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

Consultation Paper: Outline Strategic Research Agenda for biomedical research public private partnership under Horizon 2020

Please note that the purpose of this document is to gather Stakeholder input, to be used during the preparation of the full SRA.

25th March 2013
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Stakeholder Consultations

This document provides an overview of the vision and the major research priorities being proposed for the new biomedical research PPP to be funded under Horizon 2020. Stakeholders are invited to provide input to the current document which will then be used to form the basis of the first draft of the SRA expected in May 2013. Please focus any suggestions for input on content as the final wording will be developed once all input has been received. The final version is expected to be approved and launched towards the end of 2013.

Stakeholders are invited to provide feedback on the following questions:
1) The vision for the PPP is that it will address, in a collaborative and multidisciplinary way, the science, technology, regulatory, healthcare, social and other challenges that currently delay or prevent citizen/patient access to most effective and efficient diagnostics, prevention and treatment options.

Do you agree with this vision? Are there any additional opportunities to address key social and healthcare challenges that you feel should be considered for implementation through this PPP?

2) Misdiagnosis has profound impact, on one hand treatments are offered to patients which often have little chance of providing benefit while on the other hand patients are being denied access to potentially beneficial novel and approved agents due to misclassification to a different “disease class”.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address this need?

3) Sequencing of the human genome has led to a large number of associations between disease and genes. However, the research community has been slow to translate these associations into new targets for drug discovery.

From your perspective how do you think this translation could be enhanced? Do you think the current proposal will adequately address this need?

4) Many compounds in clinical development fail because of adverse effects that were not predicted by preclinical studies or due to lack of efficacy that failed to translate from pre-clinical models to the clinical setting.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address the need to better predict pre-clinical and clinical safety and efficacy?

5) To develop new and innovative medicines, novel methodologies for evaluating treatment effects are essential to support informed decision making at each stage of the drug discovery and development process. Existing methodologies such as imaging and other biomarkers are not sufficiently developed or validated to discharge risk and ensure better and faster development of new treatments, especially where disease modification and prevention are the treatment objectives.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address this need?

6) 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 B/R.

What more do you think needs to be done to improve patient engagement in the assessment of the benefit/risk of medicines?

7) 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 of new medicines. The inherent uncertainty (which may be different from country to country, as standards of care vary) often results in wide variability in access to medicines between countries due to variability in relevance of evidence and different attitudes to reimbursement in conditions of uncertainty.

The PPP aims to address this challenge – are there any additional activities that you feel should be included as objectives for the PPP?

8) The drive towards individualized applications in general and personalized medicine in particular will require further improvements, increased efficiency and flexibility, and innovation into the pharmaceutical supply chain.

From your perspective what aspects of drug delivery and manufacturing do you feel require most attention in order to make significant advances in this field? Do you think the current proposal will adequately address this need?

9) From your perspective do you agree that the areas outlined below represent major healthcare challenges for Europe? Do you think the current proposal will adequately address the needs in each of these? Are there additional activities that you feel are essential to deliver effective healthcare solutions for the treatment of the diseases listed below?

What are the main treatment gaps or unmet needs in the development of medicines in your therapeutic area?

Are there any barriers in the delivery and available of innovative treatments (lack of screening/diagnostics, reimbursement, lack of single medical file, patient care, adapted infrastructure, stigmatism, etc.)?

10) Stakeholders are invited to indentify the key research areas that they feel should be the focus of efforts in the field of Oncology.

11) Stakeholders are invited to indentify the key research areas that they feel should be the focus of efforts in the field of Rare/Orphan diseases.

12) In your opinion are impact measures presented appropriate and achievable based on the overarching objectives of the PPP? Are there additional measures that you feel should be included?
Executive summary

Building on the success and learnings from the Innovative Medicines Initiative (IMI), the proposed new biomedical research public private partnership (PPP) aims to translate cutting edge science and technology into innovative healthcare solutions which address priority societal challenges across Europe.

The new generation biomedical research PPP proposed between the pharmaceutical industry and the EU (represented by the European Commission) will focus on research and innovation that address key elements of the EU research priorities as set out in several documents relating to Horizon 2020: Understanding the determinants of health, improving health promotion and disease prevention; Environmental, behavioural (including lifestyle), socio-economic and genetic factors, in their broadest sense; Developing effective screening programmes and improving the assessment of disease susceptibility, thus improving surveillance and preparedness; Understanding, preventing and treating disease; Implementing evidence-based vaccination schemes for an expanded range of diseases; Supporting improvement and development of cross-cutting technologies for drugs and vaccines; Improving access to medicines, the quality of treatment and the cost for a more sustainable health system; Contributing to increase European employment and economic growth.

Taking diseases and medicines of priority for European society as a point of departure, the PPP will address, in a collaborative and multidisciplinary way, science, technology, regulatory, healthcare, social and other challenges that currently delay or prevent citizen/patient access to most effective and efficient diagnostics, prevention and treatment options. The partnership will drive large scale innovative collaborative consortia and set up pan-European networks of excellence to create specialised clusters able to attract world leading scientists. At the same time the PPP will also contribute to maintaining or reinvigorating research and activity in areas of high societal interest which currently suffer from disinvestment globally.

The proposed Strategic Research Agenda (SRA) is three-dimensional: 1) key research priorities, 2) industry priorities, and 3) societal healthcare priorities. Specifically the PPP will focus on seven key research axes which together address key regulatory and healthcare delivery challenges, technological and scientific challenges and key European health priorities.

![Fig 1: Summary of the research priorities to be addressed by the PPP](image)

Through creation of new tools and methodologies, new treatment and prevention options, and through enhancing clinical investigators networks, the PPP will also contribute to maintaining or reinvigorating industrial research and activity in areas of high societal interest that suffer from
disinvestment, improving competitiveness of the biopharmaceutical sector in Europe and creating employment opportunities.

1. Introduction and Background

1.1. The Scientific Research Agenda (SRA)

This current document provides an outline proposal for the SRA which will underpin a new biomedical research public-private partnership to be funded under H2020. The purpose of the SRA is to define the areas of research to be addressed during the lifetime of PPP. Learning from the IMI experience, it is important that the Strategic Research Agenda 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 scientific advances are made. It is also be of utmost importance to identify and coordinate activities with EU and national research programmes (as well as international initiatives) to ensure complementarities and best use of resources.

The SRA development is driven by EFPIA/ Vaccines Europe in partnership with the EC and key stakeholders from across the public and private research and development community. The current version of the proposed SRA is based on the integration of input from industry partners and several scientific and patient organizations conducted between June 2012 and January 2013.

Broader stakeholder consultation is now sought, the output of which will be considered during the drafting of the full SRA due to be submitted to the European Commission in mid 2013. Finalization of the SRA is expected at the end of 2013.

1.2. The challenges that underpin the public private partnership (PPP)

The following challenges and opportunities for the society and the industry underpin the need for large scale PPPs and the SRA described in next sections:

- An increasing disease and disability burden in the context of an aging population places increasing demands on health and care sectors. If effective health and care are to be maintained, efforts are required to accelerate the development of new prevention and treatment options, to identify and support the dissemination of best practice in the healthcare sector, and to support integrated care and the uptake of technological, organizational and social innovations.
- In parallel to the increased healthcare demand, the late stage failures/attrition is significantly increasing the cost of developing new vaccines and treatment modalities. This is further exacerbated by increasing regulatory demand, suboptimal connection with payers and the lack of appropriate pull mechanisms needed to drive investment in innovation.
- In some fields the regulatory and healthcare systems are not ready for new science outputs as they are based on symptomatic approach to disease management rather than disease prevention or slowing.
- The current R&D model is failing and requires investment in fundamental research from all sectors to provide the scientific advances required to decrease attrition and drive necessary change in the regulatory and healthcare systems. A PPP framework will facilitate this cross stakeholder collaboration and support large pre-competitive collaborations which is essential for success.
- Since the inception of IMI similar initiatives are being created in other geographies competing of attention of companies whose resources become more limited.
At the same time, on the opportunity side,

- Europe has a strong and evolving science base which makes it possible to rapidly build centres and networks of excellence in niche areas
- Europe offers very heterogeneous population and healthcare systems
- Great new science and unique infrastructures have been established in various IMI projects and offer the possibility to exploit them in further projects/programmes
- IMI have demonstrated that a PPP directly creates jobs and further create value from new science that can be commercialized and further add value to EU

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

To be successful in addressing the challenges outlined above and delivering effective and sustainable healthcare solutions for society, an integrated and collaborative approach is required. This new generation PPP will take as a point of departure shared interest of patients, public health systems, publicly-funded entities, industry and society. In broad terms by implementing the proposed SRA, the new biomedical PPP 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 through:

- Addressing R&D productivity and scientific bottlenecks in areas of societal interest and unmet medical need
- Focussing on major healthcare challenges in society (i.e. where the burden of disease is the highest, not just of primary care but on the entire social security and labour system).
- Conducting collaborative research to prevent, manage, treat and cure disease, disability and reduced functionality
- Addressing health issues related to the aging population

All of these activities will be undertaken in such a way as to provide support throughout the research and innovation cycle, strengthening the competitiveness of the European-based industries and creating new market opportunities.

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 the PPP and projects objectives
- Collaboration with academic scientists from all areas of science, including emerging and non life sciences and technologies
- Collaboration with regulators, 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.

Stakeholder Consultation
1) The vision for the PPP is that it will address, in a collaborative and multidisciplinary way, the science, technology, regulatory, healthcare, social and other challenges that currently delay or prevent citizen/patient access to most effective and efficient diagnostics, prevention and
1.4. The impact of the new PPP on Europe

This initiative will help to directly implement key objectives of the Europe 2020 and Horizon 2020 strategies. It will also directly support implementation of EU policies amongst others in the field of:

- Active and healthy ageing
- Mental health
- Antimicrobial resistance
- Pharmacovigilance/patient safety
- Good clinical practice

- Large scale PPPs such as IMI today and future PPPs are an essential element of moving beyond solving technology issues to addressing all facets of productivity challenges, including scientific, regulatory and healthcare delivery challenges. IMI proves that the unique and neutral set up of a European PPP combines all features necessary for achieving such objectives.
- 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.
- The PPP will establish vibrant medicines discovery hubs across Europe with the resources, skills and expertise to generate and deliver a pipeline of qualified leads and potential new development candidates in areas with high societal impact and poor levels of investment at present.
- 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.
- The PPP will address global challenges, but involvement of EU regulators and payers, as well as placing R&D activities in Europe will place EU patients at advantage as far as access to new treatments (including in clinical trials) is concerned.

2. Research Objectives of the PPP

The PPP will be implemented through focusing on seven key research axes (as outlined in Figure 1 and described in section 2) across those diseases identified as European healthcare priorities (described in section 3) which together address key:

- Regulatory and healthcare delivery challenges
- Technological and scientific challenges
- Healthcare/grand societal challenges

The seven themes/challenges are of a nature that cannot be addressed by either industry or academia alone or without participation of and constant dialogue with regulators, payers, patients, and public health decision makers. Working in partnership to address these key healthcare challenges will allow the regulatory and healthcare delivery systems to evolve at the same pace as scientific progress and knowledge and to allow real integration of innovation that would lead to more personalised medicines into drug development.
2.1 Seven Axes of Research

2.1.1 Reclassification of disease by molecular means

The opportunity to accelerate drug development and improve healthcare

Classification of disease based on the observational correlation of pathological analysis and clinical syndrome has served prescribing physicians well over past decades. While this has become more efficient as the molecular understanding of disease has improved, it is widely recognized that the system lacks sensitivity for preclinical diagnosis and often specificity in disease leading to treatments being offered which often have little chance of providing benefit to patients due to the heterogeneity of molecular mechanisms resulting in the same “disease class”. Patients are being denied access to potentially beneficial novel and approved agents due to misclassification to a different “disease class” despite a similar aetiological mechanism. This is not only unsatisfactory from a patient health perspective but also has a profound impact on the design of clinical trials. If the mechanism of the drug being tested is only effective in small proportion of disease sufferers, this can lead to the need for large numbers of patients to be included in the trial in order to demonstrate efficacy and also the risk that potentially effective new drugs are abandoned to perceived lack of efficacy. Therefore, overall the influence of disease heterogeneity on both the failure rates and the size of clinical trials is a key component in the rising costs of drug development. As you continue down the development pathway the consequence of this is further evident when considering reimbursement by payers.

The availability of the complete sequence of the human genome and the growing body of ‘-omic’ data sets in health and disease together with the increased access to tissues (dissected with
techniques such as laser capture microscopy), the availability of patients’ electronic medical records in many countries and sophisticated informatics techniques now offer the opportunity to more precisely phenotype heterogeneous disease populations into specific disease subtypes. This redefinition of disease, adding to clinical examination and practice, will provide better information about prognosis and response to treatment as well as supporting the identification of new diagnostic markers, markers of disease progression to increase the efficiency of clinical trial design and decision making as well as new targets for therapeutic intervention.

**Need for PPP:**
There is an urgent need to integrate the latest scientific advances into the taxonomy of human disease. Given the enormity of the task and the impact on all sectors, major collaborations among academic institutions, pharmaceutical and biotechnology companies, regulatory agencies are required to combine their respective expertise in a precompetitive manner to focus efforts on reclassifying those diseases at the core of Europe’s healthcare priorities.

Driving this new era in health care will be rewarded through the ability to develop a personalised medicine approach to optimising treatment paradigms and developing preventive strategies.

**Core Objectives:**
To gain a better understanding of:

- Diseases at the core of Europe’s healthcare priorities;
- The genetic, molecular, immunological, biochemical and environmental determinants of disease and their consequences;
- European and global burdens of diseases and the efficacy of existing medicines and vaccines
- Likely public health trends and prioritization of those diseases/conditions which may pose a very serious threat to global public health in the future; and to
- Validate new classifications and their impact on regulatory endpoints for clinical trials through consultations with relevant stakeholders
- Identify new or alternative targets and potential new biological markers to enhance decision making and increase probability of successful development
- Improve clinical trial design to assess targets for therapeutic and preventive intervention to reduce trial size and cost as well as increase probability of success

**Impact on R&D/public partners and society**

**For R&D: Reclassification of disease by molecular means will:**
- Reduce the complexity and cost of drug development;
- Identify potential new biological markers to enhance decision making and increase success rates of drug and vaccine development (make the drug/vaccine discovery and development process more efficient to bring better medicines faster to patients);
- Identify diagnostic markers and markers of disease progression to support patient stratification and personalised medicine efforts
- Identify new drug targets

**For Patients: Reclassification of disease by molecular means will:**
- Increase the likelihood that patients receive the right therapy and maximise the benefit from medical innovations.

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Aid medical practice with more specific diagnostic tools
Identify disorders earlier when treatment effects have a better chance of succeeding
Enable the development of more molecularly focused i.e. more specific treatments through better understand of the aetiological mechanisms of disease.
Use of more specific clinical trial paradigms for evaluation of new medicines
Better use of results, limit uncertainties and enable earlier decision making

For Society: Reclassification of disease by molecular means will:
- Decrease healthcare costs associated with misdiagnosis

Stakeholder Consultation:

2) Misdiagnosis has profound impact, on one hand treatments are offered to patients which often have little chance of providing benefit while on the other hand patients are being denied access to potentially beneficial novel and approved agents due to misclassification to a different “disease class”.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address this need?

2.1.2 Target identification and validation of disease

The opportunity to accelerate drug development and improve healthcare

Validation of new pioneer targets is required to address unmet medical need and to provide sustainability for the pharmaceutical industry. Sequencing of the human genome has led to a large number of associations between disease and genes. However, the research community has been slow to translate these associations into new targets for drug discovery. The primary reason for our failure to capitalize on the Genomic Era has been a poor track record of success in converting genetic insights into drugs with clinical efficacy. For example, there are many examples where gene silencing (e.g. RNAi) led to a different phenotype than pharmacological inhibition of the same target. There are also diseases for which animal models are not predictive of clinical efficacy or are not relevant for the human disease. Remarkably, the majority of ongoing drug research remains focused on a limited range of protein targets, almost all of which were known prior to the mapping of the genome.

At a time when there is an increased need for innovative medicines, a new initiative is required to support pharmacologic validation of drug targets from the unexplored regions of the human genome in assays predictive of clinical efficacy. Pharmacologic validation is the demonstration that direct modulation of a target protein (e.g. inhibition of activity) by an exogenous agent leads to a phenotype of clinical interest. Unlike genetic methods, pharmacologic validation can be applied to the early stages of target selection through clinical candidate selection and into the clinic; with each successive stage leading to an increase in the confidence of the therapeutic hypothesis. Thus, the generation and publication of pharmacologic validation data will enable the research community to expand the druggable genome and select the best targets for future drug discovery.

Need for PPP:
Pharmacologic validation of new targets is a challenging, resource-intensive effort which draws on multiple lines of expertise. A new call for proposals would aim to improve our collective capacity for pharmacologic target validation. By inviting public and private partners to participate openly, the initiative will dramatically improve the quantity and of quality pharmacologically-validated targets through:

- The increased resource (pooling of research efforts from multiple companies and public partners provides a larger resource base than any single partner could support);
- Complementary institutional knowledge between academia and industry;
- Diversity of thinking (different views, ideas and expertise of multiple partners, both from academia and industry);
- Shared risk across multiple participants;
- Decreased redundancy (the open process will enable partners to avoid working on the same targets using similar approaches).

Preferably, target validation projects should be built on existing initiatives as proposed in several countries (e.g. Centre for Translational Molecular Medicine (CTMM) in the Netherlands; Centres d'Excellence en Médecine Translationelle (CEMT) and Instituts Hospitalo-Universitaires (IHU) in France; European Advanced Translational Research Infrastructure in Medicine (EATRIS)) at the pan-European level, and the PPP currently being revitalized or established at the NIH.5

Core Objectives:
- Provide a framework for collaboration and exchange between private and public partners with a shared goal of discovering innovative medicines;
- Establish vibrant centres across Europe with the resource, skills and expertise to apply pharmacologic validation to unexplored targets from the human genome;
- Implement mechanisms to translate the findings of these centres into new drug discovery efforts.
- Improve the translation from pre-clinical to clinical development by focusing on translation of pharmacology (in addition to efficacy) from pre-clinical to clinical 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.
- Characterisation of the biology of novel genes/proteins in a more systemic way to understand the role of a given target in the context of the physiology and of the pathology.
- Translational medicine expertise with complementary approaches around patients.
- Exchange between disciplines and stimulation of innovation for the benefit of the patients, and public health care system

Impact on R&D/public partners and society

For R&D: Improved target identification and validation will:
- Create a sustainable infrastructure is created for pharmacologic target validation of the unexplored genome,
  a. with or without use of small molecules, and
  b. utilizing human tissues or cells in place of animal models
- Translation of discoveries into clinical-stage drug discovery programs with increased probability of success, which may include

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5 http://ppp.od.nih.gov/pppinfo/examples.asp
c. the repurposing of known drugs or partner assets, or
d. the creation of new chemical and biological entities optimized for the human disease

For Patients: *Improved target identification and validation will:*
- Generate innovative new medicines for diseases that may have been until now intractable. Due to the improved target validation these new drugs will have an increased probability of success of becoming effective medicines.

For Society: *Improved target identification and validation will:*
- Reduce healthcare costs through generation of effective medicines in a well defined patient population.

### Stakeholder Consultation:

3) Sequencing of the human genome has led to a large number of associations between disease and genes. However, the research community has been slow to translate these associations into new targets for drug discovery.

From your perspective how do you think this translation could be enhanced? Do you think the current proposal will adequately address this need?

### 2.1.3 Predictors of Drug and Vaccine Efficacy and Safety

*The opportunity to improve patient healthcare*

Critical to the development of novel therapeutics is a multi-dimensional strategy of nonclinical modelling aimed at assessing various aspects of a candidate drug from pharmacologic interaction with a molecular target, to pharmacodynamic efficacy in animal models of human disease; understanding pharmacokinetic properties to *in vitro* and *in vivo* identification, characterization and management of potential side effects. The current drug discovery and development paradigm is heavily reliant upon animal models of disease and toxicity that are the subject of much ongoing debate since the findings of this approach have questionable correlation with drug toxicity occurring during treatment of patients. Advances in chemi-informatics, bioinformatics, pharmacology and molecular toxicology in the context of biological systems are now at a point that these tools can be applied to mechanism-based drug/vaccine safety assessment and early prediction of clinical and non-clinical drug/vaccine response. Furthermore, translational safety biomarkers that can predict, detect and monitor vaccine/drug-induced toxicity during clinical studies will allow early identification, assessment and management of those injuries throughout the R&D process. Improving the prediction of the safety and efficacy aspects of compounds are major challenges for the pharmaceutical industry as well as for clinicians performing clinical trials. The availability of reliable and predictive models of human health and disease would have a revolutionary impact on discovery and development of novel preventive and/or therapeutic options.

Many compounds in clinical development fail because of adverse effects that were not predicted by preclinical studies or due to lack of efficacy that failed to translate from pre-clinical models to the clinical setting. The underlying causes of some drug toxicities are now understood at the molecular level (e.g. the hERG ion channel and its link to drug-induced Torsades de Pointes), thus enabling early identification of potential risks so that they can be eliminated during the discovery phases or managed during pre-clinical and clinical development. Developing an understanding of other toxicities would have a dramatic impact on the effectiveness and efficiency of drug and vaccine discovery by making it possible to identify and eliminate potential risks, leading to clinical candidates that have a greater chance of delivering benefit to patients. However, in most other cases, our
knowledge of the molecular mechanisms of toxicology is still relatively limited, even for compounds that have been studied for many years. The challenge is to better understand at the molecular or pathway level why adverse events and side effects occur in humans so that this information can be taken into account during future drug discovery and development. Such an increased understanding will deliver safer, better tolerated medicines to patients. Moreover, such an increase in understanding would lead to lower attrition rates, increase the speed at which new vaccines and drugs are accessible to patients and thus lead to reduced development costs.

Another major problem for many diseases targeted by vaccines is the lack of a clear immunological correlate of protection. It is important to understand the immune response in different target groups (particularly the elders and non-responders) in order to design innovative vaccines that are safe and efficacious. A better understanding of the immune response to natural infections and vaccination could help to identify immunological correlates of protection. New large-scale whole human genome sequencing programmes could allow the identification of genetic variations that could influence the response to vaccination. The identification of these gene targets could help developing novel tools to increase vaccine efficacy in non-responders. Systems biology approaches can be applied to improve understanding of the immune response to infection and to identify novel immunological correlates of protection. Moreover, new human genome programs should help understand the influence of human genetic variations on vaccine response and non-response. Some examples of novel technologies that could be used to study human immunology to improve early efficacy and safety assessment of vaccines are:

- Quantitative gene expression platforms (DNA microarray, Nanostring and RNA sequencing);
- Multi-parameter analyses of blood cell subsets (single cell RT-PCR, CyTOF);
- Deep sequencing of human genome/ genome wide association scans;
- Antibody binding/neutralization assays;
- High throughput B cell repertoire analysis;
- High throughput HLA & TCR sequencing.

**Need for PPP:**
Collectively, individual organizations and investigators have experience of significant value in the use of *in vitro* and *in vivo* models in drug/vaccine discovery and development. However, the relative predictive capacity of any given model may often vary significantly, driven by subtle differences in the experimental paradigms utilized 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.

**Core Objectives:**
- Development of new innovative tools, methods, biomarkers and models for the prediction of safety and efficacy of new drugs
- Enhanced understanding of the complex interplay of factors that lead to both therapeutic benefit and toxicities and side effects
- 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
- To develop novel biomarkers for vaccine efficacy and safety through systems biology approaches, enabling the screening of multiple candidate vaccines in 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
- To conduct genome-wide association scans of response to vaccination
- Validate prospective liabilities, including biophysical analysis to confirm binding, bioinformatics and experimental analysis to build connectivity hypotheses
- Create an informatics infrastructure to support the generation of a publicly available data warehouse(s) where data relating to in vitro and in vivo models can be held and interrogated by the scientific research community as a whole
- To integrate in silico and in vitro methods to develop a generally accepted approach for defining sufficient kinetic/pharmacological/toxicological data in a single species to support regulatory filings which will maintain or improve human safety and reduce animal use.

**Impact on R&D/public partners and society**

For R&D: Better predictors of drug efficacy and safety will lead to:

- A set of validated molecular pathways / targets with a clear link to toxicological end points
- A set of tools (assays, models, safety biomarkers) that can be directly applied in Pharmaceutical research to identify and manage such effects during drug discovery and development
- An integrated platform for the study of toxicological end-points that creates a leading position for the EU across multiple disciplines including omics technologies
- Enhanced understanding of the fundamental biology of drug-induced toxicity
- Open pre-competitive collaboration to derive learnings from our drug development successes and failures in a more integrated way and pool data to eliminate duplication and increase R&D efficiency.
- Validated alternatives to animal use that are qualified for use in drug discovery in areas of efficacy, pharmacokinetics and safety assessment
- Significantly improved models leading to a marked reduction in animal use and increased efficiency in R&D
- Clinically qualified translational safety biomarkers for identification and management of drug-induced toxicity
- Validated quantitative computer models to inform design and progression decisions on compounds
- Enhanced understanding of the complex interplay of factors that lead to both therapeutic benefit and toxicities and side effects
- Informatics infrastructure to support future modelling and research efforts
- Better understanding of the immunological mechanisms of vaccination
- Novel biomarkers to predict vaccine efficacy and duration of protective responses;
- Novel biomarkers to predict vaccine safety
- Identification of novel targets to overcome immune-senescence
- Identification of novel human sequence variants that contribute to the response to vaccination
For Patients: Better predictors of drug efficacy and safety will lead to:

- Medicines for patients that have reduced toxicological and side effect profiles
- A more tailored, individually targeted approach to drug therapy, enabling the most effective medicines to be delivered in the most appropriate dose to patients, based upon their personal characteristics and make-up and thereby maximise the benefit whilst minimizing adverse effects

For Society: Better predictors of drug efficacy and safety will to:

- Increased safety for clinical trial subjects
- Shorter drug/vaccine development timelines and, reduced drug/vaccine candidate failures during development
- Safer medicines and reduced healthcare costs

Stakeholder Consultation

4) Many compounds in clinical development fail because of adverse effects that were not predicted by preclinical studies or due to lack of efficacy that failed to translate from pre-clinical models to the clinical setting.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address the need to better predict pre-clinical and clinical safety issues?

2.1.4 Innovative methodologies to evaluate treatment effect

The opportunity to accelerate drug development and improve healthcare

In the absence of robust biological markers of pharmacology, potential new drugs are generally selected and progressed based on efficacy in pre-clinical models. However, it is now widely accepted that very few pre-clinical models fully translate to the human disease. This leaves an element of uncertainty regarding the selection of predicted efficacious doses for clinical studies, the predicted therapeutic index and indeed proof that modulation of the target in patients will indeed positively alter the disease state. In this situation a molecule is often progressed through the clinical development path up to maximum tolerated doses/maximum receptor occupancy without a confirmation that this is the most pharmacologically active dose range. As a result it is often not until large Phase 3 clinical trials that the efficacy (or indeed lack of efficacy) is confirmed using classical clinical outcome measures.

Trials designed to evaluate clinical outcomes are often of long duration and highly expensive especially where trials are designed to assess disease prevention or modification. It is therefore essential to develop biological endpoints that can inform better decision making throughout the drug discovery process to enable more informed decision making regarding dose selection and progression at each stage of development to enable efforts to be focussed on new drugs with a high probability of success while stopping efforts on those destined to fail, thus preventing patients being exposed unnecessarily to ineffective agents. Furthermore biological endpoints that allow pharmacological assessment in the clinic are essential for the interpretation of clinical trial data. In the event that pharmacology can be demonstrated, but a negative clinical outcome prevails then it can be concluded that modulation of the specific target does not affect disease outcome, rather than it being a limitation of the drug itself. However in the absence of ‘proof of pharmacology’ in the
clinical setting it is impossible to determine if the target selection was wrong or indeed the drug failed to reach sufficient target concentrations.

The move towards the need to conduct clinical trials to assess potentially preventative and disease modifying medicines also drives the need for investment in new methodologies for assessing clinical outcomes. While there are a number of efforts ongoing in this area, many of the technologies available, such as imaging, are not sufficiently validated or qualified for use by the regulatory authorities.

**Need for PPP:**
The complex nature of the challenge presented will require an integrated approach by pre-clinical and clinical scientists, regulators and patient groups in order to develop robust biological endpoints to support early decision making and novel clinical endpoints qualified for use in drug discovery. Methodological development to allow identification of suitable biomarkers, investigation and qualification of markers in the clinical setting will require access to patients as well as to human tissue samples from existing bio-banks. Conducting this research in the framework of a collaborative approach will

- Facilitate an integrated approach combining knowledge and expertise from both academic and industrial scientists ensuring the most innovative and practical approaches are explored
- Facilitate the complex collaboration required both to conduct research on technology development and to collect the clinical data and samples needed for validation and qualification of the markers.
- Facilitate participation of patients and regulatory authorities in a dialogue on novel clinical endpoints

**Core Objectives:**
- To develop novel biological endpoints to support the diagnosis clinical outcome assessment in disease prevention and disease modification trials.
- To develop pre-clinical models and identify biological markers that support translation of pharmacology from pre-clinical studies to the clinical setting
- To develop an array of novel biological endpoints to support internal decision making as depicted in the figure below:

![Diagram](https://example.com/diagram.png)
**Impact on R&D/public partners and society**

**For R&D:** Innovative methodologies to evaluate treatment effect will lead to:
- Better tools in basic and non-clinical research for evaluating treatment effect to support more effective decision making and more efficient use of R&D resources.
- Increased probability of success and decreased development costs
- New innovative tools for the clinical assessment of effects of new drugs and vaccines

**For Patients:** Innovative methodologies to evaluate treatment effect will lead to:
- Decreased exposure to ineffective drugs
- Accelerated access to effective medicines

**For Society:** Innovative methodologies to evaluate treatment effect will lead to:
- Shorter drug development timeline and, reduced drug candidate failures during development
- More effective medicines and reduced healthcare costs

**Stakeholder consultation**

5) To develop new and innovative medicines, novel methodologies for evaluating treatment effects are essential to support informed decision making at each stage of the drug discovery and development process. Existing methodologies such as imaging and other biomarkers are not sufficiently developed or validated to discharge risk and ensure better and faster development of new treatments, especially where disease modification and prevention are the treatment objectives.

From your perspective how do you think this challenge should be approached? Do you think the current proposal will adequately address this need?

### 2.1.5 Benefit/Risk assessment in individual patients

**The opportunity to accelerate drug development and improve healthcare**

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 B/R. There have been several instances (e.g., HIV and multiple sclerosis medicines, pandemic vaccines) in which patient pressure and/or the urgency of the situation has resulted in regulatory agencies reconsidering their approach to the B/R balance.

Benefit/risk methodologies, conclusions and communications are indeed being discussed in multiple venues\(^\text{6}\). However, since there is no definitive agreement amongst stakeholders, the application of the benefit/risk assessment (i.e. how it is to be used and by whom) remains a key issue. Also, use of B/R assessment in regulatory decision-making is under discussion in a number of contexts including: pre-approval data required for CA vs. ‘full’ MA, qualitative vs. quantitative assessment methodology, and the need for active comparator clinical trials; post-approval data required to maintain the B/R assessment; alignment on data required for regulatory B/R and HTA needs; and communication of B/R within medicine labels. There is a need to better understand the requirements of patients and practitioners, continuing to promote early dialogue to secure agreement on data to underpin B/R

\(^{6}\) E.g., IMI, EMA, FDA, relation to ICH E2C
and alignment with HTA needs pre- and post-approval continue to support the use of B/R assessment “frameworks” that provide a structured approach to look at the relationships between the benefit and risk outcomes of interest (and to clarify the conditions for approval of new indications based on reduced data packages where available information can be used. Activities should be conducted jointly with the EMA and centres with expertise in practical ethics, epidemiology and other key disciplines, to establish a new methodology and communicate it to relevant national policy-makers.

In a related topic, clinicians, health systems, regulators and HTA agencies are increasingly demanding real world data on the performance of medicines. With the advent of mobile health and other tools, the collection of such data has become much easier and less expensive. There should be models for use of registries or the mining of electronic health records or claims databases. For these reasons, industry must step up engagement in e-health initiatives to ensure that these efforts cater to its needs as well. In some cases, these data can offset or replace the need for formal Phase 4 studies, with clear economic advantages for sponsors. Standards are beginning to be established at a national level (e.g. by the ABPI in the UK) but it is clearly advantageous for such standards to be applicable across Europe, as much as possible.

Clinical trial data are typically collected in an artificial clinical setting and therefore there is a risk that data obtained – both safety and efficacy data cannot be reproduced in a real-life clinical setting. Post marketing drug surveillance is therefore an important component of drug/vaccine safety though it must be recognised that this data is collected in less controlled environment and therefore is subject to biases of its own. Spontaneous reports from healthcare professionals, patients and the pharmaceutical industry populate the Adverse Event Reporting Systems with information regarding adverse drug events. However, it is generally accepted that adverse event reporting is under represented. The advent of digital media and the use of Smartphone’s and Tablets have changed the way individuals connect and communicate. Together with the availability of health information and patient forums on line it is now a perfect time to leverage this technology to better understand the benefit/risk of medicines and strengthen the protection of public health.

**Need for PPP:**
To address these challenges, and meet the needs of all players, will need to harness expertise available across Europe's biopharmaceutical sector, by pooling competencies and resources from all concerned i.e. healthcare professionals, regulators, academics and patients. The public private partnership should build on the work already conducted by EMA, CIRS, IMI PROTECT and 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)

**Core Objectives:**
- Development of the regulatory framework and methodologies 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
- Development of the framework required to create a ‘community’ approach to pharmacovigilance where the patient is key
- Agree ways to approach benefit/risk balance for regulation (efficacy/safety), to benefit/risk assessment for Health Technology Assessment Agencies (effectiveness/safety).
- Better methods for understanding differences between patients in clinical trials and patients in “real” life
- Better methods to provide a basis for effective and safe introduction of new treatments for selected populations
Impact on R&D/public partners and society

For R&D: Better assessment of benefit/risk of drugs and vaccines will lead to:
Creating medicines/vaccines and providing product information that more directly address patients’ concerns

For Patients: Better assessment of benefit/risk of drugs and vaccines will lead to:
Making decisions for their own health and wellness needs based on better understanding of the impact of disease v. treatment

For Society: Better assessment of benefit/risk of drugs and vaccines will lead to:
Regulators and Payers making and articulating decisions with direct response to patient concerns

Stakeholder consultation:
6) 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 B/R.

What more do you think needs to be done to improve patient engagement in the assessment of the benefit/risk of medicines?

2.1.6 Adoption of innovative clinical trial designs/Improved access to medicines

The opportunity to accelerate drug development and improve healthcare

Clinical Trial Design
The Randomised Control Trial (RCT) design embodies the scientific experiment required to test that a medicine has a positive impact on patients. Over the years the methodology has evolved to a point where it is very well adapted to show a clear effect compared to a benchmark treatment or placebo, on a specific measure, when used in a standard way in a selected population cared for under a uniform protocol. However these are not the experiments that determine how patient benefit can be maximized through adjusting administration, dose, concomitant care, and progression through a care pathway for the variability inherent in the full range of potential patients. Nor are they the experiments that show the improvement possible against the full range of alternative treatments that are themselves adjusted in this way by the clinical team.

For many years this was not a critical issue with healthcare systems able to fund new medicines based on regulatory approval, and effectively cover the R&D costs of Pharma. However, HTA agencies and other healthcare decision makers now assess the expected future value of a medicine when used in “real world” clinical practice which requires additional information supplementing traditional RCTs. 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 of new medicines. The inherent uncertainty (which may be different from country to country, as standards of care vary) may drive further research commitments to be required post-authorisation (PASS, PAES, Reimbursement with Evidence Generation), and result in wide variability in access to medicines between countries due to variability in relevance of evidence and different attitudes to reimbursement in conditions of uncertainty. Continuing to incur very high costs of drug development without addressing the causes of uncertainty relating to the reimbursement decision puts pressure on the sustainability of the traditional drug development model. It also affects the speed and level of patient access, and therefore the extent to which patients and society might
benefit from new medicines. Addressing this problem requires multiple approaches: addressing the underlying development costs; exploring alternative regulatory pathways; and following development strategies that address the needs of all decision makers.

Alternative clinical trials can today be designed and run on drugs in development. Pragmatic trials allow more natural care; adaptive trials refocus an experiment on key questions through adjusting patient selection, dose, duration, and care protocol. Many aspects of RCT, Pragmatic and adaptive trials can be transformed or made feasible by harnessing the ability to use electronic healthcare record (EHR) systems in clinical trials.

The same EHR systems will allow efficient and high quality observational research to be conducted on medicines and full care pathways after medicines are authorized and used in clinical practice.

The role of the patient in research can be enhanced by including patient reported outcomes, patient preferences and caregiver experience through direct questioning in trials, and through observed comment in social media, diaries and other less direct ways. The willingness to participate in more natural studies may be greater than that for more invasive testing.

**Regulatory framework**

While genomics, advances in understanding of disease and the associated design of treatment, has yet to achieve its full potential, science and technology have produced several tools to improve the R&D process. Markers based on genomics, proteomics and metabolomics are now being pursued in most academic and industry programmes, but there is substantial opportunity to better integrate these advances into regulatory approval and clinical practice. While regulators in several jurisdictions have begun to show an acceptance of new approaches to trial design including new statistical tools, these need to be more broadly promoted and approaches such as progressive market authorisation explored.

It is imperative to future innovative medicines that regulatory processes and expertise keep pace with these scientific, medical, and technological advances. In general, many regulatory processes are viewed as being somewhat inflexible and slow to adapt to novel development approaches which are critically important for the advancement of cutting-edge science and more personalised medicines. Under this theme, the recommendations are to focus on the upcoming review of the Clinical Trials Directive, medical devices and in-vitro diagnostics legislation, improve and/or clarify the regulatory framework for companion diagnostics, promote new approaches to novel statistical analyses (e.g., Bayesian analysis) within Agencies, and clarify regulatory approaches to innovative fixed dose products (e.g. combinations of monoclonal antibodies, and “novel-novel” products).

Additionally under this theme, moving towards new disease definitions and setting disease priorities for future research are two pre-requisites for improving regulatory pathways, on the one hand, and increasing certainty for the product development process on the other, defining disease by its underlying molecular mechanism, rather than symptoms, has already begun to pay dividends in cancer and inflammatory diseases, and this approach should be further extended. Finally, in conjunction with clinical opinion leaders, WHO, and other key stakeholders, priorities should be agreed of practical relevance to the industry’s R&D pipeline in which redefinition could enhance the likelihood for the development of viable medicines.

**Need for PPP:**

The introduction of new trial designs pre-authorisation requires partnership of regulatory authorities with Pharma R&D: the understanding of which new designs should be introduced requires partnership of regulatory and HTA bodies with Pharma R&D and Clinical Groups. The understanding
of how to study new medicines requires all these to partner with patients and caregivers. Such PPP has been established for the IMI 7th Call (real world data in drug development).

**Core Objectives:**
- To implement novel clinical trial designs and clinical guidelines for assessment of:
  - efficacy of new drugs and vaccines using novel trial designs including co-ordinated parallel treatment group studies
  - prophylactic therapies or disease modifying agents
- To establish GCP Certified clinical trial networks to reduce the need for lengthy investigator and subject recruitment, thereby enabling rapid trial initiation
- Better understand relative effectiveness and how we can build this into the early stages of research to ensure efforts are focussed on drugs that will add real value to patients.
- Framework to allow the identification of and overcome the operational difficulties associated with generating evidence of relative effectiveness before launch.
- Improved clinical tools and trial designs for evaluating drug effectiveness
- Proof of concept for new regulatory pathways to inform discussion on regulatory guidance

**Impact on R&D/public partners and society**

**For R&D:** *Adoption of innovative clinical trial designs/Improved access to medicines will:*
- control cost of R&D;
- provide more predictable progress through access assessments

**For Patients:** *Adoption of innovative clinical trial designs/Improved access to medicines will:*
- transform patient engagement in research
- provide more predictable access to new medicine, clinical team adjust use of new medicines for patients

**For Society:** *Adoption of innovative clinical trial designs/Improved access to medicines will lead to:*
- sustainability of Pharma R&D model
- ability to target new medicines to patients likely to benefit and adjust use of medicines to maximise that benefit

**Stakeholder consultation:**

7) 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 of new medicines. The inherent uncertainty (which may be different from country to country, as standards of care vary) often results in wide variability in access to medicines between countries due to variability in relevance of evidence and different attitudes to reimbursement in conditions of uncertainty.

The PPP aims to address this challenge – are there any additional activities that you feel should be included as objectives for the PPP?
2.1.7 Development of novel preventative and therapeutic agents

The opportunity to accelerate drug development and improve healthcare
The aim of this work stream will be to jointly develop novel therapeutic agents to tackle areas of significant unmet medical need (e.g. neurological disorders, antibiotic resistance) where low return on investment or lack of other market incentives prohibits the development of new effective medicines (e.g. new antimicrobials or preventive Alzheimer’s disease treatment). Efforts will also focus on the development of novel drug delivery mechanisms required to facilitate the progression of drugs to traditionally intractable targets, the tools and capabilities required to successfully develop and manufacture such innovative drugs.

Core Objectives:
- Develop novel therapeutic agents for areas with high unmet need but low return on investment.
- Create a portfolio of platform technologies to facilitate rational design of site specific drug targeting
- Deliver a range of industrializable drug delivery platforms to help the delivery of novel therapeutic agents
- Drive advances in pharmaceutical development which support the conversion of complex and expensive chemical and biological processes into practical, cost effective manufacturing systems to lead to significant cost savings that benefit the industry, healthcare systems and society

Creating new therapeutic opportunities through improved drug delivery technologies
The design of targeted drug delivery platforms is of growing interest within the pharmaceutical community to facilitate the progression of drugs for traditionally intractable intracellular targets such as inappropriate protein /protein interactions, protein dysregulation (over production or insufficiency, protein folding defects etc.). In addition to identifying potent pharmacophores that can interact with these targets at a molecular level there are significant challenges to successful prosecution of these targets to clinical evaluation that could benefit from the use of targeted drug delivery systems, clinical evaluation. These can include improvements in: absorption from administration site, stability in extracellular compartment, productive interaction with vascular endothelium, adsorption to extracellular matrix, diffusion through extravascular tissues and access to relevant target cells, productive uptake by target cells, acceptable pharmacodynamic response dose as well as, impact of disease pathophysiology on delivery system behaviour and acceptable cell and molecular toxicity profile associated with the delivery system.

Taken together, the main challenges to the successful design of delivery systems include: 1) developing the models and appropriate analytical tools to evaluate the relative participation of each of these barriers to effective delivery of the different molecular classes of interest, and 2) identification of the relevant tools and techniques needed to effectively scale up, manufacture and characterize different drug delivery platforms.

Specific Objectives:
- Establish a vibrant advanced drug delivery hub across Europe with the resource, skills and expertise to generate analytical techniques required to characterize drug delivery platforms with nanoscale resolution
- Create better understanding of the real barriers to effective delivery as well as the interaction of proposed carriers with each of the barriers in normal and disease state
- Validate the performance of novel delivery systems in vivo and in vitro using advanced spectroscopic and imaging techniques
● Develop and validate the nanoscale imaging technology required to demonstrate cell penetration and cellular localization
● Develop the methods required to quantify cell properties combining multispectral imaging, optical and spectroscopic imaging
  ○ Development of software to compare, contrast and integrate analytical data from the various production methods in order to best characterize the final drug delivery product.
● Develop novel approaches for drug delivery (functionalized carriers, nanoparticles, biomimicry, microfactories, etc.)
● Induction of appropriate responses to vaccination, introducing novel vaccines, adjuvants and delivery systems
● Create a better understanding of the technologies needed to manufacture delivery systems in a robust sustainable manner that can meet commercial needs

**Pharmaceutical innovation to support personalized healthcare**
The drive towards individualized applications in general and personalized medicine in particular will require further improvements, increased efficiency and flexibility, and innovation into the pharmaceutical supply chain. Indeed, to improve access, quality and cost in a more sustainable health system the entire pharmaceutical supply chain, starting with the patient and ending with the patient, require a radical overhaul.

It has been appreciated that to pursue personalised healthcare, biomarkers and companion diagnostics will be needed to identify patients who are likely to respond to a given therapy and particular dose of the medicine. Less attention has been given to the dosage form itself for optimal preventive or therapeutic performance and outcome. Less attention has also been given to the associated new technologies in pharmaceutical processing, manufacturing, and supply that can underpin and enable provision of robust quality medicinal products to individual patients who require them.

Pursuit of personalised medicines concept allows that particular medicine and/or dosing would be adjusted to a particular single individual; however, it seems that targeting to a cohort (stratified therapy) is more likely. It is also essential that products for personalized medicines are manufactured and developed with similar quality standards to ‘conventional’ pharmaceutical products used across the wider population. Although the volumes of products required are likely to be reduced, it will be necessary that appropriate product quality is achieved at a cost that is acceptable to the manufacturer, patient, and society. Until we have a better understanding of future formulation approaches within personalised medication allowing the adjustment of the dose dependent on patient need, and the need of small volume products, it will be difficult for pharmaceutical businesses to determine a strategy and scientific direction for further development in a cost effective manner. Complex dosing regimens will, in addition, require advances in formulation technology to enable accurate and precise administration of the most appropriate dose. The driver for these technologies includes input from pharmacogenomics specialists and clinicians.

Although the strategic technology demands of the personalized healthcare field are uncertain, it is conceivable that a number of innovative dosage forms, device and packaging opportunities might exist which would enable customization of product functionality to patient need. These could include but are not limited to methods for flexible batch manufacture, drug and device combinations which facilitate dose titration, delivery systems which enable dosing to the appropriate exposure in individual patients and smart systems which deliver drug in response to physiological measurements and biomarkers. It is anticipated that developing the European capability and skills base will lead to valuable innovations in these and other areas of relevance.
Specific Objectives:

- Develop formulation technologies and associated scalable manufacturing processes which facilitate flexible dosing (preferably at patient level) tailored to patient needs
- Develop diagnostic technologies (analytical) which can be used (by patients) to determine the required amount of medication
- Develop intelligent systems which tailor the release of the medicine in response to biological and physiological measurements.

Increasing efficiency in the pharmaceutical processing and manufacturing, and supply of novel therapeutics

The process of converting complex and expensive chemical and biological processes into practical, cost effective and flexible manufacturing systems is an area of pharmaceutical development where increased efficiency and innovation has the potential to lead to significant cost savings that benefit the industry, healthcare systems and society. In addition, innovations in manufacturing practices such as flexible and continuous manufacturing processes will play a pivotal role in enabling right prevention and treatment to the right patient at the right time.

Broadly speaking, drug manufacturing processes can be sub-divided into small molecule and biopharmaceutical production. Small molecule drugs are traditionally manufactured through a sequential, batch production process. Although batch manufacturing usually involves unit operations that are well established and optimized, the model has numerous drawbacks and advancements in pharmaceutical production techniques have the potential to address this challenge by reducing complexity, increasing yield, addressing regulatory issues and shortening development time and overall costs. For small molecule products, the model of ‘continuous manufacturing’ has several potential advantages over traditional batch processes with overall cost savings of up to 40% predicted if the appropriate continuous process is selected.\(^7\) To be successful continuous manufacturing involves new processes, technology, equipment and possibly new facilities. However, perhaps most importantly, collaborative efforts are needed to develop and validate these new processes and ensure that the regulatory framework for pharmaceutical manufacturing standards evolves in step with the advancing technology in this area.

Special manufacturing considerations are particularly pertinent to the production of biologics. Biologics have the potential to deliver innovative therapies to address significant unmet medical need. However, manufacturing biologics is more challenging than for traditional small molecule drugs. Because they are often composed of complex molecular structures, biologics typically require complex, multi-stage manufacturing processes, which are associated with significant setup costs. The complexity and costs of production are further increased because all intermediate processing steps and associated manufacturing facilities are the subject of intense testing and regulatory review. Lastly, although progress has been made in future-proofing manufacturing facilities, where facilities are designed for specific process e.g. to suit the development of a product, the financial and organizational impact is significant should the product fail. Consequently, while new biologic targets may be identified and validated, huge infrastructure and production costs present a significant barrier to the industry in bringing innovative biopharmaceuticals to market.

Scientific innovation can also improve all steps of vaccine manufacturing from the very first step of production to vaccine release. Novel technologies in the manufacturing process can enhance

flexibility, increase yields, reduce cost, increase stability and reduce production time. For example, improvements in bioreactor technologies, including more rapid culture expansion methods that provide consistent growth environments, may lead to improved yields and reduced cost. Use of synthetic seeds in vaccines such as influenza can speed up the production by bypassing the requirements for a natural seed. This would be particularly important for the rapid response to pandemic influenza outbreaks. Innovation in research could also help to develop new in vitro vaccine release assays that do not require animal testing. New technologies in formulation platforms could improve the stability of the vaccines and may reduce the requirement for cold chain.

**Specific Objectives:**
- Develop mechanistic understanding of continuous processes (small molecules, biologics, and formulated products) together with virtual simulation capabilities
- Develop appropriate control strategies (small molecules, biologics, and formulated products) including appropriate in-line measurements with associated feedback and feed-forward control systems
- In joint exploration between industry, academia, and health agencies evaluate and adopt new science based methodologies that underpins establishment of a science and risk based regulatory framework facilitating implementation and exploitation of continuous processing in the Pharmaceutical Industry
- In joint exploration between industry, academia, and health agencies, evaluate and develop new science based methodologies for quantitative Quality Risk Assessment

**Need for PPP:**
The effective discovery and development of novel targeted delivery platform will require a multifactorial approach, leveraged key academic and industrial expertise. Due to the number of parameters that need to be considered, and the broad knowledge gaps that need to be filled to effectively design a drug carrier, it is unlikely that any single discipline can be ultimately successful at delivering a commercially viable product. Novel drug delivery strategies require a deep translational knowledge requiring collaboration between biologists, pathologists, formulation scientists, analytical chemists, engineers, materials scientists all closely aligned. Operating in isolation, each discipline can conduct elegant science independently, but will propagate the development of approaches prone to artefacts complicating data interpretation and slowing progress.

With regard to biologics manufacturing, the industry and regulators have already made progress towards the introduction of quality by design (QbD) and process analytical technology (PAT) principles, where in-process production validation and continuous quality assessment contribute to greater manufacturing efficiency. However, more research is required to consolidate expression systems, drive process convergence and develop more flexible manufacturing systems. A greater degree of regulatory flexibility has also been proposed, and is required, in order to give manufacturers the ability to refine processes and make variations, within a pre-agreed ‘design space’, that do not require repeated regulatory review and approval. A PPP is proposed to develop and establish new quality assured and cost-effective pharmaceutical manufacturing processes through shared research resources and expertise

Overall this challenging area requires a broader open innovation approach involving the industry (small and large companies), academia and technology providers and across a number of fields from biology to pharmaceutical engineering, from materials sciences to pre-clinical and clinical development.
Impact on R&D/public partners and society

For R&D: Development of novel preventative and therapeutic agents will result in:
- Novel therapeutic agents for areas with high unmet need
- A portfolio of platform technologies to facilitate rational design of site specific drug targeting
- A range of industrializable drug delivery platforms to help the delivery of novel therapeutic agents

For Patients: Development of novel preventative and therapeutic agents will result in:
- Novel therapeutic agents for areas with high unmet need
- Patients will gain access to medicines which may not have been available without the advent of sophisticated delivery mechanisms
- Improved delivery will improve the apparent efficacy/therapeutic index of drugs by avoiding adverse effects.
- In the case of long-acting injectables/depots, improved patient compliance and improved comfort (e.g. less frequent ophthalmic injections) would also be expected.

For Society: Development of novel preventative and therapeutic agents will result in:
- Preventative and therapeutic agents to address European Healthcare priorities
- Creation of a vibrant world class European drug delivery network which will attract R&D investment to Europe

Stakeholder Consultation:

8) The drive towards individualized applications in general and personalized medicine in particular will require further improvements, increased efficiency and flexibility, and innovation into the pharmaceutical supply chain.

From your perspective what aspects of drug delivery and manufacturing do you feel require most attention in order to make significant advances in this field? Do you think the current proposal will adequately address this need?

2.2 Delivering Operational Excellence

In order to fully exploit the scientific advances as described above it is essential to have the scientists, regulators, patients and payers trained to adopt the new tools and methodologies generated through the PPP.

Scientific Excellence

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. E.g. new –omics technologies, bioinformatics and systems biology open opportunities to reach a better understanding of diseases and to lay the basis for a more stratified medicine. On the other hand these new targeted therapeutic approaches require new clinical trial designs, new regulatory processes and new ways to develop the social and financial framework in this area. Well trained professionals who are familiar not only with the most recent changes in their specific area but the overall context of medicines Research and Development (R&D) are a prerequisite to successfully address these challenges.
Need for PPP:
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). To ensure that the training material and programmes are widely accepted as trustworthy high quality information, a PPP is the perfect approach to jointly develop new materials and standards in this field.

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 scientists at all stages of their careers. The courses are flexible, modular, and focussed on practical application and supporting mobility.

Based on the experiences from these programs the common framework for education and training along the entire value chain should be further developed, with a focus on the development of a range of new e-learning opportunities and competence profiles.

Core Objectives

- 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.
- Develop training in medicines development jointly with the regulators to ensure operational excellence in this area.
- 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 cooperation between projects under the new PPP in the area of education and training.
- Increased use of online-tools including social media to foster the transition of traditional training into e-learning opportunities, to address the needs of all health care professionals, and researchers including the SMEs.
- Increased collaboration with ENQA specifically in the area of QA for CPD offered by universities
- Increased collaboration with EUA to open universities for offering tailored CPD courses for professionals in medicines development
**Impact on R&D/public partners and society**

**For R&D: Scientific Excellence will:**
- Network of professionals from all functions and institutions involved in biomedical sciences to allow joint identification of training needs and development of respective trainings
- Faster and easier access to high quality training programs whenever and wherever needed
- More efficient R&D process based on increased operational excellence.

**For Patients: Scientific Excellence will:**
- Faster access to new treatments due to a more professionally managed and therefore more efficient R&D process.
- Network supporting earlier involvement of patients in the R&D process
- Opportunity for patient organisation representatives to qualify further and thereby to strengthen their role in relevant discussion and decision bodies in healthcare.

**For Society: Scientific Excellence will:**
- More efficient use of healthcare resources via more efficient processes for the development of new medicines

**Excellence in Data Management**
Robust, production quality data and 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), variety (Clinical, GWAS/RNASEq, eHR, ‘omic, Cytometry, Imaging, pharmacology, pharmacovigilence 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. Addressing these challenges will be critical for EU competitiveness in biomedical R&D requiring both focused KM research projects as well as the provision of fit-for-purpose, underpinning, and professional KM services as part of the new biomedical PPP.

A lack of investment and coordination in KM infrastructure and services will result in significant operational issues for the new biomedical PPP:

- Significant individual project inefficiencies in KM sourcing and provisioning with a profusion of local, redundant solutions.
- Lack of system interoperability and data integration: local solutions constrained to support the immediate project needs
- Significant risk in data loss and lack of data re-use due to heterogeneity in data access, myriad of local data stores (repository findability issues) and local sustained funding challenges for content post project.
- Missed opportunity to impact EU R&D beyond the new biomedical PPP through infrastructure and services re-use by industry and the wider community
- Lack of competitiveness through a missed opportunity to mobilise EU KM and biomedical informatics innovation and enterprise (both academic and commercial) through ‘big idea’ investments in enabling, underpinning infrastructure.
- Project inefficiency (and compliance risk) through a lack of coordinated governance and support in data security/privacy, de-identification/anonymisation, regulatory requirements, re-use policies and collection standardisation (e.g. patient consent form heterogeneity leading to complex downstream KM and data tracking challenges).
Systematically addressing these, in line with research project need, will establish Europe as a premier location to conduct modern, data-intensive clinical research programmes.

**Need for PPP:**
KM operational excellence in health-care research will require a concerted and coordinated effort by research partners in Pharma/Health industry sector, KM/IT industry sector, academia and the public health-care sector; getting this right is imperative for Europe in an increasingly competitive environment for clinical trial research. No one stakeholder group alone can affect the change required in KM infrastructure services – it will require a concerted endeavour. The value of a PPP is demonstrated through the IMI programme which has successfully piloted and delivered a series of knowledge-management solutions to many of the individual issues highlighted (e.g. eTRIKS, EMIF, EHR4CR, DDMore, OpenPhacts, etc). The challenge for the new biomedical PPP will be to build on these foundations, supporting and delivering these services on an unprecedented scale.

Delivery of the required KM infrastructure and services will require the cooperation and collaboration of many partners and stakeholders. The expectation is for components of this infrastructure to be standardised and open (pre-competitive) in nature, for example core data management elements, whilst other elements will benefit from more heterogeneous competitive academic & commercial services (e.g. to support advanced analytics) allowing the tailoring and optimal fit with project requirements. If implemented correctly this will result in a vibrant, diverse, fit for purpose KM ecosystem to support EU biomedical research.

Sustainability will be a major challenge – how to deliver KM services and content beyond the lifespan of typical research projects (3-5 years). This 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 KM environment resulting in significantly reduced overhead costs in setting up and executing collaborative, multicentre biomedical studies thus encouraging future biomedical R&D competitive and pre-competitive PPP investments, within and beyond Horizon 2020.

- 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).
- Provision of core data and knowledge capture, curation, management, analytics and visualization platforms, tools and services for research projects. This needs to be established early in PPP life-cycle with requirements to evaluate and validate the KM plans for each project
- Improved data discoverability and sharing by the community (pharma, academia, health providers, regulators, patient groups etc. Importantly the capture and long term security of PPP data enabling potential re-use, downstream insight generation and value creation.
- Drive innovation and best practice in data analytics, especially high dimensionality analytics across diverse data types (clinical, health, molecular etc) to support patient selection, disease understanding and patient outcome insights.
- Drive non-technical operational excellence for critical KM issues such as data security, access/privacy and associated ethical and regulatory constraints.
- Enable cross-project learning and re-use to contain costs and increase research efficiency.
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).

- Facilitate the education and development of next generation data scientists versatile in heterogeneous big data analysis and data and knowledge management
- Improved data standardization enabling re-use: incentivize scientists to store data according international standards and guidelines in collaboration with publishers and European founding organizations.
- Drive focused KM Research and Innovation that includes commercial partners outside EFPIA, e.g. the IT Sector, to develop innovative and enabling solutions for biomedical research. There is an opportunity for EU distinction in research cutting across technology fields.
- To facilitate and promote improved ethical re-use of patient data for R&D across EU member states, especially with regard clinical study and eHR data, permitting greater data reuse and impact
- 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.
- Support innovative KM research in emerging ‘Big Data’ challenges in biomedical research: for example the acquisition, handling, analysis and management of patient data from next-generation clinical trials. This includes real-time (24x7) “big data” patient monitoring through telemetric devices (blood glucose, blood pressure, motion sensors, ECG, etc) and “live” patient interactions through social media technology.

**Impact on R&D/public partners and society**

**For R&D: Excellence in Data Management will:**
- Significantly reduce the cost and complexity of individual research topics and clinical programmes.
- Effective re-use of resources and establishing of best practice to increase quality and value of generated data
- Addressing long-term sustainability, accessibility and re-use of generated research data for future studies
- Infrastructure and service ecosystems developed for pre-competitive partnerships can be readily repositioned for competitive and internal R&D activities delivering internal efficiencies gains and potentially facilitating internal data sharing with the community.

**For Patients: Excellence in Data Management will:**
- 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

**For Society: Excellence in Data Management will:**
- Strengthen Europe’s competitive position in conduction of international multi-centre clinical programmes by offering transparent and robust services and operational excellence
- Increased value and return on biomedical research investment through operational excellence and collaboration and re-use of public research infrastructures.
- Encourage the development of a robust, commercial services ecosystem, creating of high value data scientist jobs in the EU.
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.

**Excellence in clinical trial implementation**
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 diseases 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.

In addition to fostering collaboration, the sharing of information and experience of running clinical trials within the networks, the networks will provide guidance and training on:

- Running clinical studies that will support regulatory filings and meet GCP requirements
- Understanding of international regulatory processes and the evolving regulatory landscape
- Provision of ‘state-of-the-art’ data-collection tools
- Optimal and improved design for clinical trials

**Need for PPP:**
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.

**Core Objectives:**
- To establish GCP trained clinical trial networks as required across Europe to support the implementation of registrational clinical studies to support the conduct of clinical trials preventing and treating diseases as required under the PPP
- To establish a Laboratory Trial and Research Network 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:

- An 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
- Co-ordinated networks of clinical trial investigators through which academics, pharmaceutical and biotechnology companies can advance the development of new assets
- 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
- Access to public contract research organisations certified as competent to implement and monitor registrational clinical trials.
- Availability of training materials to be used to train clinical investigators
For Patients: Excellence in clinical trial implementation will result in:
- Increased opportunity to participate in ongoing clinical trials
- More efficiently run clinical trials

For Society: 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

3. European Health Priorities to be addressed by the PPP

The research to be undertaken as described above within the seven 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 the PPP, many of these health priorities will be addressed by activities conducted within the seven research axes. However it should be noted that within each health priority the order of priority of the 7 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 the seven axis of research 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.

Stakeholder consultation:

9) From your perspective do you agree that the areas outlined below represent major healthcare challenges for Europe? Do you think the current proposal will adequately address the needs in each of these? Are there additional activities that you feel are essential to deliver effective healthcare solutions for the treatment of the diseases listed below?

What are the main treatment gaps or unmet needs in the development of medicines in your therapeutic area?
- Are there any barriers in the delivery and available of innovative treatments (lack of screening/diagnostics, reimbursement, lack of single medical file, patient care, adapted infrastructure, stigmatism, etc.)?

3.1. Antimicrobial resistance

The societal impact of antimicrobial resistance

Antimicrobial resistance (AMR) is 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).
Despite the recognized need for new antimicrobials for clinical use, the reality is that in recent years research focused on the development of new antibiotics has reached such low levels 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. Meanwhile, the incidence of resistant infections is growing. Recognising that the existing global processes for product ownership and stewardship cannot be redefined simultaneously, it is nonetheless essential that the antibiotic research community all contribute and work together to tackle this growing problem.

The key barriers to the development and delivery of effective antibiotics could be summarized as follows:

- Discovery and development of novel antibacterial agents is scientifically challenging. For example, many traditional screening approaches have failed to unearth novel chemical starting points and Gram-negative pathogens have many inherent barriers and mechanisms preventing penetration of antibiotic agents
- 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

**Nature of research to be conducted: Alignment with research axis**

**Axis 2: Target Identification and Validation**
- Development of novel approaches for antibiotic lead discovery
- Robust validation of host targets for treating bacterial or viral 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 4: Innovative methodologies to evaluate treatment effects**
- Validation and research on new diagnostics
- Mechanism of action-driven identification of sepsis patient populations through the use of *in silico* mechanistic modelling and observational studies

**Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines**
- Address current regulatory hurdles related to registration of antibacterial agents
  - Harmonization of global regulatory guidelines to enable streamlined registration of new antibacterial agents for use in well-defined high need patient populations
  - Implementation of regulatory concepts currently under development to address high unmet needs

**Axis 7: Development of novel therapeutic agents**
- Establish a vibrant drug discovery hub across Europe with the resource, skills and expertise to generate a pipeline of ‘qualified leads’ and ‘development candidates’ originating from private or public partners
- Collaborative clinical development of novel agents for multi-resistant pathogens
- Validation of new modalities (e.g. mAbs, bacteriophage therapy) for treating bacterial infections

**Operational Excellence**
- 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 infections caused by ARB.
Key deliverables

- A revitalized pipeline of promising new agents for tackling antibiotic-resistant bacterial infections including tuberculosis
- A portfolio of new antibiotics with proven clinical efficacy and safety
- Validated rapid point of care diagnostics to optimise clinical trial enrolment and appropriate use of antibiotics
- Novel clinical trial designs to streamline regulatory approval
- Creation of a world class European antibiotic clinical trial network
- 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)

Impact of the research on delivering new medicines

Antibiotic resistance is an increasing threat to health across Europe and action is urgently required to support the development of new antibiotic agents. 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 and the consequences are not imaginable.

Investigators will have a unique opportunity to gain funding to support the development of their new and innovative approaches for the treatment of multi-resistant infections while at the same time gaining invaluable insight into the complexities of drug development as well as access to learnings and experience from all partners involved in ND4BB (NewDrugs4BadBugs; an IMI project). It gives partners the opportunity to build relationships with companies participating (and also those outside of ND4BB) to strengthen their ability to identify partnering opportunities for further development of promising new drugs. The opportunity to build a network of investigators through which academics, pharmaceutical and biotechnology companies can advance the pre-clinical and clinical development of new assets will attract future drug discovery efforts to Europe.

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 be effective against multi-resistant pathogens. Antibiotics are a fundamental requirement for ensuring quality of life for society as a whole. However, not only does this area suffer from a particularly low probability of success due to the challenges mentioned above, resistance is continually emerging. Hence, drugs being developed today must be developed to target resistance which is predicted to occur in 10 years’ time. To protect individuals effectively a range of molecules are, therefore, required to provide drugs to treat a range of resistant infections that may or may not occur 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 as they will only be used under limited circumstances. In these situations, the cost of development of a drug is often greater than the potential return. Indeed, this has led to only a few companies remaining dedicated to addressing this essential societal need. It is evident that a public private partnership should be formed to pool available expertise and resources to better address a problem of such scale.
3.2. Osteoarthritis

The societal impact of Osteoarthritis

Osteoarthritis (OA) is the most common arthritic disease and is becoming more prevalent as the population ages and obesity rates rise. Between 2002 and 2007, OA moved from the twelfth to the sixth leading cause of years lost to disability or morbidity (WHO data), a trend that is expected to continue. Direct and indirect costs of OA for the EU are substantial; in the UK alone, total costs are estimated to be equivalent to 1% of the gross national product (GNP) per year.

- OA is already one of the ten most disabling diseases in developed countries
- Farming for 1–9 years increases the risk of OA 4.5 times; farming for 10 or more years increases the risk 9.3 times
- Worldwide estimates are that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA
- 80% of those with OA will have limitations in movement and 25% cannot perform their major daily activities of life

In the past decade, many pharmaceutical organizations have de-emphasized or abandoned OA drug development due to real and perceived hurdles; as a result, the OA therapeutic pipeline is virtually barren despite a growing disease burden. Considering the scale of the problem, it is remarkable that the pharmaceutical industry has not produced a single treatment which slows disease progression (termed disease modifying OA drugs, or DMOADs). The absence of DMOADs has not been due to lack of effort; unfortunately, a number of highly visible and costly failures have dampened enthusiasm in the industry to pursue the development of DMOADs.

Five 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)
- Successful commercialization requires that value to patients, regulators and payers is demonstrated

Nature of research to be conducted: Alignment with research axes

An integrated research plan will be generated and implemented to deliver solutions to the above challenges. In summary:

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8 WHO Department of Chronic Diseases and Health Promotion – Chronic rheumatic conditions.
Axis 1: Reclassification of Disease by molecular means
- A strategy will be outlined to address the factors described above, providing a more tenable pathway to select and clinically evaluate potential DMOADs. The proposal is to create an OA development roadmap that will
  - match target specific molecular pathways to different OA subpopulation(s)
  - identify biomarkers which will support patient stratification and monitor disease progression
  - match target specific therapeutics to specific OA subpopulation(s)

Axis 4: Innovative methodologies to evaluate treatment effects
- The aim will be to capitalise on the shared expertise and knowledge to develop biomarkers and imaging tools to support more efficient clinical trial design and early decision making and investment checkpoints.
- Efforts to identify and qualify novel clinical endpoints will also be undertaken.

Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines
- Innovative trials designs will be implemented utilising stratified patient populations and innovative clinical endpoints

Operational Excellence
- 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 OA.

This work will build on the knowledge base and infrastructure present within the EU from ongoing research-based initiatives like TREAT-OA and The Osteoarthritis Initiative (OAI), where a strong foundation is being built on understanding the natural history of OA, disease phenotypes, and biomarkers, imaging features and genetic profiles associated with disease progression. To this foundation, the proposal adds the drug candidates, 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 reinvigorate the clinical OA therapeutic pipeline.

*Kick-starting the OA disease modifying therapeutic pipeline*
Key deliverables

Axis 2: Target Identification and Validation
- Biologic pathways of interest for potential disease modification
- Candidate therapeutics matched to pathways of interest
- Identification of candidate biomarkers to co-develop as companion diagnostics

Axis 3: Innovative methodologies to evaluate treatment effects
- Clinical imaging and pain/function endpoints qualified for use in drug discovery and development
- 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. The templates will be adaptable, as appropriate, to specific therapeutics and set clinical success criteria for each stage
- 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 6: Adoption of innovative clinical trial designs/Improved access to medicines
- Ongoing dialogue with regulators and stakeholders to define endpoint criteria for successful registration for late stage clinical development and market approval
- A collaborative network of clinical trial centres throughout the EU to enable rapid recruitment of specific OA phenotypes and to provide expert clinical trial execution

Axis 7: Development of novel therapeutic agents
- 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

Impact of the research on delivering new medicines
At present, the only pharmacologic options for patients with OA are symptomatic treatments such as NSAIDS, opioids, and intra-articular corticosteroids and viscosupplements. Joint replacement is the ultimate outcome for patients with disease that progresses to joint failure. The work proposed herein is intent on delivering disease modifying treatments that will improve function and quality of life, reduce pain, and prevent joint failure.

Approximately 60–70 million individuals in the G7 countries have symptomatic OA. The prevalence of OA is increasing due to the aging population of these countries and the increasing rate of obesity. OA is the most common pain condition treated by primary care physicians and it is the most common cause of disability in people over the age of 65. There are no therapeutic options to slow or reverse OA progression – this initiative is designed to replenish the drug pipeline for OA and provide treatment options for patients with this debilitating disease.

Multiple hurdles exist to developing DMOADs which, together with prominent late-stage DMOAD failures, have resulted in a dismal DMOAD pipeline and little enthusiasm for companies to enter this space. The consortium approach outlined here is proposed to reinvigorate R&D in the OA arena and will enable focused studies with a personalized medicine approach to best evaluate promising therapeutics.

Funding for the proposed research will add value to the EU economy and scientific capabilities in the near term via a number of factors. Of significant importance is the draw this funding would create for industry to conduct collaborative clinical development of OA therapeutics in the EU and, in parallel, it
will foster industrial–academic partnerships with EU centres. It is envisioned that, in short order, this work will provide a tangible collaboration ‘win’, demonstrating the synergies available and their value to drug development in OA.

**The need for Public Private Collaboration**

The major societal challenges highlight the need for cooperation between many interested parties. The proposal of a roadmap and the outline of the many expected deliverables demonstrate the complexity of improving the treatment of OA. At the same time the lack of ability to develop new efficient drugs is evident as mentioned and explained above. In addition, owing to the economic challenges facing the pharmaceutical industry, companies have resorted to substantial cuts in R&D spending that have often resulted in abandoning areas considered high risk, including OA. This cocktail of a large and growing societal challenge, complex research to be conducted involving many interested parties and the economic conditions in the pharmaceutical industry calls for establishing a public private partnership to tackle the problem of OA through synergies that can be attained with sharing of expertise, data and resources.

If successful, this partnership would alleviate the significant economic burden caused by this debilitating disease; specifically on the health care systems, impact on activities of daily living and employment. OA is the most common cause of disability in Europe. Joint replacements alone cost in excess of €2 billion per year in Europe (www.treatOA.eu). This proposal aims to facilitate the development of novel therapeutics to change the natural course of OA and reduce the societal and economic burden of OA.

### 3.3. Cardiovascular diseases

**The societal impact of Cardiovascular diseases**

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality globally. Having been a problem in developed countries for many years they have become a major problem of the emerging and the poorer countries and the WHO expects CVDs to remain the main cause of death and disability in the world in 2030 with more than 23 million victims. In addition to the direct effects such as myocardial infarction, heart failure and pulmonary hypertension, CVDs are often linked to other diseases such as chronic kidney disease and chronic obstructive pulmonary disease (COPD).

It seems clear that there is a correlation between the occurrence of these diseases and changes in nutrition and lifestyle, and the demographic trend fosters this development further. Despite the progress made over the last decades in the treatment of certain CVDs such as hypertension, the development of more effective therapeutic interventions is limited by the insufficient stratification of patients early in the course of their disease. A consequence of imprecise clinical phenotyping is the current huge number of patients needed in clinical trials in this field. Understanding the molecular basis of CVDs would allow for a specific and early diagnosis and the development of preventive measures and more tailor-made treatments to address the underlying cause of the disease. The necessary technologies like (epi-) genomics, proteomics and metabolomics but also next generation sequencing and bioinformatics are available but need to be used in a coordinated, systems biology-based approach.
Nature of research to be conducted: Alignment with research axis

Axis 1: Reclassification of Disease by molecular means
- Understanding and classification of CV and related diseases, especially heart failure, pulmonary heart disease, myocardial infarction and chronic kidney disease
- Identification and validation of suitable diagnostic measures for primary prevention

Axis 2: Target Identification and Validation
- Translation of better disease understanding into novel therapeutic targets
- Identification of small molecules and/or biological drugs to be used for proof of concept studies, validating targets identified

Axis 3: Innovative methodologies to evaluate treatment effects
- Identification of predictive biomarkers and animal models

Key deliverables

Axis 1: Reclassification of Disease by molecular means
- Better understanding and definition of CV and related diseases, especially heart failure, pulmonary heart disease, myocardial infarction and chronic kidney disease
- Identification and validation of suitable diagnostic measures for primary prevention

Axis 2: Target Identification and Validation
- Use of a critical mass of well-defined biosamples to perform genome-wide association studies (GWAS) as well as epigenomic and metabolomics studies to identify potential new targets

Axis 3: Innovative methodologies to evaluate treatment effects
- Use of novel technologies like non-invasive diagnostic tools or induced pluripotent stem cell-based systems for use in research and development on CVDs

Impact of the research on delivering new medicines
CVDs affect millions of patients worldwide and developing new, more specific (‘personalized’) medicines would address a high societal need. For patients, a correct diagnosis and better stratification will lead to the right treatment from the beginning, thereby significantly increasing the potential to delay disease progression, lower mortality and increase quality of life. Consequently, better patient stratification and clearly defined subgroups offer the opportunity to conduct clinical trials with a much lower number of patients involved than typically required for CVD studies, thereby increasing the efficiency of clinical development in this area. A better understanding of the disease mechanisms and predictive tools for safety and efficacy will also help to lower the attrition rate and make the R&D process more effective.

Pharmaceutical and biotech companies as well as academic research institutions will have a more robust infrastructure and scientific basis for their work, enabling them to develop new medicines for more targeted therapies. This offers the opportunity to lower development costs and to deliver a socio-economic benefit by increasing the quality of healthcare in this area. Allowing people to be active for longer in their working life and with a lower need for costly care will also have a positive effect on the economy.
The need for Public Private Collaboration
Elucidating complex disease pathways and developing evidence-based strategies requires a joint effort of many different disciplines and stakeholders. The effort needed to develop new drugs in the area of CVDs has increased significantly, e.g. as shown by the high number of patients in clinical trials. This has resulted in a reduction of resources for research in this area in several of the major pharmaceutical companies. Bringing together experts from academia, industry, patient organizations and regulatory authorities via a PPP is probably the most promising approach to make the process more reliable, predictable and productive.

3.4. Diabetes

The societal impact of diabetes
Approximately 366 million people have diabetes and another 280 million are at identifiably high risk of developing diabetes. If nothing is done, by 2030 this number is expected to rise to 552 million with diabetes and an additional 398 million people at high risk. Diabetes and its complications not only cause human suffering but are also a major economic burden to society. There is a huge unmet medical need for new pharmaceutical therapies for the prevention, treatment and cure of diabetes, especially in a multidimensional, patient-tailored treatment approach. Such an approach should take advantage of developments in genomics and extended phenotyping, enabling the disease to be characterized on an individual patient basis.

Diabetes is a multidimensional disease affecting a range of age groups from young children primarily suffering from complete loss of beta cell function to transient gestational diabetes and adult diabetes with impaired insulin secretion, subsequent failure of beta cell function, finally leading to micro- and macrovascular complications.

The treatment of diabetes and its complications is one of the major current and future healthcare costs factors worldwide due to increases in the aging and obese population. We still have insufficient understanding of the causal factors that drive development and progression of the different types of diabetes and its complications. Therefore, it is our primary goal to identify the causal factors and to quantify their individual contribution. On this basis, the development of individual treatment options taking into account different environmental, lifestyle, socioeconomic and genetic factors is set to become far more important. The ultimate goal is the prevention and cure of diabetes, supported by individual screening programs to confirm suspected diabetes.

The opportunities and challenges of this new PPP are based on project-clustering research with a global perspective. The focus will not only be on new non-competitive, science-driven research, but also on the implementation of new R&D models that drive changes in the regulatory framework, HTA assessment and incentive system and that could enhance the likelihood of the development of new viable medicines to the benefit of patients and society.

The new PPP will drive major and fundamental innovations to address the identified barriers in diabetes care and will include diagnostics, prevention and treatment options.

Nature of the research to be conducted
Research projects should respond to the identified challenges by addressing the following four key areas of activity that will be essential for success:

New treatment approaches
- 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. It will be necessary to translate these findings into validated novel treatment approaches, including the appropriate operational setup to gain access to these discovery and development platforms.
- Utilizing relevant patient cohorts and data, e.g. results and best practices from IMI Projects EHR4CR and EMIF, undertake functional characterization of novel genes/proteins to better understand the role of specific targets and pathways in the context of the development and treatment of diabetes and its complications.

Patient-focused improvements of benefit–risk assessment of diabetes drugs:
- 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. 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).

Key deliverables

Axis 1: Reclassification of Disease by molecular means
Patient-centric translational diabetes research framework and development pathways:
- 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.
- Reclassification of diabetes through advances in disease taxonomy and consultations with stakeholders for validation of new classification.
- Improved understanding of diseases and treatment paradigms through better definition of pre-clinical development strategies (with ability to discharge risk early on in the development process) and predictive markers of susceptibility and disease progression for clinical trial designs and endpoints.
- Improved disease surveillance and disease management.
- Restoration/regeneration of beta cells in vivo and in vitro (using e.g. results from the IMI project IMIDIA).
- 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.
- Vaccination for Type 1 diabetes (using framework and methods developed within the IMI Vaccination Projects).

Axis 3: Predictors of drug/vaccines efficacy and safety
- Identify markers that broaden the understanding of the influence of ethnicity on drug efficacy and drug safety.
- Innovative methods for the prediction of safety of clinical candidates, and new tools to assess them (e.g. using results, best practices and setup from the IMI project STEMBANCC).
- Establish a new methodological regulatory framework for benefit–risk assessments during Benefit–risk decision-making: develop positions on the use of benefit–risk assessment in decision-making: pre-approval regulatory data requirements, regulatory post-approval data required to maintain the benefit–risk assessment, benefit–risk labelling content, and HTA decisions

**Axis 4: Innovative methodologies to evaluate treatment effects**
- New innovative tools for precise diagnosis of diabetes and for clinical assessment of drug efficacy
- Improvement of the translation from pre-clinical target identification into clinical development
- New diagnostic solutions 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 identified approaches into the patient-centric translational diabetes R&D framework

**Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines**
- New stratified and more efficient clinical trial designs leading to new approval pathways
- Integration of the identified markers such as genomic, proteomic and metabolomic markers into regulatory approval and clinical practice
- 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 HTA project)
- Progressive licensing: 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
- Companion diagnostics: develop strategy for better clarification of and improvements to the regulatory framework for companion diagnostics
- Develop methods for understanding differences between patients in clinical trials and patients in ‘real life’
- Develop methodological tools to generate evidence of relative effectiveness
- Combination products: clarify regulatory approaches to innovative fixed dose products (e.g. combinations of monoclonal antibodies, and ‘novel–novel’ products)

**Impact of the research on delivering new medicines**
This research will enable the healthcare system to diagnose and treat patients with diabetes at an earlier stage in the disease, to monitor treatment success and to better estimate the risk of developing disease complications. Special focus will be given to personalized medicine approaches, putting the patient into the centre of the healthcare system by customizing therapy to individual patients. This approach will accommodate individual differences at all stages from prevention to treatment, leading to more effective treatment. Intensive research to address such a prominent disease, especially in the obese and the aging population, will respond to an urgent societal need.

The proposed research will also enable the pharmaceutical industry and research units to develop new innovative drugs and to move into an era of targeted therapies with improved patient outcomes. Clinical phenotyping and the identification of new diagnostic pathways by the analysis of patient records, biobanks, computational tools, lifestyle databases, habits, family history, imaging, metabolome, RNA/DNA sequencing, and functional imaging might lead to a change in disease classification.
Lastly, diabetes and its complications are one of the major cost factors for the European healthcare system. The ability to diagnose and prevent the disease and its complication at an early stage of development will have a positive impact on the efficient utilization of healthcare resources.

The need for Public Private Collaboration
Approaches to healthcare are undergoing radical shifts. Moving away from the era of blockbuster drugs as 'one-size-fits-all' therapy options toward more targeted, personalized therapies and precise medicines for the diagnosis, treatment and prevention of diabetes must involve all stakeholders of the healthcare system. Industry, medical professionals, regulators, citizens and patient organizations and funding bodies will all need to work together closely and cooperatively to achieve this overarching goal. All projects require the combination of expertise of large and mid-size pharmaceutical and biotech companies, academia and other relevant public institutions such as regulators in order to secure the necessary expertise for successful execution. This ambitious goal requires successful networking in public private consortia on a neutral EU-funded platform.

3.5. Neurodegenerative diseases
The societal impact of neurodegenerative diseases
There is a major unmet need for disease modifying treatments for neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and multiple sclerosis. AD alone affects over 15 million people worldwide and is expected to triple by 2050. If we fail in dementia research, there will be unprecedented pressure on health services across the world and costs that cannot be borne by developed let alone less developed economies. There is a real lack of disease understanding for most neurological diseases and as a result there are very few precedent mechanisms. This is confounded by the lack of robust pre-clinical models faithfully recapitulate the features of neurodegenerative pathology and to this point they have been poor predictors of clinical disease and drug efficacy.

Increasing evidence supports earlier medical intervention for patients with neurodegenerative disorders as an effective means to reduce overall costs, ease caregiver burden and allow patients to remain independent for longer. 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 progression. Misdiagnosis has profound impact, on one hand treatments are offered to patients which often have little chance of providing benefit while on the other hand patients are being denied access to potentially beneficial novel and approved agents due to misclassification to a different “disease class”. Inaccurate diagnosis 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. However, given the number of potential mechanisms that have been implicated in neurodegenerative diseases, there is at least hope that if we can target the right population at the right time there is at least a chance of success in the clinic for this urgent unmet need.

A data-driven approach that integrates subject level clinical and biomarker endpoints, independent of disease status, is required in order to accurately identify and inform individuals at risk for developing neurodegenerative disease, to appropriately stratify subjects for clinical investigation and to develop endpoints that can support internal decision making along the clinical development path especially where trials are long in duration especially in the case of preventative or disease modifying
Nature of the research to be conducted
● Collect, analyse and record a comprehensive population-based Central Nervous System Health Profile (CNS-HP)
  o Collect biomarker data (derived from imaging endpoints such as structural and functional MRI, PET as well as measurement of analytes in physiologically relevant fluid such as urine, blood, and cerebrospinal fluid), genetic signatures, a clinical battery and a lifestyle questionnaire. Data should include indices of: blood pressure, BMI, insulin resistance and LDL-cholesterol. SNP data for a short list of genes associated with increased risk of neurodegenerative disease should also be obtained from within this population.
  o Identify patients at risk for developing neurodegenerative disorders in order to initiate earlier intervention.

Key deliverables
Axis 1: Reclassification of Disease by molecular means
● Identification of core elements of the CNS-HP including biomarker measurements and clinical assessment endpoints. This activity would involve investigation and application of novel biomarkers not yet utilized for this purpose such as PET imaging ligands for various neurotransmitter systems. Additionally, opportunities to implement novel imaging agents that are currently under development for various proteinopathies, gliosis and neurodegeneration could be utilized.
● Biomarkers qualified for use to support diagnosis, assess disease progression and support patient stratification and clinical trial design.

Axis 2: Target Identification and Validation
● Identification and validation of novel targets for prevention and disease modifying therapies in specific subpopulations of patients with neurodegenerative disorders.

Axis 4: Innovative methodologies to evaluate treatment effects
● Identification of robust biomarkers to support innovative trial designs and the assessment of therapeutic effect.

Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines
● Agreed biomarker validation criteria through partnership with regulatory authorities.
● Innovative trial designs for the conduct of preventative and disease modifying trials.

Axis 7: Development of novel therapeutic agents
● Assessment of novel therapeutic asset(s) for preventative and/or disease modifying treatment of disease.

Operational Excellence
● Database management system (to allow easy access when novel and experimental diagnostics or therapies are identified).
● Infrastructure for biobanking subject biosamples for future inquiries.
● 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.
Impact of the research on delivering new medicines

Large databases with clinical and biomarker data would be available in a format that could enable rapid selection of well-defined subject cohorts for subsequent testing of novel clinical candidates. Moreover, as the development of novel biomarker endpoints progresses, these (inter)national pools of characterized subjects can be rapidly tested. Novel data generated with new therapies can also be quickly integrated into already developed systems-based analysis approaches. If longitudinal data points are also collected then clarity with regard to disease susceptibility and progression will have an even greater impact. Furthermore, given the heterogeneity of neurodegenerative disease such as AD, a more accurate and in-depth diagnosis will lead to the patients being recruited to the most relevant disease modifying drugs.

The availability of a shared research tool would also lead to financial savings through the obvious efficiencies derived from pooled resources and expertise. The economic impact of the proposed research will also be measurable as 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.

The need for Public Private Collaboration

Early and correct diagnosis of neurodegenerative diseases is important for selecting the most appropriate care at the right time. However, this is extremely difficult with the tools available today. Consequently, all interested parties must work together with the aim of 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. A framework for scaling collection of biomarker and clinical data is already in place with successful operationalization of worldwide ADNI efforts and others. What is unique about this proposal and why a large scale PPP is required is that large segments of national populations will be solicited for participation. Much like current recommendations for certain population segments to undergo mammograms, colonoscopies or PSA testing, this proposal would generate a CNS-HP to inform on the current state of health and wellbeing of brain function as it relates to neurodegenerative disorders.

3.6. Psychiatric diseases

Societal impact of Psychiatric disease

Mental disorder is a huge and growing global burden of disease, especially in the developed world, but increasingly also in emerging economies. According to the WHO, more than one third of the populations in most countries fulfil diagnostic criteria for a mental disorder at some point during their life. A 2005 review of surveys in 16 European countries found that 27% of adult Europeans are affected by at least one mental disorder in a 12 month period.11

Among the severe mental health disorders, depression is the most common, affecting 6–8% of EU citizens in any one year, corresponding to more than 20 million people of working age in the EU suffering each year from depression. The WHO estimates that over 120 million people worldwide suffer from the condition. The total annual tangible cost of depression in Europe was an estimated

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12 http://www.depressionplatform.eu/the-depression-challenge
€113 billion in 2004.\textsuperscript{13} According to the WHO, depression alone accounted for the greatest burden of disease in middle and high income countries in 2004, and this is expected to apply worldwide by 2030.

Other mental disorders, such as alcohol dependence, anxiety disorders, schizophrenia and bipolar disorder also represent major disease burdens. 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 disorders\textsuperscript{14} in Europe alone was €798 billion in 2010, substantially higher than for any comparable disease area.

Mental disorders are serious and debilitating; they can be life-threatening conditions. They invariably severely impact the lives of the individual and their relatives. Also, mental disorders 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. Unipolar depressive disorder is the third leading cause of disability worldwide, accounting for 65.5 million years lost. Mental disorders are also characterized by a large problem of co-morbidity. Thus, persons suffering from mental disorders are overrepresented also with many somatic disorders. The association and interdependency of mental and somatic disorders is currently under research as it is clear that the presence of mental disorders impacts the severity of somatic disorders.

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. Significantly, 35% of patients experience remission after first treatment. In addition, more than 30% of patients experience no remission after two antidepressants. Moreover, 75% of patients with alcohol dependence relapse within the first year. Many patients are reluctant to seek help and mental disorders are not recognized as ‘real’ diseases. However, the biggest challenges are proper diagnosis and limited response rate. 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. Although several treatments are available, positive response is limited and for most mental disorders treatment algorithms are based on trial and error. Therefore, further research is needed to gain 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.

**Nature of the research to be conducted**

Significant progress has been made in clinical models of mood disorders and biochemical brain mechanisms, leading to the development of effective new drug treatments. However, investment in research and development of more effective psychotrophic medicines in Europe is declining.\textsuperscript{15,16} Existing treatments may relieve symptoms but rarely cure the underlying diseases.

\textsuperscript{13} European Brain Council. Cost of disorders of the brain, 2011.

\textsuperscript{14} Note: brain disorders consist of a broader range of diseases than the WHO definition of mental disorders.


[www.icmpe.org](http://www.icmpe.org)
The identification of biomarkers and neuroimaging techniques promise far more effective ‘diagnostic–therapeutic’ treatments and improved patient outcomes in the future. Hence, a major effort is needed to reassess brain diseases in the light of a molecular-based system, and this will require collaboration between clinicians, academia and the pharmaceutical industry, in close coordination with regulators.

The evaluation of new drugs for prophylactic effects or other longer term benefits will require lengthy and costly clinical trials. At present new drugs are typically evaluated by reference to their short-term clinical benefits. A similar collaborative effort is, therefore, needed to develop new tools for novel drug evaluation.

Key deliverables

Axis 1: Reclassification of Disease by molecular means
- An understanding of how to stratify patients and target the treatment to individual patient and disease characteristics
- Advance the understanding of the brain processes
- Reassess brain diseases in the light of a molecular-based system, applying new taxonomy where appropriate

Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines
- Agreed biomarker validation criteria through partnership with regulatory authorities
- Innovative trial designs for the conduct of preventative and disease modifying trials

Axis 7: Development of novel therapeutic agents
- Assessment of novel therapeutic asset(s) for preventative and/or disease modifying treatment for mental disorders

Impact of the research on delivering new medicines
Societal benefits would include the provision of both prevention and effective treatments for a large and growing patient population, whom today do not receive adequate treatment. Because of the impact of these diseases on not only health, but also people’s ability to function socially and at work, addressing this area offers huge potential savings for society, reducing healthcare costs and social benefit expenditure while increasing employment and productivity.

The symptom-based treatment approach for managing these diseases needs to be enhanced with the application of treatment approaches that take advantage of the latest evidence and tools available. Furthermore, the number of untreated patients is high. Hence, there is a major unmet medical need which, if properly addressed, will improve the health and quality of life of patients and their families.

The need for Public Private Collaboration
With an average duration of 13 years, the development time for a typical psychiatric medicine is longer than for other disease areas. The failure rate of medicines in psychiatry is higher than that for other disease areas and many medicines fail late in the development process – at Phase 3 or even at registration – leading to particularly high financial losses.\(^\text{17}\) 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.

Therefore, steps need to be taken to ensure that research into mental disorders is encouraged for the benefit of patients and society. The PPP, based on a commitment to overcome the challenges above, would allow the pharmaceutical industry to enter a high risk healthcare area and to start collectively a dialogue with a range of stakeholders beyond health and research needed to address this huge healthcare challenge.

3.7. 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. There remain considerable unmet needs which, if addressed, could lead to further benefits for patients. The scale of unmet need in respiratory disease means there can be no respite in fighting what is one of the biggest health challenges in the world today. The WHO estimates that respiratory diseases are responsible for one in six deaths worldwide.\(^{18}\) This burden continues to grow, presenting enormous challenges to patients, HCPs and payers. 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.\(^{19}\) Unlike asthma, COPD remains a relatively poorly understood disease despite one person dying of COPD every 10 seconds, more than the combined number of lives claimed by breast and lung cancer.\(^{20}\) By 2020, COPD is predicted to become the world’s third most common cause of death.\(^{21}\)

Asthma and COPD represent a staggering economic burden. In 2010, COPD alone was estimated to have cost the global economy $2.1 trillion.\(^{22}\) 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. This issue may have led to failure of promising drug candidates due to the conduct of clinical trials in a broader population, thus masking clinical efficacy which may be observed in a subset of responsive patients.

To improve the success rate of new drug development, changes in the R&D model will be required, including a focus on stratified medicine and streamlined clinical development. What are missing to facilitate these approaches are tools for evaluating the impact of therapeutic candidates on disease

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\(^{19}\) GARD. Chronic respiratory diseases. [http://www.who.int/gard/publications/chronic_respiratory_diseases.pdf](http://www.who.int/gard/publications/chronic_respiratory_diseases.pdf)


activity in early-phase drug trials. 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. However, due to methodological complexity, volume of data collection and the resources required for developing and qualifying biomarkers and other endpoints, it is unlikely that a single pharmaceutical company can develop these tools alone.

Nature of the research to be conducted

- To identify and replicate/qualify candidate biomarkers:
  - Several biomarkers that may be useful in characterizing subgroups of patients and/or predicting clinical outcomes have been proposed.
  - There is a need for independent replication of existing data to validate/qualify these biomarkers for use in intervention studies or regulatory submissions.
  - New biomarkers will need to be identified.
  - There is a need to develop regulatory pathways to permit the use of respiratory disease markers in early clinical testing.

- To identify/confirm predictors of disease exacerbations:
  - Acute exacerbation is an important event associated with disease morbidity and mortality and high societal burden. The heterogeneity in an individual patient’s propensity to experience an exacerbation is poorly understood. Defining long-term risk factors and predictors of exacerbations is essential for a personalized medicine approach in respiratory diseases. However, the identification of predictors/markers for exacerbations and their resolution provides an example of one of the key problems in developing a biomarker: the need for a precise definition of the disease phenotype.

- To better characterize systemic disease or co-morbidity in respiratory disease:
  - The prevalence of co-morbidities is increased in respiratory disease as compared to a matched general population. Many co-morbidities share smoking as a major risk factor or disease-related component, e.g. cardiovascular disease, depression, osteoporosis. None of the studies published so far was capable of determining causality of co-morbidities associated with respiratory disease. It is not known if co-morbidities in respiratory disease are directly related to the respiratory disease or a consequence of shared risk factors unrelated to respiratory disease pathogenesis.

- To better define the characteristics of known and novel respiratory disease phenotypes:
  - Recognising the different phenotypes within different classifications of respiratory disease is important for understanding underlying disease processes. These phenotypes are clinically relevant due to potential differing responses to therapeutic interventions.

Key deliverables

Axis 1: Reclassification of Disease by molecular means
- International consensus on means to identify disease manifestations in subsets of patients

Axis 4: Innovative methodologies to evaluate treatment effects
- Qualified biomarkers for stratification, dose-ranging and assessment of efficacy

Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines
- Streamlined drug development by enabling drug discovery teams to better identify and target patient populations and optimize development plans.
- Establishment of a co-ordinated respiratory disease clinical trial network to enhance the efficiency of drug development.
Impact of the research in delivering new medicines
Streamlined clinical development has the dual intent of getting new medicines to patients in a timely manner and reducing the number of failures during drug development, particularly failures in late stage clinical testing. Investigators will have a unique opportunity to gain funding to support the development of their new and innovative approaches to the identification and validation of biomarkers while at the same time gaining invaluable insight into the complexities of drug development. The opportunity to build a network of investigators through which academics, pharmaceutical and biotechnology companies can advance the pre-clinical and clinical development of new assets will attract future drug discovery efforts to Europe. Furthermore, utilizing the European clinical trial network, as well as new diagnostic and biomarker tools, will improve efficiency and reduce the cost of clinical development.

The need for Public Private Collaboration
To improve the success rate of new drug development, changes in the R&D model will be required, including a focus on stratified medicine and streamlined clinical development. Stratified medicine, an effort to get effective medicines to patients who can benefit most, will require the development of intermediate biomarkers and surrogates that improve the ability to both select patients and to measure efficacy using outcomes that are meaningful to patients and relevant to their disease progression.

There is recent consensus about the need for better understanding of newly proposed and existing 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 process of identifying appropriate measures and outcomes is not straightforward and must reflect the needs of various parties with differing priorities. Qualification of such measures is time-consuming and involves a substantial commitment of resources.

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.

3.8. 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 artherosclerosis. 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. As a result, they are the subject of 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.

**Nature of the research to be conducted**

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 OMERAICT, 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.

*Kick-starting the autoimmune and inflammatory disorders management pipeline*
Key deliverables

Axis 1: Reclassification of Disease by molecular means
- 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.

Axis 4: Innovative methodologies to evaluate treatment effects
- 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
  - 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 6: Adoption of innovative clinical trial designs/Improved access to medicines
- Dialogue with regulators and stakeholders to improve definition of endpoint criteria for successful registration
  - Existing therapies on novel endpoints
  - Novel uses for existing therapies
  - Novel therapies and novel endpoints

Impact of the research in delivering new medicines
The proposed research is intent on delivering improved methods for recognition and diagnosis, and disease modifying treatments that will improve function, quality of life and prevent complications among patients with autoimmune and inflammatory disorders (AIIDs). This will translate into societal benefits. Approximately 10 million individuals in the G7 countries suffer from one or other AIID. Prevalence of these disorders is increasing as disorders are more frequently recognized. There are limited therapeutic options which reverse disease progression; this work is designed to provide improved recognition, diagnosis and management options for affected patients.

Multiple hurdles exist to developing new treatments for many AIIDs. The consortium approach outlined here is proposed to reinvigorate R&D in the AIID arena and will enable focused studies with a personalized medicine approach to best evaluate promising therapeutics. Funding for the proposed
research will add value to the EU economy and scientific capabilities in the near term via a number of factors. Of significant importance is the draw this funding would create for industry to conduct collaborative clinical development of AIID therapeutics in the EU.

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.

3.9. Ageing-associated diseases

Societal impact of ageing-associated disease
The proportion of individuals aged 60 years and older, which accounted for approximately 10% of the total world population in 2000, will increase to approximately 22% of the population by 2050. This fact presents new challenges both to individuals and to society. Advanced age is often accompanied by chronic disease and an increased susceptibility to infections that negatively impact an individual’s quality of life. These diseases pose enormous challenges both for individuals and societies in terms of life quality and economic burden, thereby necessitating an urgent need for aging societies to address these health concerns. Some consequences of aging are age-related changes in vision, hearing, muscular strength, bone strength, immunity and nerve function. Examples of aging-associated diseases are CVD, cancer, arthritis, dementia, cataracts, hearing loss, osteoporosis, sarcopenia, diabetes, hypertension and Alzheimer’s disease. The incidence of all of these diseases increases rapidly with aging, often exponentially. Furthermore, an often neglected but common phenomenon of aging is the multi-morbidity of this patient group.

Specific medical conditions of an aging population, in particular aging-associated diseases of the cardiovascular, neurological and musculoskeletal organ systems, are specific challenges of aging biology. Aging mechanisms outside of disease pathways are not well understood and the fact that aging is an incremental, whole-body problem is often neglected. All cells, tissues and organs age in different ways, at different rates, in different people. An exciting area of research – the genetic regulation of aging – has emerged over the past ten years. Aging projects under Horizon 2020 will broaden our understanding of the genetic and molecular basis for the aging process, gained by new genetic, molecular and proteomic techniques, and support the development of new medicines for the aging population.

Nature of the research to be conducted
By identifying basic molecular and physiological mechanisms that underlie age-related dysfunction, with a focus on molecular studies performed primarily in cell culture and model organisms, new treatment pathways for an aging population might be identified. New trial designs could be developed based on a better understanding of the physiological conditions, the specific pathologies of elderly, and of the variability of clinical outcomes of trials with geriatric patients. This will also be supported by a better understanding of the effect of aging on drug responses.

A dialogue with the health authorities will be opened to review criteria for pharmacological profiles, safety, clinical endpoints, patient stratification and trial inclusion criteria for the aging patient population. A specific challenge in aging is that aging per se is not a disease – it is the disability and
loss of function that occurs with aging that interests health authorities. Thus, there will not be indications for ‘old age’, but rather specific indications for each facet of the organ system declines listed above. The ‘aging’ drugs that the health authorities currently utilize are typically those that target a single specific disease long after the microscopic seeds of the problem have blossomed into significant morbidity. Together with health authorities, novel and tailor-made approval pathways for drugs for the aging population will be considered.

The following key areas of research will be investigated:

- Basic research on genetic manipulations that affect the length and/or quality of life, i.e. genetics of healthy aging, genome stability and aging as well as metabolic regulation of aging
- Physiology research to identify age-related changes affecting tissue and organ function. These activities could be divided along various age-associated disease conditions, such as Immunology, Metabolism, Respiratory, Musculoskeletal and Neurological Diseases
- New research models for aging could be investigated
- Benefits and adverse effects of clinical interventions for age-related conditions could be investigated along with specific pathologies of old age. The variability of age-related clinical outcomes could be investigated with emphasis on old-age patient cohorts and their specific physiological conditions

**Key deliverables**

**Axis 1: Reclassification of Disease by molecular means**
- Greater understanding of genetic and physiological factors relating to aging and age-associated diseases
- Database of key informational resources

**Axis 4: Innovative methodologies to evaluate treatment effects**
- Validated new research models for the study of aging

**Axis 6: Adoption of innovative clinical trial designs/Improved access to medicines**

**Vaccines**
Develop appropriate vaccine formulation allowing to circumvent the immunosenesence and induce protective immune responses against ageing associate diseases. Infrastructure for biosample collection, archiving and access

**Impact of the research on delivering new medicines**
Across the developed and now the developing world, human societies are aging rapidly. The traditional ‘age pyramid’ with many young people and fewer old people is being replaced with an ‘age rectangle’ or even an ‘inverse pyramid’, where there is an equal or greater number of older people in society. The hope is that chronological age can be dissociated from disability. There is evidence that this is already happening in that people in their 60s and 70s today are much more functional than people of the same age were 40 years ago. Pharmacological solutions to accelerate this dissociation are in their infancy but are crucial to ensuring that the aging population can lead productive and fulfilling lives for the benefit of individuals and society as a whole.

**The need for Public Private Collaboration**
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.

3.10. **Oncology**

10) Stakeholders are invited to indentify the key research areas that they feel should be the focus of efforts in the field of Oncology.

3.11. **Rare/Orphan Diseases**

11) Stakeholders are invited to indentify the key research areas that they feel should be the focus of efforts in the field of Rare/Orphan diseases.

3.12. **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, 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. Furthermore, reduced childhood mortality, increased longevity and changing birth rates are dramatically changing 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 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.

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 and new vectors 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.

**Core Objectives:**

- 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)
Link to Axis 2: Target identification and validation
- 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

Link to Axis 3: Early prediction of efficacy/safety
- Identify novel biomarkers for vaccine efficacy and safety through systems biology approaches, enabling the screening of multiple candidate vaccines in 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

Link to Axis 7: Development of novel preventive/therapeutic agents
- 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

Other
- 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)

Key deliverables
**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) and non-respondent 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 antigen design and the ability to steer the immune response using novel adjuvants and delivery systems
- Cost-effective manufacturing systems with significant cost savings that benefit industry, healthcare systems and society
- Pathways to inform discussion on regulatory guidance

**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)
- Accelerating development of novel therapeutic vaccines for treatment of cancer and other areas of high unmet medical needs
• 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
• Shorter development times, favouring faster patient access to highly innovative vaccines

For Society
• Rational design of clinically meaningful vaccines capable of responding to priority public health and disease challenges
• Allow Europe to maintain its leadership in vaccine research and production by strengthening and pooling capacity, capability and critical mass scattered across key centres of excellence in the EU
• Strengthened coordination across sectors and stakeholders, resulting in improved structures and governance for joint action to tackle societal challenges
• Contribution to the EU research base and economic competitiveness in the global market.

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.

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.
Appendix 1: Measuring the impact of the PPP in Europe

The table below lists key outputs which could define the success of the PPP for each axis of activity described in the previous section:

<table>
<thead>
<tr>
<th>Axes</th>
<th>Deliverables by 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reclassification of diseases by molecular means</td>
<td>Reclassification of four diseases by molecular supporting personalised medicines approach</td>
</tr>
<tr>
<td>Target identification and validation</td>
<td>Up to 10 new targets identified and up to 5 clinically validated</td>
</tr>
<tr>
<td>Predictors of efficacy and safety</td>
<td>Improved predictability of non-clinical safety models by up to 10%</td>
</tr>
<tr>
<td>Innovative methodologies to evaluate treatment effect</td>
<td>Novel biological endpoints to support internal decision making and where possible clearly linked to clinical relevance implemented with regulatory approval for at least four diseases</td>
</tr>
<tr>
<td>Benefit/risk assessment in individual patients</td>
<td>Develop an IT framework to allow real-time monitoring of benefit/risk including direct engagement with the patient</td>
</tr>
<tr>
<td>Innovative clinical trial designs and access to medicines</td>
<td>Adoption of innovative clinical trials design and approaches to real world data for at least two diseases Establishment of two clinical trials networks in areas with unmet need</td>
</tr>
<tr>
<td>Development of novel preventive and therapeutic agents through new research models and associated regulatory pathways</td>
<td>Development of at least two new therapies or preventions in areas with high unmet need and limited market incentives Validation of at least two novel delivery mechanisms for new drugs Up to 40% savings on the manufacturing costs of at least one novel therapy</td>
</tr>
</tbody>
</table>

As the different milestones are achieved, the above outcomes will in medium to long term improve the R&D productivity and efficiency of healthcare delivery:

![Right prevention and treatment, for the right patient at the right time](image)

**Figure 2 : Impact/value added of the PPP deliverables**

**Stakeholder Consultation**

12) In your opinion are impact measures presented appropriate and achievable based on the overarching objectives of the PPP? Are there additional measures that you feel should be included?

Consultation document 18th March 2013