose, drug and device combinations which facilitate dose titration, point of care production, delivery systems which enable dosing to the appropriate exposure in individual patients and intelligent mobile health applications which deliver a wide degree of functionality including drug delivery systems which respond to biological stimuli. It is also likely that better diagnostics, sensors and imaging technologies will be required to track progress on personalized therapies which will allow timely adjustment of treatment as and when necessary. Manufacturing process will need to be tailored to handle low volume manufacture while ensuring that appropriate product quality is achieved at a cost that is acceptable to the manufacturer, patient, and society.

As the health care paradigm becomes more patient centric with greater emphasis placed on gathering evidence to support the use of interventions which are purportedly effective in improving health outcomes, it is necessary that measures are put in place alongside the product which are able to track and manage the safety and effectiveness of these therapies whilst ensuring maximal engagement and adherence to treatment. The revolution in mobile communications, diagnostics and advanced sensor technology undoubtedly has a role to play and will enable provision of a highly customised intervention for individual patients.

Specific Objectives:

- Conduct the research required to understand citizen and patient behaviours (for example failure to make lifestyle changes or adhere to prescribed medicine dosing regimens), develop and implement tailored solutions (along the continuum of education and prevention) that will enable patients and citizens to play a more active role in the management of their own health and treatment options.
- Integrate data sources pertaining to real life use of medicines to support the creation of models to predict patient adherence based on risk factors and demographics to ensure new therapeutic opportunities have programmes to provide tailored follow up and support.
- Information on medicines tailored to the needs of patients
- Address the technology demands associated with precision medicines and vaccines.
 - a. Develop innovative delivery systems which will result in greater acceptability to patient and health care practitioners and provide resultant improvements in adherence and clinical outcomes.
 - b. Develop formulation technologies and associated scalable manufacturing processes which facilitate flexible dosing (preferably at patient level) tailored to patient needs
 - c. Develop and validate nanoscale imaging and diagnostic technologies (analytical) which can be used (by patients) to measure exposure levels and clinical response to targeted therapies, to determine the required amount of medication and enable timely tracking of treatment outcomes
 - d. Develop intelligent systems and devices which are able to track adherence and outcomes (safety and efficacy) of novel medicines remotely and facilitate the customization of interventions such as the release of the therapeutic agent in response to biological and physiological stimuli.
 - e. Develop flexible manufacturing methods to support the production and delivery of low volume stratified medicines and precision medicines for diverse patients groups
 - f. Induction of appropriate responses to vaccination, introducing novel vaccines, adjuvants and delivery systems
- Develop and apply patient centered predictive models using diverse information sources to better understand differences between patients in clinical trials and patients in “real” life, to better predict adherence and probable outcome of a specific treatment (good and bad)

for a given patient given that patient's background and diagnosis so that patients, providers and other key stakeholders can make informed decisions with regards potential benefits and risks of different treatment regimens to patients and healthcare practitioners

- Develop methodologies which evaluate the holistic impact of new medicines and vaccines as well as their accompanying support systems on direct and indirect healthcare and societal costs.
- Developing an efficient regulatory and HTA strategy for evaluating integrated treatment programs rather than single medicines or vaccines
- Create the education and training materials and platforms effort to establish an adequate skill base in industry, academia, and health agencies to implement new integrated treatment options

Collaboration with other global, European and national initiatives

There are a number of PPPs ongoing which aim at designing the manufacturing process required to support the production of low volume medicines and vaccines. IMI2 will therefore aim to collaborate with these major PPPs such as CMAC, building on their advances with a focus on areas where multi-stakeholder engagement is essential.

The European Alliance for Personalised Medicine (EAPM) brings together Europe's leading healthcare experts and patient advocates to improve patient care by accelerating the development, delivery and uptake of Personalised Medicine and diagnostics. It will be essential to form a strong collaboration between IMI2 and EAPM to maximally leverage skills and expertise and make best use of resources.

The IMI funded project "European Patients' Academy on Therapeutic Innovation" (EUPATI), aims to provide scientifically reliable, objective, comprehensive information to patients on medicines research and development. It will increase the capacities and capabilities of well-informed patients and patient organisations to be effective advocates and advisors in medicines research, e.g. in clinical trials, with regulatory authorities and in ethics committees. IMI2 will build on the advances made in EUPATI and utilise outcomes to maximise patient input into the work being conducted.

3.2. Impact of the outcomes from Axes 1-4 on R&D/public partners and society

For R&D:

- The tools and capabilities required to support precision medicine and vaccine approaches, increase the efficiency of the drug discovery and development process
- Identification of new therapeutic concepts and the tools required to support their systematic validation driving new and innovative approaches to diseases with high unmet need and disease prevention.
- Better understanding of how innovation is valued and how this relates to global access which will lead to more efficient use of R&D resources by focussing efforts on new therapeutic approaches that more directly address patients' concerns and the needs of healthcare providers thus reducing the complexity, duration and cost of drug development
- Mobile health applications beyond the product to maximise engagement of patients with their treatment pathways and track the safety and effectiveness of these interventions.

For healthcare providers:

- Improved quality of care through more accurate and earlier diagnosis and tailoring therapeutic approaches to the needs of the individual
- Earlier availability of more cost-effective new therapies targeted to patients most likely to benefit and the ability to adjust use of medicines to maximise that benefit
- Healthcare programmes reaching beyond the medicine or vaccine to provide more effective healthcare options and improve patient compliance

For Patients and Citizens:

- A more tailored, individually targeted approach to drug therapy maximising the benefit whilst minimising adverse effects
- Ability to play a much more active role in clinical research, improved access to information and support allowing individuals to make more informed decisions on the management of their own health and treatment options
- More predictable, consistent and earlier access to new range of vaccines and medicines tailored to their individual risk factors and lifestyle choices
- Innovative new medicines for diseases that may have been until now intractable

3.3. The unique opportunity that IMI2 brings

Although there is already a huge amount of research ongoing in the field of precision medicine and vaccines development, advances being made in the understanding of disease and in the generation of the tools and capabilities required will only be achieved if the framework is available to efficiently translate these into new patient centred healthcare solutions. IMI2 offers the unique opportunity to facilitate the much needed partnerships between drug developer, patients, citizens, regulators HTA agencies and healthcare providers to inform early research activities, facilitate uptake of innovation into development programmes and clinical practice and accelerate patient access. By bringing key stakeholders together, IMI2 has the opportunity to revolutionise the current drug discovery and development process and continue to build Europe as a global leader in the delivery of healthcare solutions for medicines of priority to society.

Multi-stakeholder input will ensure that efforts to develop biomarkers or models are tailored to their intended purpose whether for internal decision making, regulatory submissions or demonstration of effectiveness. This will not only increase the quality of the biomarkers and models identified, reduce duplication of effort where biomarker development is applicable to the disease indication and/or drug classes, while facilitating the uptake of these scientific advancements into development programmes and clinical practice. The introduction of new trial designs pre-and post authorisation requires partnership of regulatory and HTA bodies with pharma R&D and clinical groups to fully understand which new designs, outcomes measures or composite endpoints should be introduced and what level of validation is needed for their utilisation. Working in partnership will also enable the earlier identification of the need for and the development of new regulatory or value assessment frameworks required to realise the value of such innovation, and facilitate patient access.

Ultimately greater understanding and alignment of the needs and expectations of all parties from the early stages of research will ensure efforts are focussed on research and development of new vaccines and medicines that will add real value to patients and society as a whole.

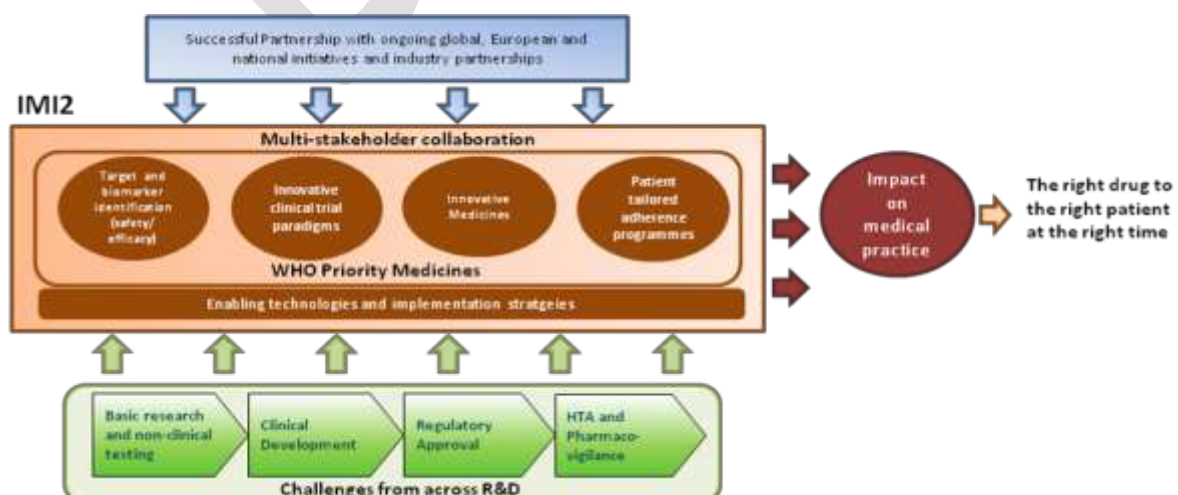


Fig 9. The new biomedical PPP being proposed will partner with ongoing initiatives (and funding bodies) to create cross disciplinary, international research teams with the aim of delivering integrated and effective healthcare solutions for priority diseases. The PPP will not only focus on the technical and scientific advances required, but will also support the implementation of these advances through the development of appropriate training materials and networks.

4. Enabling Technologies

4.1. Excellence in Data Management

The challenge to be addressed

The increasing volume (terabytes/patient), diversity (clinical, GWAS/RNASeq, eHR, 'omic, cytometry, imaging, pharmacology, pharmacovigilance etc) and velocity (e.g. real time telemetric monitoring of patients, social media feeds, etc) of biomedical data available as described above creates significant opportunity for healthcare R&D. However, common data standards, as well as robust, production quality data and knowledge management (KM) solutions and services will be essential if the full value of these data sets is to be realised in the development of innovative precision medicines. Furthermore, as healthcare delivery systems change, clinical trials move to more adaptive designs, new monitoring devices become more sophisticated and "live" patient interactions through mobile enabled, social media technology, there will be a need to engage with the IT sector to collaborate on the development of novel enabling technologies to facilitate the efficient capture and interrogation of these data sets to ensure effective healthcare practices for patients.

Collaboration with other global, European and national initiatives

IMI has successfully piloted a series of knowledge-management solutions to many of the individual issues highlighted (e.g. eTRIKS, EMIF, EHR4CR, DDMore, OpenPhacts, etc). The opportunity for the new biomedical PPP will be to build on these foundations, supporting and delivering these services on an unprecedented scale and supporting the realisation of the vision of IMI2.

To secure a sustainable vibrant, diverse, fit for purpose KM ecosystem to support EU biomedical research will require coordination/collaboration with European biomedical research infrastructures through European Strategy Forum on Research Infrastructures (ESFRI) as well as exploration of innovative sustainable business models involving, for example, EU/member state grant funding, direct revenue streams, industry (pharma funding) as well as funding from commercial organisations delivering professional services over core KM assets.

Core Objectives:

- Create a game changing, up-to-date European KM environment to provide the infrastructure and services and storage solutions required to facilitate potential ethical use and re-use of patient data for R&D across EU member states, and exchange of data to support the delivery of the objectives outlined in IMI2.
- Support innovative KM research in emerging 'Big Data' challenges in biomedical research for example: real-time (24x7) "big data" patient monitoring through telemetric devices and "live" patient interactions through mobile enabled, social media technology; the super compute capabilities required for real time NGS / functional genomics and omics analytics, and also in advanced biostatistics and simulation, for example supporting "adaptive trial design".
- Maximise the opportunity to impact EU R&D beyond IMI2 through infrastructure and services re-use by industry and the wider community and significantly reduced overhead costs in setting up and executing collaborative, multicentre biomedical studies

- Drive innovation and best practice in core data and knowledge capture, data standardisation, data analytics, curation, management, analytics and visualization platforms, tools and services for research projects.
- Increased co-operation with major public initiatives in KM infrastructures e.g. ESFRI research infrastructures, public clinical genomic and health-care projects and public European organizations (e.g. EMBL, EMA).
- Prevent project inefficiency (and compliance risk) through preventing a profusion of local, redundant solutions, and driving non-technical operational excellence for critical KM issues such as data integrity, re-use policies and collection standardisation, data security, access/privacy and associated ethical and regulatory requirements,.
- Provision of a collaboration infrastructure to optimize project delivery across multiple delivery centers (e.g. contact lists, document management, project plan management, meeting management, instant messaging, etc).
- Facilitate the education and development of next generation data scientists versatile in heterogeneous data analysis and data and knowledge management
- Encourage the engagement of patient and disease advocate groups to educate on science of clinical trials and translational research and inclusion of these groups via KM platforms in clinical and translational research in such aspects as sample collection, data sharing, collaborative study design and analysis.

Impact on R&D/public partners and society

For R&D:

- Robust KM solutions and operational excellence required to allow integration and analysis of diverse data sets, addressing long-term sustainability, accessibility and re-use of generated research data for future studies
- Innovative IT/analytical solutions required to support new clinical trial paradigms and monitoring devices

For healthcare providers:

- Increased value and return on biomedical research investment through operational excellence and collaboration and re-use of public research infrastructures.
- More cost effective, improved R&D processes, enabled by fit-for-purpose KM infrastructures, has the potential of improved scientific insight and so downstream healthcare improvements for Europe.

For Patients:

- Develop coherent and transparent framework to address data privacy and personal integrity issues inherent in the use of health records and personal genomic data
- Improved transparency of data re-use and impact on R&D

5. Implementation strategies

5.1. Education and Training required to implement new scientific advances

The challenge to be addressed

IMI2 aims to take a holistic approach to medicines development, driving collaboration between scientists, the regulatory and HTA bodies and the healthcare providers to develop the tools and infrastructure required to accelerate the delivery of the right treatment to the right patient at the right time. However, the ultimate success of these scientific advances will only be realised if the innovation created is taken up and implemented in the heart of the research and development process, the regulatory and HTA framework, and healthcare delivery systems. For this to occur, professionals operating at all stages in the medicines development and healthcare provision

ecosystem, patients and citizens must be kept abreast of the scientific, technological and regulatory advances being made and receive training on the implementation of these advances.

A complex and highly regulated process like the development of new medicines requires the professional interaction of all stakeholders. This includes not only the people working in industry (pharmaceutical companies and SMEs) and regulatory agencies but also in academic research institutions, hospitals, healthcare IT, patient organisations and healthcare management. A prerequisite is the access to up-to-date, high quality information which will allow the participants in the process not only to have the specific skills and competences for their current job but to also understand the overall context of R&D. In the long run it would be advantageous if new scientific and process knowledge will also reach the educational arena, e.g. by devising programmes for students specifically addressing medicines R&D. Nevertheless, it is important to make training opportunities in new areas available at short notice and also to ensure that such training opportunities exist for Continuing Professional Development (CPD).

Collaboration with other global, European and national initiatives

An excellent start has been made with the postgraduate Education and Training projects within IMI. Specific training programmes in the area of safety sciences (SafeSciMET) and pharmacovigilance and pharmacoepidemiology (EU2P) have been implemented, as well as an integrated medicines development programme (PharmaTrain) and a programme for patients and other lay audiences (EUPATI). In addition, the IMI education and training projects have developed and implemented a set of quality standards for the new programmes. The EMTRAIN project has developed a comprehensive European online training catalogue “on-course®” works on establishing a common framework for CPD in biomedical sciences via the LifeTrain-Initiative, and is developing a cohort of industry aware PhD students. Furthermore, the programmes have been devised to address the needs for scientist at all stages of their careers. The courses are flexible, modular, and focussed on practical application and supporting mobility.

Core Objectives

- In partnership with key stakeholders (ie patients, healthcare providers, regulators etc) develop high quality, globally recognised, tailor made training materials and infrastructure required to provide the training required to facilitate the uptake and implementation of the outcomes of IMI2 as well as more general training in medicines development.
- Develop a unified strategy for education and training, including the increased use of online-tools including social media, to foster the transition of traditional training into e-learning opportunities, such that all activities are coordinated, cost effective and address the needs of all patients, citizens, health care professionals, and researchers including the SMEs.
- Further develop and implement the common framework for CPD in biomedical sciences jointly with other stakeholders in the field, based on the work started in the LifeTrain initiative.
- Increased cooperation with other initiatives in this field like the ESFRI-BMS, Marie-Curie programs, KIC on Healthy Ageing, EAPM and others to address emerging scientific knowledge.
- Increased collaboration with EUA to open universities for offering tailored CPD courses for professionals in medicines development and ENQA specifically in the area of QA for CPD offered by universities

Impact on R&D/public partners and society

For R&D:

- Faster and easier access to high quality training programs whenever and wherever needed
- More efficient R&D process, more rapid uptake of scientific advances by regulators and HTAs and new medicines by healthcare providers, based on increased operational excellence

For healthcare providers:

- More efficient use of healthcare resources via more efficient processes for the development of new medicines
- Faster and easier access to high quality training programs whenever and wherever needed

For Patients:

- Faster access to new treatments due to increased awareness of key decision makers the at all stages in the medicines development process
- Opportunity for patients and citizens to have earlier involvement the R&D process and for patient organisation representatives to qualify further and thereby to strengthen their role in relevant discussion and decision bodies in healthcare.

5.2. Excellence in clinical trial implementation

The challenge to be addressed

The concept of precision or personalised medicine will involve the implementation of innovative trial designs. However different countries often have different approaches to the conduct of clinical trials meaning that the acceptance of a new design in one country may not be supported by another, making the conduct of global trials challenging. The overall objective of this work will be to establish, train and maintain European networks of investigators within all EU countries, with ample expertise and experience in designing and executing clinical trials for diagnosing, preventing and treating disease as required to support delivery of clinical trials that address the priority health diseases underpinning the PPP. To be successful, these networks will not only consist of hospitals with disease management expertise, but also individuals who are expert in clinical trial design, the regulatory and HTA framework as well as expertise in developing and delivering training.

The need for public-private partnership:

The establishment of networks that are able to address all aspects of clinical trial implementation requires the collaboration of multiple stakeholders with wide ranging expertise. Furthermore to establish a network with global recognition as a network of excellence will require participation from all across Europe.

Collaboration with other global, European and national initiatives

IMI2 will build on the progress made by COMBACTE and other ongoing networks such as EORTC to establish best practice, standardised training materials and feasibility assessment criteria.

Core Objectives:

- The overall objective of this work will be to establish, train and maintain European networks of investigators within all EU countries, with ample expertise and experience in designing and executing clinical trials for diagnosing, preventing and treating disease as required to support delivery of clinical trials that address the priority health diseases underpinning the PPP.
- Develop a standardised charter for clinical trial networks including clear criteria for inclusion of sites, certification, quality control and plans for sustainability which is agreed by all key stakeholders across academia, industry and the regulators
- To establish a Laboratory Trial and Research Networks as required to support the conduct of clinical trials preventing and treating disease as required under the PPP

Impact on R&D/public partners and society

For R&D: Excellence in clinical trial implementation will result in:

- Significant reduction in study set up times due to increased ease of access to GCP trained clinical sites and survey reports describing the up to date characteristics (standard of care diagnostics, patient flow, time process for IRB and contracting) of clinical sites within the network
- Availability of training materials to be used to train clinical investigators

For healthcare providers: Excellence in clinical trial implementation will result in:

- Creation of a vibrant world class European drug delivery network which will attract R&D investment to Europe
- Reduction in clinical development costs resulting from efficiency in clinical trial operations

For Patients:

- Increased opportunity to participate in ongoing clinical trials
- More efficiently run clinical trials

6. European Health Priorities to be addressed by IMI2

The research to be undertaken as described above within the four axis of research will be applied to deliver new medicines addressing the key European health priorities. At present twelve key health priorities have been identified and it is anticipated that throughout the lifetime of IMI2, many of these health priorities will be addressed by activities conducted within the four research axes. However it should be noted that within each health priority the order of priority of the 4 axes of research differ. The following section attempts to provide an indication of the type of research that will be initially implemented in each of these areas to address the most significant and urgent challenges facing each of these health priorities. This section is not intended to represent a comprehensive summary of all therapy areas that could benefit from activity under IMI2 or indeed of all the specific research projects that may be conducted under this PPP, which is beyond the scope of this document.

These sections reflect the initial thoughts of stakeholders that have contributed to the development of the SRA to date and should be viewed as a starting point for discussion.

6.1. Antimicrobial resistance

The societal impact of antimicrobial resistance

Antimicrobial resistance (AMR) has been declared as a major global public health threat. In Europe 25,000 deaths were reported in 2007 as a result of AMR, with two-thirds of these deaths being due to Gram-negative bacteria. This clinical burden is associated with soaring treatment and societal costs with the cost of AMR being estimated at around €1.5 billion per year in Europe (statistics taken from a report published by the Office of Health Economics, April 2011). The incidence of infections due to Gram negative bacteria continues to rise at a time when drug companies have more or less withdrawn from antibiotic research and the number of newly approved antibiotics is at an all time low. Despite the recognized need for new antimicrobials, the reality is that as a society we are faced with the potential situation where prescribers could have few, if any, therapeutic options to treat certain bacterial infections.

Continuous efforts are therefore required if the key barriers to the development and delivery of effective antibiotics are to be overcome. These barriers can be summarized as follows:

- Discovery and development of novel antibacterial agents is scientifically challenging.
- There are substantial regulatory challenges to the introduction of novel antibacterial agents

- Antibiotics have a low return on investment relative to other medicines making them an unattractive prospect for drug developers, thereby limiting the future antibiotic pipeline

The need for Public Private Collaboration

Antibiotics are a class of drug that society takes for granted. However, as the level of resistant infections grows there is an urgent need to develop new generations of antibiotics that will a) prevent infection and therefore reduce the emergence of resistance and b) be effective against multi-resistant pathogens that do emerge in the future. Companies can no longer be expected to, nor are they financially able to support the development of drugs which will potentially have a low level of use due to promotion of appropriate use and stewardship programmes. In these situations, the cost of development of a drug is often greater than the potential return.

Without a joint and urgent action from public and private sectors, society will no longer have access to effective antibiotic agents to combat these resistant infections the consequences of which are not imaginable. If successful, the PPP will lead to transformational advances in the way drug discovery and development of new antibiotic agents is performed from target identification all the way through to patient access. Only with such comprehensive efforts, does Europe and indeed the rest of the world have any hope of reducing the health threat that AMR poses.

Collaboration with other global, European and national initiatives

In recognition of the significant health threat that AMR poses to society, various international organisations have responded through numerous meetings, task forces, workshops and publications. Within the EU, the ND4BB €430Million has been initiated to address major bottlenecks in the discovery and development of new antibiotic agents and the European technology Platform on nanomedicine and IMI funded RAPP-ID have also been created to create new rapid diagnostic tools. In addition surveillance programmes have been initiated at local, national and international levels for example EARS-Net.

IMI2 should aim to build on the progress made in each of these initiatives, utilising already established networks and ND4BB Info Centre.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Better understanding of the mechanisms underlying bacterial resistance in order to elucidate potential new targets to support single pathogen-based approaches and resistance mechanism-based approaches.
- Development of new cost effective and point of care rapid diagnostic tools/technologies support identification of infection and prudent use of antibiotics
- Robust validation of non-directly acting anti-infectives such as host defense, virulence and adhesion targets for treating bacterial infections, including evolutionally conserved host/pathogen pathways and targets that will enable the development of broad antimicrobial agents to treat less common or emerging infections

Axis 2: Adoption of innovative clinical trial paradigms

- Build on the clinical trial network established within COMBACTE to establish, train and maintain a network of investigators within all EU countries and across the globe, with ample expertise and experience in designing and executing clinical trials for diagnosing, preventing and treating infections caused by anti-biotic resistant bacteria.
- Build on outcomes of COMBACTE and promote the use of innovative clinical trial designs

Axis 3: Innovative Medicines

- Develop new therapeutic approaches to Gram negative infection including antibody approaches, combination therapies and non-directly acting anti-infectives such as host defense, virulence and adhesion approaches
- Develop novel prevention strategies including vaccines approaches in order to prevent infection and therefore reduce the likelihood of the emergence of resistance
- Ensure that the regulatory, HTA and reimbursement framework supports and facilitates the efficient development of new antibiotic agents and attracts reinvestment by the pharmaceutical industry.

Axis 4: Patient tailored adherence programmes

- Better understand the reasons for non-compliance to prescribed dosing regimens and develop new formulations and delivery technologies to improve patient adherence to prescribed antibiotics
- Partner with healthcare providers to better understand the challenges they face when treating infection and simplify the approach to anti-microbial prescribing
- Creation of campaigns promoting prudent use of antibiotics, implementation of stewardship campaigns and other control strategies.

Impact on R&D/public partners and society

For R&D:

- A pipeline of promising new agents for tackling antibiotic-resistant bacterial infections
- The tools required to support the generation of new therapeutic and preventative approaches and conduct of efficient clinical trials using stratified patient populations supported by fit for purpose regulatory and HTA framework.
- Engagement of companies back to the field of antibiotic research and creation of a vibrant antibacterial research environment in academia and small and medium-sized enterprises (SMEs)

For healthcare providers:

- Access to a range of preventative and therapeutic options with proven clinical efficacy and safety and better point of care rapid diagnostic tests to support prudent use of antibiotics
- Simplified approaches for healthcare practitioners, improved formulation, delivery and monitoring technologies/devices to support adherence which will together reduce the incidence of AMR.

For Citizens/Patients:

- Access to a range of preventative and therapeutic treatment programmes tailored to individual needs
- Novel vaccines able to prevent the onset of infection and thus the emergence of resistant strains

6.2.Osteoarthritis

The societal impact of Osteoarthritis

Osteoarthritis (OA) is the most common cause of disability in older adults (Laupattarakasem, et. al. Cochrane database of Syst Rev, 2008) with 10-15% of all adults over 60years suffering from some degree of OA, and is becoming more prevalent as the population ages and obesity rates rise. Direct and indirect costs of OA for the EU are substantial; in the UK alone, total costs for adaptive aids and devices, medicines, surgery and time off work are estimated to be equivalent to 1% of the gross national product (GNP) per year. Although there are a wide range of devices and palliative medicines

available that can relieve pain and improve quality of life, there is no pharmaceutical product that can halt or reverse the onset of OA.

Despite a growing disease burden, many pharmaceutical organizations have de-emphasized or abandoned OA drug development due to real and perceived hurdles including a number of highly visible and costly failures. Six interrelated factors that have contributed to these failures are as follow:

- Lack of understanding of OA pathogenesis. Emerging data suggest it is a heterogeneous disease with a variety of pathophysiologic drivers, some of which are amenable to pharmacologic intervention, and some of which are expected to be less so
- The majority of an unselected OA population do not progress radiographically or clinically in a given 2 year window; companies have not had the tools or knowledge base to prospectively identify patients at risk of progression who stand to benefit the most from effective therapies
- X-ray-based joint space narrowing (the current standard endpoint to demonstrate disease modification) is insensitive and slowly evolving. Validated biochemical and image-based markers are needed to quickly and sensitively detect the impact of treatments in smaller, shorter duration studies
- Clinical development plans have frequently used a 'one size fits all' approach rather than matching mechanism of action to specific OA patient subpopulations (i.e. personalized medicine)
- OA occurs in older individuals who may have multiple chronic conditions and who are likely to be treated for these conditions with multiple drugs.
- Successful commercialization requires that value to patients, regulators and payers is demonstrated

The need for Public Private Collaboration

In order to begin to tackle this major societal challenge, there is a need to better understand the mechanisms underlying the disease, develop the tools and capabilities required to support a precision medicine approach, novel patient centred outcome assessments and new clinical trial paradigms based on these new outcomes (rather than x-ray) are required. In order to address this challenge in the most effective way cooperation between scientists, regulators, patients, HTAs and healthcare practitioners will be required to ensure investment is focused on approaches most likely to yield cost-effective preventative or therapeutic approaches. Moreover regulatory and HTA involvement will be key to ensure the framework is in place to facilitate development and accelerate uptake of new advances.

Collaboration with other global, European and national initiatives

IMI2 will build on the knowledge base and infrastructure present within the EU from ongoing research-based initiatives like TreatOA and The Osteoarthritis Initiative (OAI), where a strong foundation is being built on understanding the natural history of OA, disease phenotypes, genetic profiles, biomarkers, and imaging features associated with disease progression. IMI2 will build on this foundation, focussing on the challenges facing clinical development, integrating diagnostic and other precision medicine approaches. IMI2 offers the unique opportunity to engage all key stakeholders required to facilitate the implementation of scientific advances into clinical care and reinvigorate the clinical OA therapeutic pipeline.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Better understanding of the molecular mechanisms underlying disease in order to identify distinct subpopulations, identify biomarkers (genetic, biochemical, proteomic, and image-

based) that will support patient stratification, monitor disease progression and have the potential to be developed as companion diagnostics

- Build in demographic, disease burden, imaging and pharmaco-epidemiologic data from patients to include a whole joint and/or whole body scale to further inform stratification, treatment options and potential risks for drug-drug interactions with commonly used medications
- More comprehensive biomarkers: including quantitative imaging, pain and function, and serum markers will provide quantitative or semi-quantitative markers of severity qualified for use in drug discovery and development.

Axis 2: Adoption of innovative clinical trial paradigms

- Capitalise on shared expertise and knowledge present within the academic, diagnostic and pharma/biotech sectors to develop biomarkers and imaging tools to support more efficient clinical trial design and early decision making and investment checkpoints.
- Identification and qualification of novel clinical endpoints including more responsive patient reported outcomes (PRO) measures, clinical observed outcomes assessment to demonstrate patient benefit/risk of treatment.
- Design templates for Proof-of-Mechanism (PoM; the realization of a mechanism of action by demonstrating that a study drug molecule modulates its intended target)/Proof-of-Concept (PoC; the realization of clinical benefit) clinical trials to assess for OA disease modification.
- Innovative trials designs will be implemented utilising stratified patient populations and innovative clinical endpoints that should speed clinical assessment of therapeutics and ultimately enable targeted treatment of patients.
- Establish, train and maintain a network of investigators within EU countries, with ample expertise and experience in designing and executing clinical trials for diagnosing, preventing and treating OA.
- Establish an ongoing dialogue with regulators and stakeholders to define endpoint criteria for successful registration for late stage clinical development and market approval

Axis 3: Innovative Medicines

- Progress those assets that meet defined PoM success criteria to PoC trials which will utilise MRI-based imaging and novel biomarker panels to enable detection of disease modification signals with smaller, shorter studies than previously possible with x-ray-based endpoints
- New therapeutics not solely directed at maintenance of cartilage but also at ameliorating whole joint or whole body changes.
- Conduct small, hypothesis-driven PoM clinical trials to assess viability of therapeutic mechanisms of interest to identify specific patient subsets most likely to respond and support an overall personalized medicine approach

Axis 4: Patient tailored adherence programmes

- Investigate novel delivery methods that enable longer residence time of a therapeutic to decrease effective dose and/or reduce systemic exposure and increase compliance.
- Design and test multi-modality health care solutions, customized to the patient which encompass lifestyle changes as well as increased adherence to prescribed medicines.

Impact on R&D/public partners and society

For R&D:

- Better disease understanding, the biomarkers and capabilities required to support new precision medicine approaches for the treatment of OA.

- The regulatory and HTA framework and more patient/carer orientated outcome measures required to support clinical development in stratified populations

For healthcare providers:

- Better range of treatment options and therefore significant reduction in long-term healthcare costs
- Better diagnostic tools to support early intervention and devices to support monitoring adherence to treatment paradigms

For Citizens/Patients:

- Disease modifying treatments that will improve function and quality of life, reduce pain, and prevent joint failure.
- Reinvestment in R&D for OA

Kick-starting the OA disease modifying therapeutic pipeline



6.3. Cardiovascular diseases

The societal impact of Cardiovascular diseases

Cardiovascular diseases (CVDs) remains the largest single cause of death (26.6%) in Europe and accounts for 11.8% of total disease burden (Murray et. al. *Lancet* 2013). Of these deaths, 57% have been attributed to risk factors such as smoking, poor diet (including low fruit and vegetable intake), low rates of exercise, high blood pressure and blood glucose, obesity and high cholesterol. Despite the evidence now available which demonstrates that adherence to lifestyle guidelines promoting moderate physical activity, good diet and reduction in smoking can reduce the incidence of CVD by 80% compared to the normal population; neither the general population nor patients with CVDs typically adhere to these recommended guidelines.

A more personalised approach to the management of CVDs is required, that is one that integrates both scientific understanding of disease and therefore the development of more precision medicines, with better understanding of patient behaviours leading to a more integrated treatment programme which maximises benefit to each individual patient.

The need for Public Private Collaboration

The prevalence of CVDs continues to rise with burden of illness set to increase as the population ages, people lead more sedentary lifestyles and demographics change. This is at a time when several of the major pharmaceutical companies have withdrawn from the area due to the lack of understanding of the complex mechanism underlying disease, combined with increasingly high

expectations from regulatory authorities and HTA agencies. To stimulate research and reinvigorate the field requires a joint effort of many different disciplines and stakeholders. Bringing together experts from academia, industry, patient organizations and regulatory authorities, HTA agencies and healthcare providers will ensure that all new efforts initiated take into account the needs of patients, regulators and HTAs ensuring that R&D efforts are focussed at developing tailored to the needs of society.

Collaboration with other global, European and national initiatives

Research into CVDs is a high priority of the WHO, visible in their Cardiovascular Health Research Initiative and the activities of the World Heart Federation. Several projects funded under FP7 also address specific aspects of CVDs. There are national cohort studies ongoing e.g. in Germany, UK, Sweden, and the Netherlands, which include research on CVDs, and bilateral cooperations do already exist in specific areas. Nevertheless, a coordinated overarching approach to address the challenges in this area is missing. IMI2 aims to provide the overarching strategy required to reinvigorate pharmaceutical development in CVDs and will collaborate with ongoing initiatives as well as initiate new activities to implement this strategy.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Use of a critical mass of well-defined biosamples to perform genome-wide association studies (GWAS) as well as epigenomic and metabolomics studies to reach a better understanding of the classification of CVDs, to identify disease relevant genomic variations, to identify new targets supporting new approaches towards prevention and therapy.
- Utilise improved knowledge of disease subgroups to create more predictive pre-clinical models including pluripotent stem cell-based systems, to support target validation and translation of efficacy and safety from the pre-clinical to clinical setting.
- Develop and evaluate novel non-invasive technologies to improve diagnosis, monitor disease progression (including likelihood of re-hospitalisation) and therapeutic intervention. In heart failure in particular, re-hospitalization of patients is a major concern, both from clinical and reimbursement perspectives.

Axis 2: Adoption of innovative clinical trial paradigms

- Establish models to assess of the usefulness of genetic data of polymorphisms and genomic variations in individual patients to support the stratification of patients most likely to benefit from therapeutic intervention.
- Devise methods to study, quantify and incorporate caregiver burden of disease in clinical trials.

Axis 4: Patient tailored adherence programmes

- Evaluation of novel medical devices and technologies for monitoring patient's health status under "real world" conditions and improve patient adherence.
- Better understand the needs and behaviours of those individuals most at risk from CVDs as well as the challenges facing healthcare providers treating these individuals, in order to support the development of individualised integrated treatment programmes.
- Improve the current level of engagement of patients and citizens in the management of their own health and maximise the benefit of intervention.

Impact on R&D/public partners and society

For R&D:

- The tools and capabilities required to develop and implement stratified medicine approaches for CVDs.
- More efficient R&D process, more rapid uptake of scientific advances by regulators and HTAs and new medicines by healthcare providers, based on increased operational excellence

For healthcare providers:

- Increased quality of healthcare options, more integrated healthcare solutions lowering the cost of healthcare

For Citizens/Patients:

- A range of treatment options and programmes tailored to individual patient needs leading to potential to delay disease progression, lower mortality and increase quality of life.
- Opportunity for patients and citizens to have earlier involvement the R&D process.

6.4. Diabetes

The societal impact of diabetes

Diabetes and its related illnesses not only cause human suffering but are also a major economic burden to society. Approximately 366 million people suffer from diabetes and another 280 million are at identifiably high risk of developing diabetes, a number which is expected to rise to 552 million with diabetes and an additional 398 million people at high risk by 2030¹ as the population ages and sedentary lifestyles lead to an increase in obesity. There are primarily two types of diabetes. Type 1 diabetes is an autoimmune disease which typically onsets below the age of 15 the mechanism underlying which remain relatively unknown². Type 2 diabetes dominates the total diabetes burden largely associated with adults over 60 years, however incidence is increasing in children as the level of obesity in children increases. Currently no treatments exist so slow or prevent the progressive loss of islet B-cell function/mass or provide long-term glucose lowering.

The complex mechanisms underlying Type 1 and Type 2 diabetes result in many subpopulations within each disease classification which drives the need for the development of more tailored treatment programmes which not only consider the mechanistic classification of disease, but also the management of risk factors which drive disease onset. Only with a better understanding of the underlying disease mechanisms, the identification of novel diagnostics and prognostics will this be possible.

The need for Public Private Collaboration

In order to slow the increasing prevalence of diabetes an integrated approach that focuses on the development of new precision medicines, better patient focussed outcome measures as well as better lifestyle management and adherence to prescribed medicines is required. To be successful in driving a significant improvement to current healthcare practices will require collaboration between industry, medical professionals, regulators, citizens and patient organisations.

Collaboration with other global, European and national initiatives

There are currently several EU-wide and global projects ongoing as well as IMI projects such as SUMMIT, IMIDIA and DIRECT that are sequencing data, performing genome-wide association studies (GWAS), metabolomic and epigenomic studies in a large number of patients with the hope to identify new targets as well as biomarkers that will predict disease progression and drug response.

IMI2 will aim to build on the progress made through each of these initiatives continuing to build the science base required to support personalised/precision medicines approaches for diabetes. The

¹ International Diabetes Federation (IDF) Global Diabetes Plan 2011–2021. www.idf.org/global-diabetes-plan-2011-2021

primary focus of IMI2 will be to utilise the opportunity the PPP brings to engage all key stakeholders i.e. patients, regulators, HTAs and healthcare providers to translate the scientific progress made into meaningful novel treatment approaches.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- To better understand the the risk factors for diabetes (e.g. obesity and sedentary behaviour, ethnicity, genetic background), and quantify how these affect disease onset and progression, drug efficacy and safety.
- Reclassification/better definition of diabetes using Electronic Health Records (using results from IMI Project: EH4CR and EMIF) based on molecular patterns, genomic and phenotypic characterization, leading to better understanding of the disease, mechanisms of drug action and predictors of patient response
- Alternative strategies to studies in animals such as the use of system models and strategies combining technology, biology, computational methods with information retrieved from historical compounds tested in preclinical models (using e.g. results and procedures from the IMI Project eTOX) to improve translation of efficiency and safety from pre-clinical studies to clinical development
- Identify markers and innovative methods and tools (including stem cells) for the prediction and assessment of efficacy and safety of clinical candidates (e.g. using results, best practices and setup from the IMI project STEMBANCC)
- New innovative tools for precise diagnosis of diabetes, predictive markers of susceptibility and disease progression and for the evaluation of treatment effects in preclinical and clinical research and clinical practice. These could be based on e.g. molecular markers or imaging techniques (e.g. using results, procedures and development strategies from IMI projects SAFE-T and MIP-DILI)
- Integration of the identified markers such as genomic, transcriptomic, proteomic and metabolomic markers into regulatory approval and clinical practice

Axis 2: Adoption of innovative clinical trial paradigms

- Develop, clarify and gain alignment with regulators and HTA bodies on the regulatory assessment methodology and data requirements for benefit–risk assessment in pre and post-approval settings (e.g. using methods developed within the IMI project PROTECT as well as the IMI GetReal project)
- Develop a proposal of a new, optional conditional approval pathway. Considerations to include e.g. applicability of diseases/conditions/ unmet clinical needs, number of trials required, and appropriate surrogate endpoints
- Develop new, cost-effective diagnostic methodologies to monitor treatment effect and disease progression for use in clinical practice and in the development of new compounds based on the integrate perspectives of the regulatory agencies and HTAs
- Integration of HTA bodies into the early R&D process leading to understand the value of potential new approaches and establish methodological tools to generate evidence of relative effectiveness in order to better predict outcomes between patients in clinical trials and patients in ‘real life’
- Clarify regulatory approaches to innovative fixed dose products (e.g. combinations of monoclonal antibodies, and ‘novel-novel’ products) Set up of clinical studies conducted in the context of the environmental realities (diet, physical activity and social life) of modern living to improve benefit-risk ratio of clinical outcomes

Axis3: Innovative Medicines

- Vaccination for Type 1 diabetes (using framework and methods developed within the IMI Vaccination Projects)
- Beta cell replacement therapies by transplantation (using e.g. the IMI Project STEMBANCC). These approaches require the development and approval of methodologies to produce non-proliferating human beta cells or cell lines fulfilling GMP/GCP requirements and monitor location, functionality and proliferation of transplanted beta cells in patients. New stratified and more efficient clinical trial designs leading to new approval pathways

Axis 4: Patient tailored adherence programmes

- Development of individual screening programs to identify persons at risk for diabetes and confirm suspected diabetes thus providing improved disease surveillance and disease management
- Development of individual multi-modality treatment programmes (including non-pharmacologic interventions), taking into account different environmental, lifestyle, socioeconomic and genetic factors
- Develop advanced formulations for long-acting injectables/depots that will improve patients compliance and comfort
- Evaluate novel approaches of drug delivery systems/devices for mono- or combination therapies or complex dose regimens to ensure optimal therapeutic performance and outcome by accurate and precise administration of the most appropriate dose(s)
- Develop an adherence program that identifies predictors of non-adherence, designs intervention depending upon risk of non-adherence, and measures outcomes

Impact on R&D/public partners and society

For R&D:

- The tools and capabilities required to develop and implement stratified medicine approaches for diabetes, moving into an era of targeted therapies with improved patient outcomes
- More efficient R&D process, more rapid uptake of scientific advances by regulators and HTAs and new medicines by healthcare providers, based on increased operational excellence

For healthcare providers:

- The ability to diagnose and treat patients with diabetes at an earlier stage in the disease, to find treatments that address the narrow therapeutic window for insulin treatment, to monitor treatment success and to better estimate the risk of developing disease complications.
- Increased quality of healthcare options, more integrated healthcare solutions lowering the cost of healthcare

For Citizens/Patients:

- A range of treatment options and programmes tailored to individual patient needs leading to potential to delay disease progression, lower mortality and increase quality of life.
- Tailor made adherence programmes to support patients in managing their treatment and maximise the benefit gained from interventions.

6.5. Neurodegenerative diseases

The societal impact of neurodegenerative diseases

In 2012, the WHO declared dementia to be a public health priority^{xx,xxi} estimating that in 2010 35.6 million people worldwide were living with dementia a number which is predicted to double every 20 years. The financial burden of treating and caring for dementia sufferers is enormous; in the UK the

cost of managing dementia (£23 Billion) was almost equivalent to the combined costs of treating cancer (£12 Billion), CVD (£8 Billion) and stroke (£5 Billion). Failure to improve the management of dementia research will place unprecedented pressure on health services across the world and result in healthcare costs that cannot be borne by developed countries let alone less developed economies.

The lack of available therapeutic interventions is symptomatic of the lack of disease understanding for most neurological diseases, and by the lack of robust pre-clinical to predict drug efficacy and safety. This means that developing new therapeutic approaches is high risk, and costly as exemplified by recent failures in this area. Despite the urgent need for new medicines, the pharmaceutical industry is being forced to withdraw efforts until science advances to the stage where these risks can be mitigated.

Significant progress has been made to further the understanding of how genetics and lifestyle may influence the probability of developing neurodegenerative disorders. However, an early and correct diagnosis for any one of these disorders is difficult to attain in the primary care setting and many individuals are simply unaware of their overall risk and/or any potential lifestyle changes that they may incorporate to delay disease onset or slow progression. Misdiagnosis has profound impact, on the treatments that are offered to patients and also directly impacts the conduct of clinical trials with heterogeneity in the patient population often resulting in a dilution of any drug effect observed in clinical trials, even after chronic treatment.

The need for Public Private Collaboration

Given the healthcare burden that neurodegenerative diseases pose, together with the current disinvestment by major pharmaceutical companies a joint and urgent action from public and private sectors is essential. Early and correct diagnosis of neurodegenerative diseases is important for selecting the most appropriate care at the right time, and for the development of more preventative treatment approaches. The risk of clinical development must be reduced through the development of innovative patient focussed endpoints, trial designs, simulation and analytical approaches to devise new clinical trial paradigms both pre-and post-marketing which permit the assessment of outcomes (good and bad) in small patient populations balancing the needs for regulation (efficacy/safety) and HTA agencies (effectiveness/safety) as well as the risk and cost for pharmaceutical companies. Consequently, all interested parties must work together with the aim of conducting large scale data collection and database creation. In addition to collaborations between the pharmaceutical industry, academia and health care organizations, there is a clear opportunity to capitalize on the expertise and tools of imaging technology industry partners.

Collaboration with other global, European and national initiatives

A framework for scaling collection of biomarker and clinical data is already in place with successful implementation of worldwide ADNI efforts and other European initiative such as IMI EMIF-AD, Joint Programme – Neurodegenerative disease research (JPND) and the Center of Excellence Network (CoEN) supported by the MRC and the German Center for Neurodegenerative diseases (DZNE) and others. Any new initiatives undertaken in IMI2 must collaborate with such initiatives and available data resources available from academia across Europe to ensure synergies are maximised and efforts are not duplicated. Meanwhile the IMI project PharmaCog and NIH's CAMD initiative aim to develop better tools to support the translation of efficacy and safety from pre-clinical models the clinical setting.

IMI2 will build on the scientific advances being made in these ongoing initiatives and utilise the multi-stakeholder framework to ensure that the advances are translated into new approaches to the management and treatment of neurodegenerative conditions.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Better understand the mechanisms underlying disease in order to more accurately identify and inform individuals at risk for developing neurodegenerative disease, to appropriately stratify subjects for clinical investigation and to develop innovative biomarkers and patient focussed outcomes to support internal decision making, regulatory approval and HTA assessments.
- Identification and validation of novel targets for prevention and slowing of disease in specific subpopulations of patients with neurodegenerative disorders
- Development of novel non-invasive methodologies for assessing disease progression and drug efficacy and safety (e.g. imaging and EEG)
- Create an integrated database with subject level clinical and biomarker data to enable rapid implementation of novel therapies and treatment biomarkers as they are approved or as they undergo clinical evaluation.

Axis 2: Adoption of innovative clinical trial paradigms

- Innovative trial designs for the conduct of preventative and disease modifying trials
- Development of PROs/Clinical Outcomes Assessment/Caregiver assessment of patients with neurodegenerative diseases to more fully demonstrate impact of disease and resultant benefit of treatments

Axis3: Innovative Medicines

- Assessment of novel therapeutic asset(s) for preventative and/or disease modifying treatment of disease.

Axis 4: Patient tailored adherence programmes

- Develop a framework to support proactive and comprehensive screening (including imaging, biomarkers, genetic signatures, a clinical battery and a lifestyle questionnaire, indices of: blood pressure, BMI, insulin resistance and LDL-cholesterol) in order to identify those individuals at risk of developing dementia.
- Better understand the risk factors associated with neurodegenerative diseases and develop tailor made intervention paradigms.
- Establish, train and maintain a network of investigators within all EU countries, with ample expertise and experience in designing and executing clinical trials for diagnosing, preventing and treating neurodegenerative diseases.
- Improve the collaboration between scientists, clinical researchers, nurses and clinicians to improve understanding of scientific advances and how these can inspire better clinical practice
- Develop better formulations and delivery methods to support improved adherence to medicines and risk factor management

Impact on R&D/public partners and society

For R&D:

- The tools and capabilities required to develop and implement stratified medicine approaches for neurodegenerative disease, moving into an era of targeted therapies with improved patient outcomes
- More efficient R&D process with a higher probability of success, more rapid uptake of scientific advances by regulators and HTAs and new medicines by healthcare providers

For healthcare providers:

- An overall reduction in the direct and indirect costs associated with the management of neurodegenerative disease through more accurate patient risk assessment and earlier therapeutic intervention.

For Citizens/Patients:

- Better understanding of their individual risk of developing dementia and therefore the ability to actively manage this risk
- Access to better treatment programmes, treatment delivery and adherence programmes tailored to individual needs

6.6.Psychiatric diseases

Societal impact of Psychiatric disease

More than a quarter of all Europeans are estimated to experience at least one form of mental disorder during their lives, with more than 20 million affected in any one year. A recent study commissioned by the European Brain Council estimated that the cost of brain disorders² in Europe alone was €798 billion in 2010. Mental disorders are serious and debilitating; they invariably severely impact the lives of the individual and their relatives, they affect the ability to work, study and perform other normal functions of daily living, thereby imposing enormous costs not only on healthcare systems, but on society more generally including loss of productivity and loss of work days. In terms of total disability-adjusted life years (DALYs), mental disorders rank amongst the most disabling conditions, mental or physical.

Although several treatments are available, positive response is limited, and for most mental disorders treatment algorithms are based on trial and error. Less than 25% of patients with depression have access to appropriate treatment options and existing treatments – including currently available anti-depressants – are not always effective even when properly prescribed. 30-35% of patients experience no remission after first and second treatments. Moreover, 75% of patients with alcohol dependence relapse within the first year. Current diagnosis of mental disorders is in most cases reliant on the patient’s reporting of symptoms because biomarkers or physical tests are not available to group or classify the disease further. However, many patients are reluctant to seek help and mental disorders are often not recognized as ‘real’ diseases. Therefore, further research is needed to create better holistic care for patients suffering from mental health disorders. A better understanding of the disease biology and potential biomarkers of psychiatric disorders, which will be the key to increasing rates of diagnosis and treatment success, and to development more targeted medicines.

The need for Public Private Collaboration

Despite the magnitude of unmet need, a number of major pharmaceutical companies have withdrawn from the area in recent years because of the scientific and regulatory challenges it presents. The current decline in brain disorder research needs to be reversed if we are to avoid a shortage of new medicines in the coming decades. Steps need to be taken to ensure that research into mental disorders is encouraged for the benefit of patients and society. IMI2 will provide the framework to generate the tools required to allow the pharmaceutical industry to enter a high risk healthcare area and to start collectively a dialogue with a range of stakeholders beyond research that is needed to address this huge healthcare challenge.

Collaboration with other global, European and national initiatives

² Note: brain disorders consist of a broader range of diseases than the WHO definition of mental disorders.

The NEWMEDS project funded under IMI is focussed on validating new pre-clinical models to support the prediction of efficacy and safety as well as developing new clinical endpoints and clinical trial paradigms.

Nature of the research to be conducted

Axis 1: Target validation and biomarker development

- Better understanding of the molecular mechanisms underlying disease to support the development of new therapeutic interventions and identification of biomarkers to support patient stratification
- Better understand the role of co-morbidities in the development and maintenance of mental illness
- Understand the role of aberrant plasticity in brain disorders and explore manipulation of plasticity as a new approach for preventative and therapeutic intervention.
- Development and validation of biomarkers and neuroimaging techniques required to provide more accurate diagnosis, stratify patients and monitor efficacy and safety of new approaches (both short and long-term effects).

Axis 2: Adoption of innovative clinical trial paradigms

- Qualification for use of novel biomarkers and outcome measures to support a precision medicines approach
- Utilise new biomarkers to drive the development of new innovative trial designs for the conduct of preventative and disease modifying trials

Axis3: Innovative medicines

- Assessment of novel therapeutic asset(s) for preventative and/or disease modifying treatment for mental disorders

Axis 4: Patient tailored adherence programmes

- Conduct the research required to understand lifestyle factors and co morbidities associated with adult, child and adolescent mental health develop and implement tailored solutions (along the continuum of education and prevention) that will enable patients and citizens to play a more active role in the diagnosis and management of their own health and treatment options.
- Create integrated adherence programmes tailored to the needs of juvenile and adult patients.
- Create the education and training materials and platforms effort to establish an adequate skill base in industry, academia, and health agencies to implement new integrated treatment options.

Impact on R&D/public partners and society

For R&D:

- Tools and biomarkers required to support a precision medicine approach to mental health, and more efficient R&D processes.

For healthcare providers:

- Provision of both prevention and effective treatments for a large and growing patient population, whom today do not receive adequate treatment.
- Reduction in healthcare costs and social benefit expenditure.

For Citizens/Patients:

- Greater availability of treatment options and improved health and quality of life of patients and their families.

6.7. Respiratory diseases

Societal impact of Respiratory disease

Despite improvements in the way respiratory diseases are managed, they continue to pose a significant burden on patients and healthcare systems. Huge strides have been made in the treatment of asthma yet it remains a major health burden, affecting over 300 million people. Under-diagnosis and under-treatment of asthma remain high and, worldwide, it accounts for 250,000 deaths annually^{xxii}. Unlike asthma, COPD remains a relatively poorly understood disease despite one person dying of COPD every 10 seconds^{xxiii}, more than the combined number of lives claimed by breast and lung cancer^{xxiv}. By 2020, COPD is predicted to become the world's third most common cause of death.^{xxv}

Asthma and COPD represent a staggering economic burden. In 2010, COPD alone was estimated to have cost the global economy \$2.1 trillion^{xxvi}. Much of this cost is as a result of sub-optimal management, which can lead to exacerbations, hospitalisations and reduced productivity. Other respiratory diseases also continue to have a significant impact on health. Allergic rhinitis is one of the world's most common chronic illnesses affecting one in every five people, while conditions such as idiopathic pulmonary fibrosis, acute lung injury, cystic fibrosis, lung cancer and pulmonary arterial hypertension also present a significant burden.

With advancing knowledge of the pathology of various diseases and their clinical manifestations, it is becoming clear that many chronic respiratory diseases are not uniform with heterogeneous pathways resulting in similar clinical characteristics. There is therefore a need for the development of targeted therapeutic approaches tailored toward specific subpopulations.

The need for Public Private Collaboration

The biomarkers and endpoints currently accepted by regulatory authorities are either major events, which are difficult to interpret in early stage trials with limited numbers of patients (e.g. mortality, disease exacerbations), or reflect outdated or limited disease understanding. Regulators in Europe and the United States are now establishing processes for the qualification of new drug development tools and clinical measures so that researchers and regulatory agencies can be more informed and hence make better decisions when assessing new drug therapies for chronic diseases. However, the methodological complexity, volume of data collection and the resources required for developing and qualifying biomarkers and other endpoints, requires a joint action between academic, SME and industrial scientists, regulators, HTAs and patient groups to be successful.

Within the respiratory field there are already a number of collaborations underway between major stakeholders, which are starting to approach some of these challenges. However, this model needs to continue to ensure success and delivery of effective solutions that are acceptable to regulatory authorities. Collaboration will allow streamlining of the process of selecting the most useful biomarkers and clinical assessments, developing new patient-, observer- or clinician-reported outcomes and better applying limited resources from all participants. Ultimately, patients will benefit from close collaboration between industry, academia and governmental bodies pursuing the same goal, i.e. delivering innovative medicines to the patients who need them most.

Collaboration with other global, European and national initiatives

The COPD Foundation Biomarker Qualification Consortium is an international public private partnership formed with the aim to qualify drug development tools where sufficient evidence supports their qualification^{xxvii}. The UK Technology Strategy Board funded ERICA or the Industry-funded ARCADE and ECLIPSE cohort studies are insufficient as the large datasets will be required to provide robust evidence to support stratified medicine approaches. IMI2 will work closely with this

group to build on scientific advances and ensure translation of these new advances into meaningful healthcare solutions.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Develop an international consensus on means to identify disease manifestations in subsets of patients using clinical assessments, patient reported outcomes and diagnostic biomarkers to support patient stratification approaches
- Development of innovative tools for evaluating the impact of therapeutic candidates on disease activity in early-phase drug trials.
- Identification and qualification of biomarkers to support stratification, prediction of exacerbation events, dose-ranging and assessment of efficacy and safety

Axis 2: Adoption of innovative clinical trial paradigms

- Integrate the use of biomarkers in early clinical testing.
- Establishment of a co-ordinated respiratory disease clinical trial network and patient registries to enhance the efficiency of drug development Initial efforts to understand potential relationships of co morbidities in COPD.

Axis 3: Innovative medicines

- Areas for future focus will be to develop mechanisms of boosting host defence and innate immunity so antivirals/antibacterials can be substituted by preventive therapy promoting health rather than curing disease.

Axis 4: Patient tailored adherence programmes

- Better understand the interactions between environmental, social and lifestyle factors and endogenous factors which clearly drive health and disease, disease treatment and prevention, to inform the most beneficial interventions.
- Test the application of guidelines in patients with multiple morbidity and develop individualised multi-morbid treatment approaches, including pharmacological and non-pharmacological strategies.
- Increase capacity and accessibility of rehabilitation programmes and self-management approaches, by innovating models of delivering these forms of care, in line with pharmacotherapy.
- An implementable, practical patient and clinician decision support system to support the clinical implementation of scientific advances
- New delivery devices capable of monitoring patient status and administering tailored doses

Impact on R&D/public partners and society

For R&D:

- The tools and capabilities required to developed and implement stratified medicine approaches for respiratory diseases, moving into an era of targeted therapies with improved patient outcomes
- More efficient R&D process, more rapid uptake of scientific advances by regulators and HTAs and new medicines by healthcare providers, based on increased operational excellence

For healthcare providers:

- An overall reduction in the direct and indirect costs associated with the management of neurodegenerative disease through more accurate patient risk assessment and earlier therapeutic intervention.

For Citizens/Patients:

- A range of treatment options and programmes tailored to individual patient needs leading to potential to delay onset, disease progression, lower mortality and increase quality of life.
- Opportunity for patients and citizens to have earlier involvement the R&D process.

6.8.Autoimmune diseases

Societal impact of autoimmune disease

Autoimmune diseases are caused by alterations in the normal functioning of the immune system resulting in an immune response directed against the body's own tissues. The resulting injury may be localized in a single organ system or may affect multiple organs. Although most of the autoimmune-related diseases disproportionately strike women, men and women of all ages, races and ethnic and socio-economic groups are affected. To date, over 100 distinct diseases and syndromes have been described, together affecting approximately 5% of the population of Europe, with two thirds of the patients being female. Examples of autoimmune disorders include rheumatoid arthritis, multiple sclerosis, juvenile diabetes, cardiomyopathy, antiphospholipid syndrome, Guillain-Barré syndrome, Crohn's disease, Graves' disease, Sjogren's syndrome, alopecia, vitiligo, myasthenia gravis, systemic lupus erythematosus (SLE) and psoriasis. In addition, such disorders complicate other diseases that are not autoimmune in origin, such as arteriosclerosis. Because some of these conditions are chronic and debilitating diseases, while others are less serious, total societal costs are hard to estimate. However, arthritis alone is estimated to cost almost €100 billion per year, indicating that autoimmune disorders as a group are among the most costly diseases faced by society today.

Although autoimmune diseases are subject to significant research, progress has been slow in developing new therapies for many autoimmune rheumatic conditions, including SLE, Sjogren's syndrome and scleroderma. Autoimmune diseases are often complex and therapies for these disorders have often been only partially effective. Historically, treatment of autoimmune diseases has consisted primarily of agents that provide some symptomatic relief but often do not prevent inflammation-related tissue damage. In addition, treatments may lose effectiveness over time and most are associated with problematic side effects. Clearly, more effective treatments are needed that are beneficial to the majority of patients, especially those with early-stage autoimmune disease.

The pathobiology of many autoimmune disorders is poorly understood. It is thought that better understanding of the molecular pathology of autoimmune diseases may enable improved targeting of currently available treatment as well as advances in therapy for specific disorders. Such research may also serve to identify molecular markers for improved diagnosis as well as measures of disease response to treatment.

The need for Public Private Collaboration

The burden of autoimmune disease crosses medical and scientific boundaries and requires cross functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. With the economic challenges facing the pharmaceutical industry, companies have resorted to substantial cuts in R&D spending and as a result research teams are small and often highly focused leading to a need for external collaboration to tackle complex multisystem diseases. Public private consortia are well-suited, if not essential, to tackle the problem of autoimmune disorders through synergies that can be attained through the sharing of expertise, data and resources.

Collaboration with other global, European and national initiatives

The proposed work will build on the knowledge base and infrastructure present within the EU from ongoing research-based initiatives e.g. Eumusc.net, EMEUNET, EUSTAR, ERS/ELF, ECCO, BILAG, EUVAS and Euro Lupus OMERACT, which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders. To this foundation, the proposal adds the drug candidate, diagnostic and clinical development expertise present within the pharmaceutical and biomarker/diagnostic industry. By bringing together a diverse partnership, we seek to identify therapeutic opportunities and design and implement clinical strategies which will transform the diagnosis and management of autoimmune diseases.

Nature of research to be conducted under IMI2: Alignment with research axis

Kick-starting the autoimmune and inflammatory disorders management pipeline



Axis 1: Target validation and biomarker development

- Identification of biologic pathways which provide greater understanding of disease aetiology and pathogenesis
- Consider role immune and resident organ cells together with possibilities for tissue protection and repair
- Matching of exploratory therapeutics to key pathogenic processes in autoimmunity, including potential for combining mechanisms
- Use of ongoing observational patient cohorts to identify markers of potential disease modification.
- Identification of disorders which may benefit from treatment with established therapies and conduct clinical trials to establish the place of these therapies in the management of specific disorders
- Evaluate the impact of genetic aspects together with previous immunomodulating processes such as infectious diseases, allergies, stress, immune-suppression, other than vaccines.
- Incorporation of new or improved imaging modalities such as MRI and high resolution computed tomography into the development process and clinical practice

- Establish design templates for clinical trials to assess PoM/ PoC for disease modification. The templates will be adaptable, as appropriate, to specific therapeutics and set clinical success criteria for each stage
- Identify candidate biomarkers to monitor/predict disease progression; monitor/predict disease response to specific therapy; monitor remission maintenance; act as surrogate markers for probability of later clinical response for use in short-term studies of novel therapies and identify subjects at risk of disease flare to enable proactive intervention and flare prevention in disorders with flare/remission pattern (e.g. vasculitis, lupus)
- Improved understanding of factors relating to primary and secondary treatment non-response

Axis 2: Adoption of innovative clinical trial paradigms

- Dialogue with regulators and stakeholders to improve definition of endpoint criteria for successful registration both utilising existing therapies with novel endpoints and novel uses for existing therapies.
- Implementable reimbursement strategies/processes which place greater emphasis on preventative treatment modalities for chronic autoimmune diseases in defined patient populations
- Adaptation of regulatory environments to place greater emphasis on drug combinations that can achieve sustainable remission from autoimmune diseases

Axis 4: Patient tailored adherence programmes

- Delivery technologies which enable patients to be treated with combinations of different biologicals in a more effective manner
- Improved solutions for delivery of antibody or antibody like fragment drugs to the central nervous systems, particularly for neuro-inflammatory conditions
- Methods, processes, technologies to enhance compliance or effectiveness of treatment options in the real world environment

Impact on R&D/public partners and society

For R&D:

- Enable focused studies with a personalized medicine approach to best evaluate promising therapeutics.

For healthcare providers:

- improved methods for recognition and diagnosis of autoimmune and inflammatory disorders (AIIDs) and a range of treatment options

For Citizens/Patients:

- improved methods for recognition and diagnosis of autoimmune and inflammatory disorders (AIIDs)
- disease modifying treatments that will improve function, quality of life and prevent complications among patients

6.9.Ageing-associated diseases

A number of medical conditions are common in an ageing population, in particular ageing-associated diseases of the cardiovascular, neurological and musculoskeletal organ systems, are specific challenges of ageing biology. Ageing mechanisms outside of disease pathways are not well understood and the fact that ageing is an incremental, whole-body problem is often neglected. All cells, tissues and organs age in different ways, at different rates, in different people. In order to

improve quality of life for the ageing population a better understanding of the pathophysiologic mechanisms underlying ageing, the specific unmet medical needs of older persons, and a better appraisal of the variability of clinical outcomes of clinical trials with geriatric patients will be required. In addition, a better understanding of the effect of ageing on drug responses and the safety of long term therapy in the aged population will be essential as developing medicines for effectively healthy individuals requires very low adverse effect liabilities. In this context novel and tailor-made approval pathways for innovative medicines responding to the specific needs of the ageing population are also required.

Recently the EMA has shown a willingness to consider the geriatric syndrome of frailty. Although not a yet a disease, frailty, both physical and cognitive, believed to result from cumulative declines across multiple physiological systems, actually causes increased vulnerability to adverse outcomes and high risk of death. Identifying, preventing or slowing key components of frailty (e.g. sarcopenia or cognitive decline), will markedly improve quality of life and decrease healthcare costs.

The need for Public Private Collaboration

The European Commission has identified active and healthy ageing as a major societal challenge common to all European countries, and an area which presents considerable potential for Europe to lead the world in providing innovative responses to this challenge. Ageing projects under IMI2 will broaden our understanding of the genetic and molecular basis for the ageing process, gained by new genetic, molecular and proteomic techniques, and support the development of new medicines for unmet needs of the ageing population. A large-scale public private collaboration would allow the pharmaceutical industry to enter a high risk health care area and to start collectively a dialogue with the health authorities on this subject.

Collaboration with other global, European and national initiatives

The European Innovation Partnership on Active and Healthy Ageing (EIPAHA) aims to increase the average healthy lifespan by 2 years by providing the infrastructure required to bring together key stakeholders (end users, public authorities, industry); all actors in the innovation cycle, from research to adoption (adaptation), along with those engaged in standardisation and regulation to tackle current bottlenecks in the provision of healthcare to the elderly. IMI2 will work closely with the EIPAHA to maximise synergies and avoid duplication of effort.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Better understanding of the molecular and physiological mechanisms that underlie age-related dysfunction and the genetic variations that affect the length and/or quality of life.
- Identification of age-related changes affecting tissue and organ function in relation to age-associated disease conditions, and the inter-play between physiologic systems, such as Immunology, Metabolism, Respiratory, Musculoskeletal and Neurological Diseases,
- Develop a better understanding of the importance of competing risks in older patients with comorbidities at the individual basis.
- The development and refinement of pre-clinical models (including human tissue and stem cell models), that translate to mature and senescent human physiology to support prediction of efficacy and safety of new medicines.
- Development of status biomarkers adequately mapping physiologic system vulnerability (e.g. muscular metabolism in physical frailty and sarcopenia) to support the identification of

specific 'indications'; development of pharmacodynamic biomarkers to detect early response to therapeutic intervention

Axis 2: Adoption of innovative clinical trial paradigms

- Agree criteria for pharmacological profiles, safety, clinical endpoints, patient stratification and trial inclusion criteria for the ageing patient population.
- A better understanding of the effect of ageing on drug benefit/risk and effectiveness/risk and of the variability of clinical outcomes of trials with geriatric patients.
- Explore innovative trial designs such as adaptive and pragmatic trials to overcome the difficulties in enrolling and retaining older adults in clinical trials.
- Explore novel tailor-made approval pathways for drugs for the ageing population

Axis3: Innovative Medicines

- Regulatory definition of at-risk population to enable the development of innovative medicines for geriatric conditions generating huge public health burden
- Develop appropriate vaccine formulation allowing to circumvent the immunosenescence, and induce protective immune responses against ageing associate diseases.

Axis 4: Patient tailored treatment programmes

- Develop better formulations and delivery methods to support improved adherence to medicines and risk factor management
- Increase health and function awareness providing empowerment of older persons to self-monitor their health status and manage their wellbeing

Impact on R&D/public partners and society

For R&D:

- Defined target populations and increased efficiency in R&D

For healthcare providers:

- Decreased cost associated with falls and relapse due to non adherence to medication

For Citizens/Patients:

- An ageing population that can lead productive and fulfilling lives for the benefit of individuals and society as a whole.

6.10. Oncology

The societal impact of cancer diseases

Over the next decade the incidence of cancer is expected to increase by approximately 60%. This increase is driven largely by the combination of an ageing population and the advances in diagnosis and treatment of cancer in many countries which has led to an increase in the number of patients living for cancer for many years. The situation is augmented where lifestyles include poor diet, lack of physical exercise and and exposure to tobacco smoke all of which are associated with increased risk of cancer. This increase in prevalence of cancer poses a major burden to the global healthcare systems. Cancer patients require regular checkups, often require hospitalization for continued care and often have long-term physical and psychological complications.

Although treatment success is increasing, a number of challenges remain for the future. The fact that patients are now living longer with cancer also impacts the type of medicines required. Previously therapies were deemed to be for short term use, however as life expectancy increases

there is a need for more research to be conducted in order to better understand the long term benefit/risk of new medicines. Over the past decade multiple drugs have been developed against the proteins and biological pathways that are activated in cancer through somatic mutations. In most cases these drugs are only effective against a subset of cancers. As the basic understanding of tumour biology and new tumour types are classified, the need for new markers for early identification of disease onset, targeted therapies and accompanying diagnostics will increase. This revolution in cancer care brings challenges with respect to the regulatory framework required to assess and approve these new precision medicines. Furthermore given the need to discover and develop companion diagnostics and treatment markers in addition to the new medicine is driving up the cost of cancer care which brings additional challenges for health technology agencies who will be required to assess the value of these new medicines and make decisions for reimbursement. Collaboration between pharmaceutical companies, regulatory authorities and healthcare payers will be required to develop a new and sustainable model for cancer care.

The need for Public Private Collaboration

In the purely scientific front, the collaboration challenges remain substantial. If any improvement in the current cancer drug attrition rate is to be achieved, close cooperation of biologists, computer scientists, pathologists, physicists, statisticians, physicians is mandatory and it cannot be expected that it will happen by chance; instead, a platform that fosters and structures collaboration towards the common goal is needed. For example the successful classification of molecularly defined subtypes requires access to good quality clinically annotated tumor samples, accurate identification of the molecular alterations, reliable diagnostic assays, robust statistical analysis for the discovery and validation cohorts, efficient development of agents targeting the identified molecular alterations through preclinical and clinical models, and the capacity for prospective randomized trials after screening of large patient samples to assess the impact of molecularly driven treatment. In order to address this grand challenge, it will be essential to gather samples from 10's of thousands of patients and conduct an integrated and systematic characterisation at the molecular level.

None of the challenges outlined above can be adequately addressed by any one given institution. Harmonizing all stages of cancer research as much as possible is vital to allow researchers and private sector partners to focus on delivering value for society while avoiding wasteful duplication of efforts. Patient input will be essential in order to develop better tools for the assessment and communication of the benefit/risk of new medicines. Furthermore scientific input from the regulatory authorities into emerging profiles and their subsequent qualification and validation for use in drug development will be critical to the success of such an initiative.

Collaboration with other global, European and national initiatives

Efforts undertaken in the proposed PPP should be synergistic with other ongoing initiatives working in this field to ensure international collaboration and maximise the use of resources. Of particular note is the EurocanPlatform consortium which aims to build clinical registries from clinical trials and biorepositories of the same patients as well as integrating innovative imaging technologies for better description of the tumour mass(es), biological characterization of tumours and evaluation of treatment effects. Parallel biomarker research (circulating tumour cells, DNA, RNAs and proteins) will generate new ways to monitor treatment effects.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Reclassification of tumours based on the molecular drivers to enable personalised/precision medicine with existing therapies and facilitate the discovery and development of new agents as mono-therapies and rational drug combinations.

- Identification of new molecular signatures which play a key role in driving tumour formation and are accessible as new targets for new drug development and/or to inform rational combination therapy. Integration of genetic analysis and tumour biology with bioinformatics and systems biology approaches to identify novel targets. Validated pharmacologically clinically where possible and *in vitro* and *in vivo* in animal models in order to accelerate drug development and reduce its failure rate.
- High quality biomarker assays able to support early prediction of disease, diagnosis, patient stratification and treatment effects to inform internal decision making.
- Host-related biomarkers that may identify patients at risk for adverse reactions during treatment, and biomarkers and/or models able to predict intrinsic or acquired resistance and long-term side-effects of new medicines. Validation of at least one mechanism-based functional imaging biomarker across tumor types.
- Better understanding of the relationship, role and interaction of histology-based (lung cancer, breast cancer, kidney etc) and molecular-based (BRAF inhibitor, etc) tumour types and agree the standard of evidence that would be required to extend use of new medicines into other histologies in patients with the same mutation.

Axis 2: Adoption of innovative clinical trial paradigms

- Development of markers of unwanted side effects with sufficient sensitivity and accuracy to support benefit/risk assessment in small numbers of patients (stratified medicine approach) with a focus on developing patient-centered outcome measures that truly reflect the benefit of new medicines to the patient as well as regulators and payers.
- Validate progression as a surrogate marker and analyze overall survival using methods that attempt to adjust for unavoidable confounding. In addition, agree (between regulators, payers and industry) acceptable primary endpoint criteria for oncology trials that allow development to proceed in cases where overall survival is not a feasible endpoint
- Better understanding of how the individual patient assesses the benefit/risk equation.
- Where appropriate, accelerate access to new drug and drug combinations through implementing the new MAPP initiative being piloted by the EMA, while continuing to gather benefit/risk an effectiveness/risk information
- Validated statistical methods for delivering high quality results from post-marketing clinical trial and patient-centred community data
- Continue discussions regarding the harmonization of trial procedures across Europe. Harmonization may include technical considerations, for example, uniform data collection procedures and data formats for post-marketing data, thus removing barriers to relevant research.
- Establish collaborative multicenter screening platforms that deliver high quality and reliable marker data that can identify the patient populations with suitable molecular and clinical phenotype required to test new medicines increasing efficiency of recruitment.

Axis 4: Patient tailored adherence programmes

- Build on the outcomes of the PROTECT project to communicate the state of science and benefit/risk of new medicines to the (newly diagnosed) patient in a common language, with correct information.
- Develop pre-emptive approaches which integrate prevention, early detection, genetic susceptibility, lifestyle changes or by chemoprevention and therapeutic interventions.
- Establish of continuous patient screening strategies coupled with early clinical trials
- Identification of relevant premalignant and early malignant lesions is an important field now made possible by current advances in biomarker research. In early lesions biological and genetic complexity is usually limited. Different types of chemoprevention are already in place in the cancer area and this represent a promising field with potentially major impact.

Impact on R&D/public partners and society

For R&D:

- Tools and capabilities required to support precision medicine approaches, with the associated regulatory framework required to accelerate patient access.

For healthcare providers:

- Better early detection and management of disease reducing overall cost of healthcare

For Citizens/Patients:

- New therapeutic options tailored to tumour type, lifestyle and genetic susceptibility.

6.11. Rare/Orphan Diseases

Societal impact of rare diseases

Delivering effective treatments for patients suffering from rare diseases has been described as one of the major global health challenges for the 21st century. Although, by definition, individual patient numbers for a defined disease are low (prevalence limit set at <1 in 2000 in the EU, for example), the sheer number of rare diseases (>7000) means that collectively an estimated 250 million people worldwide are affected by a rare disease, comprising approximately 30 million in the EU and 25 million in the US. In terms of unmet need, the position is undeniable: fewer than 10% of rare disease patients receive treatment and only 1% are managed using an approved treatment in EU; 30% of babies born with a rare disease will not survive their first birthday. Furthermore, the impact of rare diseases often extends well beyond the patient and immediate carers; for example 60% of families affected by a rare disease have a lower income than average.

The challenges to the delivery of rare disease medicines are many. Individual disease patient numbers are low, experts in each condition are few and patients are usually geographically widely dispersed. Patients are often misdiagnosed and, historically, there has been limited understanding of the molecular basis of the disease. Patient populations may be heterogeneous within the same disease even when the disease is monogenic, and in general the natural history of many rare diseases is not well-described. As a result, traditional trial designs may be inappropriate or simply not feasible, the tools to measure clinical response to therapy may be lacking, and the relative costs of development (compared to non-rare disease treatments) are high.

The net result has been that research into treatments for rare diseases has been limited to a small number of biotechnology companies and academic champions, often funded through charitable grants. Notwithstanding these clear challenges, the benefits of rare disease research are many and are not confined to rare disease patients. The pathways of disease that are present in some rare disease conditions are often enabling in illustrating similar pathways that are present in more common diseases. For instance recent research into the role of α -synuclein in both Gaucher and Parkinson's disease pathways has indicated some commonalities of pathogenesis. In addition, a natural marriage exists between new molecular therapeutic platforms and rare disease programs: for decades research in rare diseases has been pioneering by addressing those challenges that the emerging field of precision medicine is now discovering.

The need for Public Private Collaboration

The field of rare diseases research is characterised perhaps more than any other by academic champions focusing research activity on individual rare diseases. Furthermore, the economics of drug development in rare diseases mitigates against individual companies undertaking long-term, costly research to develop natural history databases or potentially complex, validated patient reported outcomes. It is also recognised that rare disease research and development is very much an equal partnership between commercial organisations, academic groups and patient organisations, and there is therefore great need to find ways to facilitate co-operation between these stakeholders; in addition, input from regulatory authorities and payers is crucial to ensure that any research and development activity in rare diseases leads to an approvable medicine with recognised value. At present, within the EU policy context for Rare Diseases, such collaboration would certainly be facilitated through the research and care infrastructures that the EU is putting in place at the national and supranational level (the European Networks of Centre of Expertise for Rare Diseases).

Collaboration with other global, European and national initiatives

It is also noteworthy that The International Rare Disease Research Consortium (IRDiRC), which was launched in 2011, already supports projects and collaborations expected to deliver 200 new orphan medicinal products to market by 2020 and to provide diagnostic tools for all rare diseases; thus there is clear scope to align and create synergies between IRDiRC and IMI to translate whatever finding into validated novel treatment approaches, and allow access for all involved participants to the discoveries and development platforms generated by each of the two initiatives.

Nature of research to be conducted under IMI2: Alignment with research axis

Axis 1: Target validation and biomarker development

- Explore and characterise the molecular basis of selected rare diseases (for example by using techniques such as whole genome sequencing and other “-omics” approaches), to allow a clearer understanding of the underlying pathophysiology and tractability for pharmacological intervention (including non-traditional approaches such as cellular and gene therapies).
- Develop effective methods to diagnose pathologies at an early stage and identify prognostic factors for disease severity or specific organ involvement to define relevant subpopulations and/or to understand the timing for intervention in individual patients.
- Determine and describe the natural history of selected rare diseases, including the use of disease registries, to allow a clearer understanding of the unmet needs and to provide a basis for understanding the likely benefits of therapeutic interventions
 - Support translational research to increase the translation of disease knowledge into drug development and evaluation of relevant rare disease animal models, pre-clinical and clinical biomarkers that can be used to predict both efficacy and safety in patient populations.
 - Development of tools to evaluate long-term safety of treatments for rare diseases, including patient registries
 - Rare Diseases are in general chronic and progressive and early interventions are required to slow or stop the manifestation and progression of the associated debilitating symptoms.
 - Support the development of predictive and validated pre-clinical *in vitro* and animal models; for specific rare diseases.
 - A better understanding of the molecular basis of the disease and of its progression should enable the identification and validation of diagnostic tests, biomarkers and

surrogate end-points that would allow a faster development of therapeutic interventions, thus accelerating access to impactful products.

- Develop novel tools for evaluating the disease and the impact of therapeutic intervention (for example, novel imaging techniques).
- Support the widespread development of tools to evaluate risks and benefits of rare disease treatments, for example databases and patient registries; facilitate where feasible the harmonisation of patient registries and biobanks for rare diseases.

Axis 2: Adoption of innovative clinical trial paradigms

- Develop novel methods for understanding the benefits and risks in rare disease patient populations that accommodate the increased uncertainties associated with sparse data.
- Evaluation of novel clinical trial designs and related novel (non-traditional) statistical methodologies that permit demonstration of efficacy and safety of new treatments in rare diseases with low patient numbers, of sufficient robustness to permit regulatory approval.
- Development of novel validated instruments to measure patient reported outcomes that can fully reflect the impact of the specified disease on the patient, and accurately measure the benefits and adverse effects of novel treatments.
- Support research on the development of newborn screening in order to improve access to medicines for selected rare diseases where it has been shown that early detection improves the clinical outcome for a patient.
- Build a regulatory framework (EU; global) that is receptive to innovative approaches to drug development in rare diseases, and which has in place appropriate guidance and legislation (e.g., Clinical Trials Directive) that is adopted to, and which can accommodate, the specific challenges of drug development in rare diseases.

Axis3: Innovative Medicines

- Support research and provide where feasible incentives to leverage existing knowledge and optimise the use of existing drugs (e.g., innovative delivery systems and drug repurposing).

Axis 4: Patient tailored adherence programmes

- Reflect on economic models to stimulate improvement in standard of care (e.g., patient convenience, combination of therapies, different dosing, etc).
- Explore methods to provide easy access to available health care for patients, regardless of where they live (e.g., home therapy, distance monitoring, etc).
- Support the development of education and training programs for physicians, biologists and other related specialities interested in rare diseases, to improve the delivery of high quality diagnosis and care to patients with rare diseases.
- Develop tools and methods to allow a holistic understanding of the value of treatments for rare diseases and foster through appropriate mechanisms collaboration between regulatory authorities, patient groups and industry to improve the efficient use of orphan medicinal products.
- Develop specific HTA frameworks that are adapted to the type and quality of evidence that is feasible to generate in rare diseases; investigate how to include societal and patient preference in the decision making; develop social science methods to include patient narratives/stories in the therapeutic evaluation.
- Development of a 'toolbox' or information centre that provides information, advice, recommendations, guidance, examples that can be used by anyone who wants to set up a disease-specific network for structured collaborative interaction between interested

parties (e.g., pharma, experts, patients, regulators and payers), in order to address any area described in this and the other axes.

Impact on R&D/public partners and society

For R&D:

- Greater depth of understanding of selected diseases, moving away from a characterisation based solely on phenotype, and incorporating a detailed knowledge of genetic, molecular and pathophysiological mechanisms.
- An improved regulatory framework for the approval of medicines in rare diseases

For healthcare providers:

- Effective treatments for patients with rare diseases.

For Citizens/Patients:

- Effective treatments for patients with rare diseases.

6.12. Vaccines

Excellence in Vaccines R&D

Vaccination is one of the most valuable and cost effective public health measures to prevent and control the spread of viral/bacterial infectious diseases responsible for high mortality and morbidity, saving at least three million lives every year globally. Despite the outstanding progress, a significant number of infectious diseases and chronic disorders are still not preventable by vaccination and remain a major cause of death and morbidity worldwide. While the SRA attempts to capture the major activities required to advance Vaccine therapeutics, a more extensive overview can be found in the recent review published by Vaccines Europe^{xxviii}.

Furthermore, reduced childhood mortality, increased longevity and changing birth rates are dramatically changing demographics in Europe and around the world. Populations are facing increasing challenges from ageing, emerging health threats such as healthcare-associated infections and antimicrobial resistance, high chronic disease incidence, low levels of prevention awareness, as well as suboptimal uptake of existing cost-effective vaccines across different stages of life, particularly for adults and the elderly population.

With these changes comes the need to extend the vision of vaccination from early life and childhood alone to the whole life span and from prevention to prevention and treatment. The resulting research & development on vaccines need to address the changing risks and immunological characteristics of this life span. This requires innovative solutions to understand and measure the immune system maturation, and tackle emerging/unmet medical needs. Research is also needed to better understand drivers underpinning inconsistent utilisation of available immunisation measures as hesitant behaviours increase and undermine individual and societal public health and exacerbate challenges to maintain healthcare systems financially sustainable.

A significant number of infectious diseases and chronic disorders is still not preventable by vaccination such as HIV, tuberculosis, malaria, healthcare associated infections (HAIs), cytomegalovirus (CMV), and respiratory syncytial virus (RSV) for which new generation vaccines are needed. Advancement in the fields of genomics, immunology, microbiology, formulation and antigen optimisation could allow the design of new generation vaccines that are potentially more efficacious than traditional approaches. Novel technologies such as adjuvants (including immunomodulators and molecular targeting), new vectors and new devices can also enable effective vaccines for difficult target populations such as newborns, elderly and the immune-compromised and could help

developing effective therapeutic vaccines targeting not only infectious diseases but also cancer and other chronic disorders (therapeutic vaccines are also included in therapeutic topics of section 8).

The need for Public Private Collaboration

Innovation is driven by both the requirement to answer unmet needs and by new discoveries in fundamental science. An important factor for the success of the human immunology approach to improved vaccines is the integration of centres of excellence in immunology, genetics, bioinformatics and other fundamental disciplines making up the meta-discipline of vaccinology. Many of the most advanced laboratories working in these fields are in the public sector and located in Europe. Europe is thus very well positioned to be competitive in the field of human immunology with a potential impact not only on vaccine development but also more broadly on medical interventions based on immunotherapy. Vaccine companies in Europe are world leaders in the complementary expertise areas of antigen production, formulation and clinical development. Combining these skill sets through the PPP will greatly increase Europe's ability to lead vaccine R&D towards 2020. In addition, the public private collaboration is necessary to help inform discussions to empower the regulatory authorities to develop new regulatory guidance and allow critical mass, expertise and resources to be maximized in pursuit of common societal goals and for the development of sustainable models for all stakeholders encouraging sustained delivery of innovative solutions.

Collectively, individual organisations and investigators have experience of significant value in the use of *in vitro* and *in vivo* models in drug discovery and development. However, the relative predictive capacity of any given model may often vary significantly, driven by subtle differences in the experimental paradigms utilised between investigators and also the disease mechanisms under investigation. In order to drive change in the way pre-clinical models are used within drug discovery a multi-disciplinary approach that brings together a wide spectrum of expertise such as toxicology, physiology, computer modelling, metabolism and systems biology. Critical to success will be to create a fully integrated effort that places the model and the modeller at its core. Access to a wide range of relevant data from animal, clinical and *in vitro* systems will be essential to help guide any model-building approaches. Furthermore, the huge volumes of data generated by the new '-omics' methods may have an important role to play in driving the development of models that can explain inter-patient variability. Indeed, the integration and analysis of such data may require expertise from disciplines beyond those hitherto involved in the life sciences. Such a broad spectrum can only be achieved through a combination of public and private efforts that would also involve the pooling of data and resources.

Collaboration with other global, European and national initiatives

In the field of Vaccines a number of these large research infrastructures already exist such as CIMT/CIC (T-cell Immunity), and EC-funded OPTIMALVAC/EMVDA (Malaria Vaccines) and TRANSVAC (vaccines in general). This provides an excellent opportunity to drive collaboration between these existing initiatives, bringing together industry and public research organisations, maximising synergies the benefits of which could be even further enhanced by linking to other European infrastructures such as Biobanks and IT infrastructures. IMI2 would represent a new but needed collaborative initiative in vaccine R&D which could have a significant impact on reducing the costs of vaccine development and on increasing the speed at which new vaccines would be available to the patients. Due to its pre-competitive nature and by being disease-overarching, apart from focusing on European healthcare priorities IMI2 would also allow to support the development of vaccines against neglected, poverty-related diseases and would thereby be a project offering a high level of shared value.

Nature of research to be conducted under IMI2: Alignment with research axis

- Develop well established and qualified biobanks stored in good conditions, with well clinically annotated information, of human blood, tissue, as well as stools and urine samples as well as comprehensive parasitic, bacterial, fungal and viral strain collections will be key drivers of success for the development of new vaccines. Although these needs are well recognized, there are only a handful of well-characterized biobanks in the field of infectious disease, worldwide.
- Establish integrated databases and additional surveillance systems to identify the burden of infectious and non-infectious diseases in different populations and across countries, collect and collate data on new pathogens and all relevant clinical presentations (incl. through the development of appropriate eHealth tools and applications, thereby generating spin-off opportunities and benefit beyond vaccination and healthcare)
- To establish a Vaccines research network in order to drive:
 - joint qualification of assays and technologies followed by, harmonisation and possible standardisation of assays used to determine the benefit/risk profile of new Vaccines.
 - the development of a platform to allow investigators to search for biomarkers through the aggregation of critical mass of infrastructures such as clinical trials, molecular analysis tools and bioinformatics.

Axis 1: Target validation and biomarker development

- Enhance understanding of the immunological mechanisms and host–pathogen and host–vaccine interactions to enable improvements in the design of both preventive and therapeutic vaccines
- Identify novel biomarkers for vaccine efficacy and safety through systems biology approaches, enabling the screening of multiple candidate vaccines in pre-clinical and early clinical trials to reduce development times and costs
- Improve the profiling of immune responses to infection and to vaccination in different age groups, identifying novel correlates of protection against infectious diseases and possibly other non-infectious conditions

Axis3: Innovative Medicines

- Induction of appropriate responses to vaccination, introducing novel vaccines, adjuvants and delivery systems
- Advances in pharmaceutical development which support the conversion of complex and expensive biological processes into practical, cost effective manufacturing systems to lead to significant cost savings that benefit the industry, healthcare systems and society

Axis 4: Patient tailored adherence programmes

- Investment in the identification of evidence-based and innovative pathways to improve adherence and compliance to national programmes through improved understanding of factors impacting and underpinning hesitant behavior towards vaccines and vaccination
- Identify and describe hurdles to current industry investment and drivers for a sustainable commercial model valuing innovation and facilitating fast access to innovative vaccines
- Increase investment in understanding the link between human and veterinary research, which could generate innovative ideas for the rapid diagnosis of diseases, the set-up of new diagnostics for personalised human vaccines, and novel delivery approaches capable of maximising efficacy, reducing side effects and possibly inducing other types of immunity (e.g. mucosal)
- Monitor and measure impact of existing vaccines in the reduction and promotion of a more rational use of antimicrobial agents and continue to generate data on the value of comprehensive use of current vaccines

Impact on R&D/public partners and society

For R&D:

- Optimised/harmonised methods to collect, collate, share and analyse medico-socio-economic data on infectious and non-infectious diseases
- Delivery of better vaccines in response to target group-specific needs, particularly the elderly, pregnant women (incl. their role in neonatal immunisation), infant and non-responder subjects
- Improved durability of protective measures and new understanding of their mode of action
- Shortened development times and costs through reduced late stage clinical trials failures and earlier prediction of vaccine efficacy and safety
- Validated alternatives to animal testing and models
- Design of new types of prophylactic and therapeutic vaccines
- Better vaccine design through reverse genetics or synthetic biology and through the ability to steer the immune response using novel Immunomodulators, delivery systems and devices
- Cost-effective manufacturing systems with significant cost savings that benefit industry, healthcare systems and society
- Pathways to inform discussion on regulatory guidance

For healthcare providers:

- Rational design of clinically meaningful vaccines capable of responding to priority public health and disease challenges
- Strengthened coordination across sectors and stakeholders, resulting in improved structures and governance for joint action to tackle societal challenges
- Better understanding of the benefit/risk of new vaccines

For Citizens/Patients:

- Better preventive vaccines in response to specific population segments' needs which are currently unable to fully benefit from vaccination (e.g. due to immune senescence)
- Accelerated development and access to novel therapeutic vaccines
- More comprehensive and evidence-based vaccination schemes for an expanded range of diseases leading to better community health and herd immunity
- Identification of delivery routes and systems alternative to injections
- Better understanding of drivers underpinning hesitant behaviours and impacting adherence

7. Translating research to tangible benefits for European and Global Healthcare infrastructures

As outlined above, the challenges facing healthcare in Europe or indeed across the world cannot be addressed by any one sector alone. In order to create an efficient and sustainable healthcare system which is able to provide all citizens and patients with equal access to the best treatment options, researchers, drug developers, regulators, HTA agencies and healthcare providers must all work together. IMI proves that the unique and neutral set up of a European PPP combines all features necessary for achieving such objectives and continuing with this PPP framework will play an integral role in accelerating the delivery of healthcare solutions.

A detailed impact assessment understanding the economic value of the PPP to Europe has been conducted by the European Commission and lies outside of the scope of this document. However in general terms, the PPP will focus on conducting the research required to drive the delivery of new innovative prevention and treatment approaches, from their discovery through to their delivery to the patient.

Direct outputs of the PPP will therefore include:

- 1) New tools and methods, accepted by the regulatory authorities to increase the productivity of R&D from vaccine or drug discovery to its delivery to the citizen/patient thus decreasing the cost of drug development and increasing patient access
- 2) New manufacturing processes to cut development costs and reduce carbon emissions
- 3) Discovery and development of new therapeutic approaches with accompanying optimised delivery and patient adherence systems
- 4) New technology, or novel use of existing technology, to provide tools for patients and providers to more thoroughly monitor and manage disease and to provide immediate feedback on disease progression and the impact of interventions
- 5) Provide training and infrastructure needs to support effective implementation of the research outcomes
- 6) Drive widespread translation of the resulting and existing knowledge into innovative, effective products, strategies, interventions and services through long term and coordinated co-operation between all players in the healthcare ecosystem
- 7) Cooperation between Europe and the rest of the world to ensure synergies are maximised and resources used effectively.

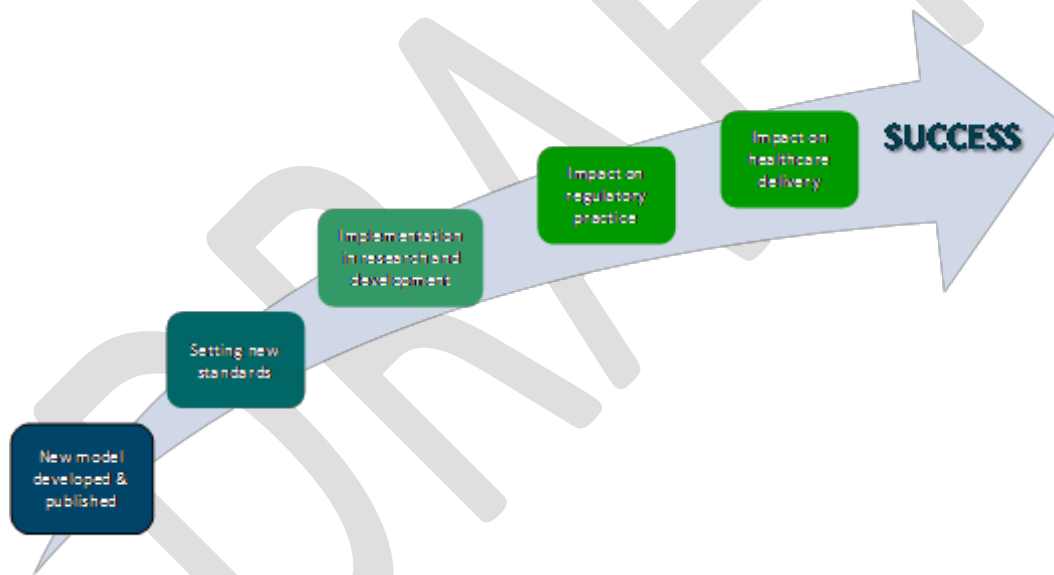


Fig 10: Impact of the PPP on Europe and globally. The PPP will focus on conducting the research required to drive the delivery of new innovative prevention and treatment approaches, from their discovery through to their delivery to the patient.



Figure 11 : Impact/value added of the IMI2 deliverables

The PPP will strengthen and create networks of excellence which will create ecosystem/conditions for further investments and collaborations in Europe to take advantage of the evolving model towards externalisation of R&D/open collaboration and contribute to putting Europe in a leadership position in certain critical biomedical research areas. Vibrant medicines discovery hubs will be established across Europe with the resources, skills and expertise to generate and deliver new development candidates in areas with high societal impact and poor levels of investment at present.

In addition, IMI has demonstrated its ability to generate high quality jobs. Continuing PPP with an ambitious agenda and close to market activities will see more jobs maintained and created within and outside industry. It is estimated that one direct job in the pharmaceutical sector generates three to four indirect jobs upstream and downstream.

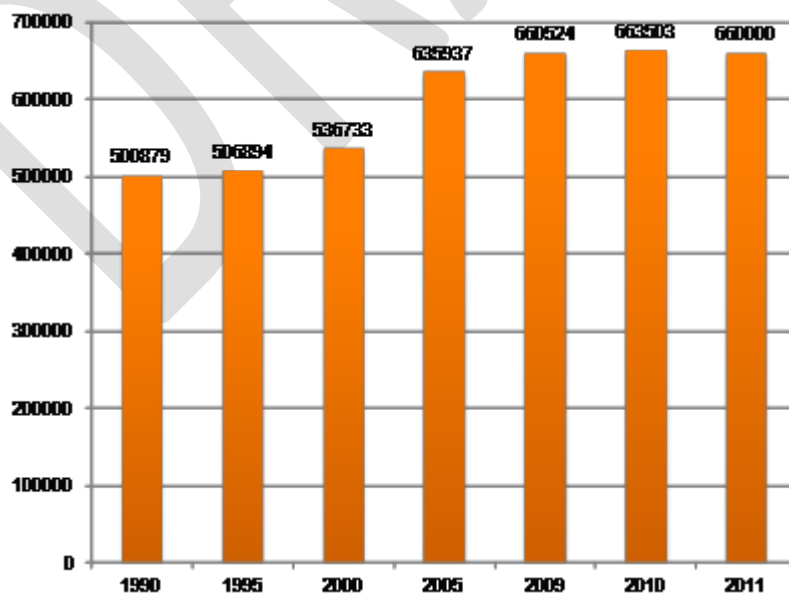


Fig 11: European Employment in the pharmaceutical Industry. EFPIA Companies alone directly employ 660,000 people in Europe, of this, 113,000 jobs are in R&D. It is estimated that one direct job

in the pharmaceutical sector generates three to four indirect high-value and high-productive jobs upstream and downstream. Source: EFPIA Key Data 2012.

8. Impact of IMI2 on the use of animals in research and development

Many of the medical advances of the past would not have happened without animal research. For well over a century, research on rats, dogs and pigs has helped to find new treatments for conditions as diverse as heart disease, infections, brain disorders and arthritis.

The advances in studies of the human genome, breakthroughs in high-speed information processing, and the promise of nanotechnology highlighted elsewhere in this SRA hold out the prospect of developing new or improved medicines with less dependence on animal models. However, knowledge of physiological processes and mechanisms of disease development are currently insufficient to enable us to depend totally on in vitro and/or in silico models. Many questions can still only be answered by research that makes use of animals. Thus studies in animals will continue to be an essential part of the work conducted under this SRA.

There may even be parts of the plan outlined under this SRA which may require new types of animal models to be developed or more animal studies to be conducted in the short term (e.g. evaluation of the efficacy and safety of new delivery systems; innovative methodology to evaluate treatment effects - see section on CVD)

However, as knowledge accumulates as a result of concentration on better understanding of the underlying causes of human disease and other research activities outlined in this SRA, there will be an increasing number of opportunities to either replace existing animal models with non animal alternatives, to adjust the animal model so that it becomes more predictive of clinical outcomes, require fewer animals to evaluate, or uses a more humane endpoint (e.g. biomarker rather than development of clinical disease). This together with continuing efforts of researchers across the EU to implement 3Rs as illustrated in EFPIA 3Rs report and as mandated by EU Directive 2010/63 will result in more and more of the medicine discovery and development process being progressed without the need for animal research.

Where animal studies continue to be essential to progressing the scientific imperatives of this biomedical research PPP, there will be a requirement for excellence in study design and execution ensuring that animal use is kept to a minimum, and high standards of care and welfare to be practiced and this will be monitored throughout the PPP.

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