IMI Socio-economic Impact Assessment Expert Group

Final Report

May 2016

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This report has been drafted on behalf of the Expert Group by **BiGGAR Economics**, Pentlands Science Park, Bush Loan, Penicuik, Midlothian, EH26 0PZ, Scotland, +44 (0)131 514 0850

info@biggareconomics.co.uk www.biggareconomics.co.uk

1. Foreword

I am happy to present the first in-depth socio-economic impact report on the first IMI projects.

The legislation creating the Innovative Medicines Initiative (IMI) notes that IMI 'should provide socio-economic benefits for European citizens'. As the first IMI projects are drawing to a close, now is a good time to analyse what they have delivered and assess whether or not IMI is on track to achieve this ambitious goal.

To this end, IMI asked some of Europe's leading experts in health economics, research evaluation and innovation policy to analyse in detail the outputs and impacts of the first nine IMI projects now completed.

The results of their work are contained in this report, which in my opinion is at the cutting edge of evaluation research and represents a critical step in understanding the impact at all levels of the unique partnership that is IMI.

The findings of the report are all the more impressive when one considers that the projects featured account for less than 10% of the total IMI 1 budget. This means that we can be optimistic that more good news will emerge from IMI's growing project portfolio in the months and years to come.

I would like to take this opportunity to thank the participants of the projects studied for providing IMI and the experts with the information needed to carry out this study.

Finally, I would like to thank the experts and rapporteur, as well as the IMI staff involved in this project, for producing a report that contains a wealth of data and information yet is eminently easy to read. I am convinced that it will provide IMI with much inspiration and food for thought in the months and years to come. We will of course be implementing the findings of the report in the evaluation of the rest of the ongoing IMI project portfolio.

Pierre Meulien, IMI Executive Director

May 2016

2. Executive summary

The Innovative Medicines Initiative (IMI), a Joint Technology Initiative of the European Commission in medicines development, appointed an Expert Group to undertake a socio-economic impact assessment, focused on nine IMI1 projects that had been completed by early 2016.

2.1. Participation and Investment

Each of the nine projects reviewed involved a large number of public and private sector collaborative partners. Eight were research focused and had between 12 and 50 participants with the mean number being 27 and the median 21. The other was an education and training standards project involving 15 European Federation of Pharmaceutical Industries and Associations (EFPIA) members and 35 universities.

The nine projects received funding of €82.3 million from IMI, representing 8% of the IMI public sector budget for the period from 2008 to 2013. This levered a total investment of €104.8 million from EFPIA members and €30.5 million from other sources, giving a total investment of €217.6 million.

2.2. IMI Projects and Rationale

Of the projects reviewed, one was focused on training (covering the whole medicines development process), two were focused on pre-clinical research, one on clinical research, four spanned pre-clinical and clinical research and one was focused on post-marketing.

This profile is quite different from most publicly funded medical research initiatives where the focus is usually on fundamental and pre-clinical research. The IMI projects are generally closer to market, as might be expected given that they are collaborative projects involving the pharma sector.

Each project was designed to address a ‘bottleneck’ that had been identified. In most cases, the rationale for the project was that there was an area where both public and private sectors were under-investing, but where a problem could be tackled by acting in concert. The projects were envisaged as a range of activities that would improve the conditions for medicines development in Europe and remove barriers to the development of medicines and the growth of the medicines sector.

2.3. Mediators & Intermediate Outcomes

This impact evaluation has proposed a system of innovation approach that describes the steps in the process of getting final product and process innovations materialised and so can be used to understand the “pathways to socio-economic impact”. This includes consideration of ten activities that are the main determinants of innovation processes, and also intermediate outcomes in innovation processes (Figure 2-1).

Figure 2-1: Determinants of Innovation Processes

I. Provision of knowledge inputs to the innovation process

Provision of R&D and, thus, creation or recombination of new knowledge, primarily in engineering, computer sciences, medicine, life sciences and natural sciences.

Competence building, e.g. through individual learning (educating and training the labour force for innovation and R&D activities) and organisational learning.

II. Demand-side activities

Formation of new product markets.

Articulation of quality requirements emanating from the demand side with regard to new products.

III. Provision of constituents for Systems of Innovation (SIs)

Creating and changing organisations needed for developing new fields of innovation. Examples include enhancing entrepreneurship to create new firms and intrapreneurship to diversify existing firms; and creating new research organisations, policy agencies, etc.

Networking through markets and other mechanisms, including interactive learning among different organisations (potentially) involved in the innovation processes. This implies integrating new knowledge elements developed in different spheres of the SI and coming from outside with elements already available in the innovating firms.

Creating and changing institutions – e.g., patent laws, tax laws, environment and safety regulations, R&D investment routines, cultural norms, etc. – that influence innovating organisations and innovation processes by providing incentives for and removing obstacles to innovation.

IV. Support services for innovating firms

Incubation activities such as providing access to facilities and administrative support for innovating efforts.

Financing of innovation processes and other activities that may facilitate commercialisation of knowledge and its adoption.

Provision of consultancy services relevant for innovation processes, e.g., technology transfer, commercial information, and legal advice.

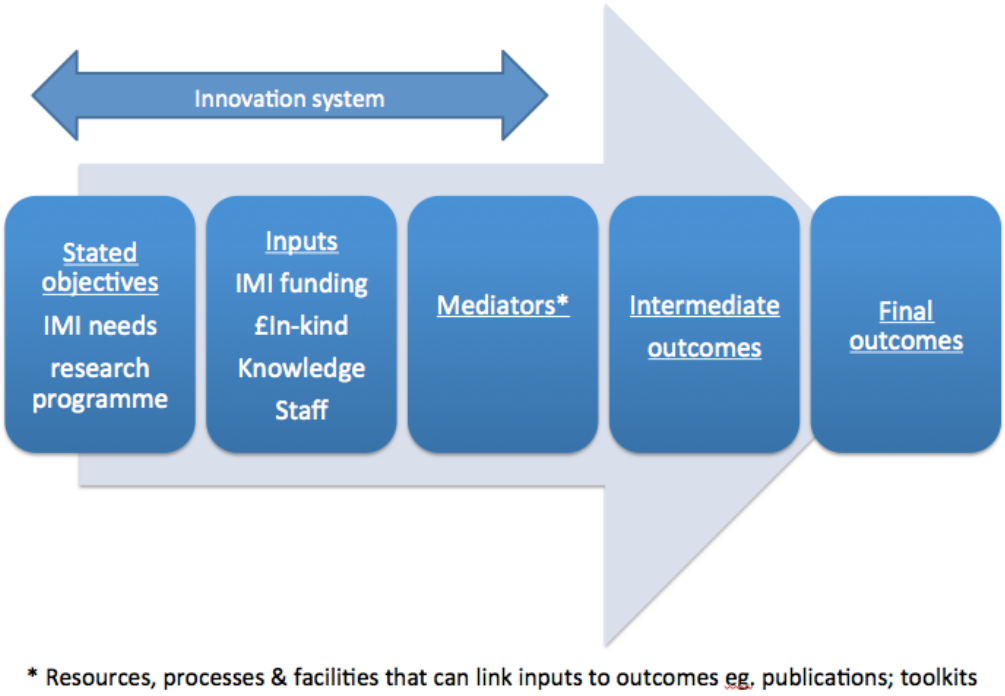
Source: Edquist (2011)

The IMI projects reviewed in this impact assessment have delivered outcomes that are relevant to five of these ten activities. In particular the projects have facilitated *networking through markets and other mechanisms*, promoting interactive learning and the sharing of knowledge. The scientific outputs (scientific publications and new models, tools, methods, biobanks and databases) also provide evidence of the *provision of R&D* by the projects.

There are also examples of *competence building* (through both training and spreading best practice in approaches to research), *articulation of quality requirements* (in particular safety) and *creating and changing institutions* (including the provision of evidence required by regulators). However, the scope of the IMI1 projects reviewed did not intend to deliver outcomes related to the other five determinants of innovation processes identified.

While the systems of innovation approach recognises the complexity of inter-related actors and activities, it can also be useful to consider a simplified model to help identify those mediators and intermediate outcomes that may be conditions and indicators of the final outcomes, including socio-economic impacts (Figure 2-2).

Figure 2-2: Objectives to Final Outcomes



Source: Edquist C., Jönsson B., Payne K., Tijssen R. (2015)

In terms of mediators and intermediate outcomes, almost all of the projects delivered scientific research publications, impact from scientific publications (citations) and R&D collaborations.

There were also many examples of databases of research findings, technical standards, tools for clinical research, animal models, human tissue or cell based models, imaging techniques, biobanks, patient cohort databases, biomarkers and new processes.

There were some examples in some projects of patents, new product development, targets for medicines development, methods for identifying and screening targets, training programmes developed, people trained and guidance and recommended best practices.

2.4. Socio-economic Impacts of Projects Reviewed

The main potential socio-economic impacts that have been identified are those that act on the medicines development process, delivering future cost savings, time savings, reductions in risk, reductions in attrition rate and reduced need for animal testing.

There were also some examples of new products (for example, new tools for medicines development), some industry impacts (including some new businesses and growth of existing businesses) and some potential changes to regulations.

The IMI1 projects reviewed were not designed to directly bring new medicines to market. Rather they will impact on new product development by acting on the medicines development process itself, usually in particular disease areas.

There was no evidence yet of noticeable socio-economic impacts on the health system (such as improved access to new treatments, improved work productivity or more effective use of healthcare budgets or reduced costs) or health benefits for patients. Such socio-economic impacts may occur in future, if the improvements to the medicines development process mean that new medicines come forward for approval and are accepted by health systems (the payers).

The IMI projects may be necessary to deliver the socio-economic impacts described above but in most cases, they are not by themselves sufficient to generate impacts. In some cases the actions that are necessary to build on the IMI projects to deliver socio-economic impacts will be strategies, investments and actions by companies. In other cases, there will be a need for action from actors such as regulators, the healthcare system and policy makers. It is therefore important for the potential socio-economic impacts and the necessary follow-up actions to be identified – and to be included within dedicated dissemination plans.

2.5. Wider Benefits

The IMI model has provided a platform for effective collaboration, particularly industry-academia, but also industry-industry, and academia-academia. There were many examples of continued collaboration, after the end of the project, building on the networks that had been created by the project. One of the benefits of the collaborative model was that it allowed for technical standards and common protocols to be developed.

While the IMI1 projects that were reviewed had been completed, there were many examples of follow-on projects, indicating that the IMI1 projects have had some influence on the R&D agenda in the European pharma sector.

IMI projects have helped to demonstrate that there is a strong research base in Europe that the pharma sector can work with, and from which it can get value.

2.6. Recommendations

Rather than the linear, sequential view, based on addressing specific pre-identified 'bottlenecks', it is recommended that IMI should take a broader 'systems of innovation' approach which considers a wider range of innovation determinants. This impact assessment has proposed a model for understanding the road to socio-economic impact from the medicines innovation system. It is recommended that IMI use this systems model to monitor and evaluate existing projects and to inform decisions on future priorities and investments.

There would be considerable merit in considering potential socio-economic impacts at the project scoping stage, before IMI decisions are made on the allocation of resources. The questions that should be asked at this stage would include:

- What socio-economic impacts are possible in the short-term and / or in the longer-run?
- How does that affect the project's scope, objectives and creation of impact pathways?
- Which partners need to be involved to help create impacts?
- Where in the innovation system will the project impact?
- What output and outcome measures, and associated monitoring system, would be appropriate to identify whether progress has been made towards delivering such (anticipated) impacts?

At the project design stage consideration should also be given to the justification for (financial and in-kind) investments, including:

- What is the current or anticipated market failure that is being addressed?
- How will the project's organisational model, activities, outputs or impacts address that market failure?

At the design stage, the market failure addressed and the additionality of IMI support should be fully considered. Projects should be supported only when it can be shown that a problem exists in the innovation system that will not be addressed by private actors and where public actors have the *ability* to solve or mitigate the problem.

These changes at the project design stage should stimulate greater involvement by other stakeholders, including healthcare systems (the payers for most medicines), patient representatives and regulators. There is also a role for a wider range of stakeholders to be engaged at the stage where IMI is making decisions on calls for new projects.

Such involvement will be important in generating socio-economic impacts since business related impacts associated with the pharma sector and health benefits are not delivered as a result of the development of new medicines per se. Rather they are delivered by the availability of medicines in the healthcare system and for that it is necessary to secure approval from regulators and for the healthcare system payers to agree that the medicine should be made available.

The socio-economic impacts that will be achieved in future will generally require follow-on activity. To increase the chances that such follow-on action will be taken, part of the project completion process should be a review of the actual and potential socio-economic impacts and what needs to happen next to enhance or speed up those impacts. This should involve all of the main partners in the collaboration.

3. Expert group terms of reference

This document is the report of the Expert Group appointed to undertake a socio-economic impact assessment of the Innovative Medicines Initiative (IMI).

3.1. Terms of Reference

The Expert Group was established by IMI to undertake a socio-economic impact assessment of IMI1. The terms of reference provided guidance to the Expert Group by posing a number of questions:

- What impact do the outputs of the selected IMI1 project outputs have on industry/open innovation/collaboration/ways of working and externalisation trends?
- How do the outputs of the selected projects impact on the medicines discovery and development process (including the replacement, reduction and refinement guiding principles relating to animal research; cost; effectiveness; attrition rates; and reducing risks)?
- What impacts have the selected IMI1 project outputs had on regulatory requirements and review processes?
- Have the selected IMI1 project outputs created any follow-on investment from internal/external actors, measurable economic benefits for Europe, for example job creation and/or Small to Medium-sized Enterprise (SME) creation in Europe?
- If the selected IMI1 project had not tackled the project-defined area of industry/public health needs, what would the consequences have been? What unique outputs were realised as a result of collaboration between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and academia that would not have been possible before?
- What impacts have the selected IMI1 project outputs had on individual and public health? How relevant were the project's results to public health, especially in areas of unmet need, progress towards potential treatments and improved safety for patients? What has been the impact on medical practices?
- What impacts have the selected IMI1 project outputs had on key areas of the medicines development and discovery system in terms of knowledge generation and employment?
- What impacts have there been at health policy level for intervention strategies, therapeutic approaches and disease management?

3.2. Expert Group

The members of the Expert Group were:

Charles Edquist (S-M) is Professor of Innovation at the Centre for Innovation Research and Competence in the Learning Economy (CIRCLE) and was involved with the IMI1 Impact Assessment in 2007. His expertise is in systems of innovation and innovation policy: technologies, institutions and organisations and he contributed to the development of the systems of innovation (SI) approach.

Bengt Jönsson (S-M) is a Professor Emeritus in the Department of Economics at Stockholm School of Economics. His expertise covers a broad range of health economics issues including financing and organisation of health services, the economics of innovation in health, and economic evaluation of public health and medical care.

Katherine Payne (UK-F) is Professor of Health Economics at the Manchester Centre for Health Economics, The University of Manchester. Her expertise is as an academic health economist working with different clinical research groups (pharmacy, psychiatry, and genetics) with a particular interest in stratified medicine and the impact of new genomic technologies.

Robert Tijssen (NL-M) is the Professor of Science and Innovation Studies at Leiden University. He was also was involved with the IMI1 Impact Assessment in 2007. His expertise is in quantitative studies of research

cooperation, performance indicators for university rankings, university research and industrial R&D, socio-economic impacts of science.

The rapporteur to the group was **Graeme Blackett** (UK-M), Director of BiGGAR Economics, an applied economist with 25 years of experience in economic consultancy including economic appraisal, evaluation and economic impact experience of universities and of the life sciences sector.

4. Introduction

This document is the report of the Expert Group appointed to undertake a socio-economic impact assessment of IMI. The impact assessment focuses on IMI1 projects from the first funding round, in particular the nine IMI1 projects that had been completed by early 2016.

4.1. Report Structure

This report is structured as follows:

- Section 3 provides contextual and background information on IMI and the assessment of socio-economic impacts;
- Section 4 summarises the methodology, including models for considering the pathways to socio-economic impacts;
- Chapter 5 discusses the IMIDIA project;
- Chapter 6 discusses the MARCAR project;
- Chapter 7 discusses the NEWMEDS project;
- Chapter 8 discusses the PharmaTrain project;
- Chapter 9 discusses the PROTECT project;
- Chapter 10 discusses the SAFE-T project;
- Chapter 11 discusses the EUROPAIN project;
- Chapter 12 discusses the U-BIOPRED project;
- Chapter 13 discusses the SUMMIT project;
- Chapter 14 contains conclusions based on the IMI1 projects reviewed; and
- Chapter 15 sets out Expert Group's recommendations on maximising the socio-economic impacts of IMI.

Appendix A contains tables summarising the Expert Group's initial impressions on outcomes and impacts, Appendix B contains the Framework used to gather information on the projects and Appendix C contains the Topic Guide used for interviews with Project Co-ordinators and Managing Entities.

4.2. Context and Background

The European Commission (EC)'s Seventh Framework Programme (FP7), which ran from 2007-2013, introduced the concept of Joint Technology Initiatives (JTIs). IMI was identified by the EC as one of the potential areas for the establishment of a JTI resulting from the work of the Innovative Medicines for Europe Technology Platform. IMI's purpose was to respond to the needs of industry and other stakeholders.

The initial impact assessment of IMI's potential societal and economic effects was prepared by an independent expert group in March 2007[1]. They were invited by the EC to focus on the state of the European pharmaceutical sector, identification of possible policy options and to provide an in-depth assessment of the potential economic and societal effects of IMI. In their analysis, the experts screened data from the OECD and EUROSTAT data and statistics, and background documents relating to the IMI Technology Platform (European Federation of Pharmaceutical Industries and Associations (EFPIA) vision paper, IMI Strategic Research Agenda, etc.). Extensive stakeholder consultation led by EFPIA was also conducted at the same time.

The first impact assessment outlined the problems within European biopharmaceutical R&D and asserted that properly implemented, IMI would have high potential to make a significant contribution to promoting competitiveness, growth and jobs, social cohesion – all necessary for sustainable development of Europe. In

[1] Gillespie I., Rosenmöller M., Tijssen R., Edquist C., Sauer F. (March 2007), The Innovative Medicines Initiative Assessment of Economical and Societal Effects

brief, IMI's target was to make the early medicines discovery R&D value chain more efficient in a number of ways.

A second evaluation of IMI, undertaken for DG Research in 2013[2], noted that IMI's €2billion budget for the period 2008 to 2013 made it the largest life sciences public private partnership (PPP) in the world and its main objectives have been to address the bottlenecks currently limiting the efficiency, effectiveness and quality of the medicines development activities needed to bring innovative medicines to the market. The evaluation concluded that IMI has successfully demonstrated the feasibility of large, multi-stakeholder PPPs for research and development in biomedicine. The business model created by IMI is well established and has leveraged the research strengths across the European pharmaceutical industry, academia and SMEs. It has established over 40 public-private consortia, which are delivering projects of high relevance to healthcare challenges.

The study came to the conclusion that the IMI contributed to halting the decline private sector investment in European biopharmaceutical R&D and has even led to its increase over the past two years, unlike the US in the same period. Overall, the study shows that IMI has played a major role in consolidating the European pharmaceutical research base by acting as a "one stop shop" for biomedical R&D in Europe. This has contributed to reinforcing Europe's attractiveness for pharmaceutical R&D, stemming the flow of investment away from Europe to the USA and Asia.

During its first phase IMI launched 59 projects with start dates between June 2009 and March 2015. Of these 59 projects, 9 have completed their full project life cycle at the end of 2015 (Table 4-1) and so were reviewed as part of this socio-economic impact assessment.

[2] Hunter, J., Szumowski, M., Andersen, T., Rosaria, M., Nucci, D., Wijnberg, B.(2013), Second Interim Evaluation. Innovative Medicines Initiative Joint Undertaking. 64

Table 4-1: Projects complete their full project life cycle by the end of 2015

Project acronym	Start date	End date	Disease area
IMIDIA	01/02/2010	30/09/2015	Metabolic
NEWMEDS	01/09/2009	28/02/2015	Brain
PROTECT	01/09/2009	30/04/2015	Medicines safety
SAFE-T	15/06/2009	14/06/2015	Medicines safety
MARCAR	01/01/2010	30/06/2015	Biomarkers/Cancer/Medicines safety
EUROPAIN	01/10/2009	30/09/2015	Brain
U-BIOPRED	01/10/2009	30/09/2015	Lung
SUMMIT	01/11/2009	31/10/2015	Metabolic
PharmaTrain	01/05/2009	30/04/2015	Education & training

Source: IMI

4.3. Purpose, Objectives and Scope

The objective of this study was to identify, categorise, measure and, where possible, value the socio-economic impacts that IMI projects have had at a European level. The analytical challenge for this impact assessment was to find or develop high-quality performance indicators to measure or gauge relevant socio-economic outputs, and wider contributions made by the first round of IMI1 projects as they complete their life cycle. This work needed to take account of the context of IMI's initial aims for these projects.

The findings of this impact assessment study are intended to:

- provide evidence on potential socio-economic impacts to IMI's stakeholders, in the public and private sectors;
- inform the evaluation on how IMI's initial projects have justified their funding; and
- provide insights and suggest possible methodologies for creating new metrics and indicators for future monitoring and assessment of these impacts, and reporting of key findings.

A number of specific key performance indicators have already been deployed and these are systematically included in IMI's annual reporting to its Governing Board and eventually to wider stakeholders.

In addition, IMI itself measures scientific and technological outputs through its regular bibliometric reports, complied by analysts at the information provider *Thompson Reuters*, as well as recording scientific achievements and outputs from projects in each IMI Annual Activity Report, and additionally through a variety of communications media and materials.

The socio-economic impact assessment sought to connect project-related resource inputs, organisational throughputs and scientific and technological outputs with 'downstream' outcomes and impact measures – either short-term or medium-term impacts. There exists a wide range of 'mediators' that link inputs to outcomes and impacts. The inter-relationships, interactions and feedback loops between the various intermediate stages may represent 'impact pathways'', processes and infrastructures that enable or enhance the creation of impacts as a direct result of an IMI project.

In undertaking this impact assessment, it was recognised that medicines R&D, such as that undertaken with the majority of the IMI1 projects under consideration, always has a long lead time, and one of the challenges is that most of the outputs and impacts made by the IMI projects under consideration are at the early stage in the R&D value chain.

Previous studies have found that pharmaceutical R&D is an investment with immediate and tangible costs, but with uncertain impacts and long-term benefits. Studies of the returns to pharmaceutical R&D[3] have long shown that it is a few projects that result in the majority of benefits, while the majority of projects show a zero or negative return. However, the total return on investment is higher than the costs.

On this basis, it would be reasonable to expect that some projects may deliver very significant socio-economic impacts while others may deliver limited outcomes. However, 'failed' projects will nonetheless add to the knowledge base, and that may or may not at a later stage contribute to generate a significant impact.

Socio-economic impacts generally take several years to materialise, especially external impacts in the wider environment and within health systems. In effect, to accurately identify and measure the longer-term societal and economic impacts of these types of IMI achievements, there would be a need for further investment in prototype development, manufacturing, marketing and other downstream investments, which is outside the scope of IMI's initial overall mission.

The Expert Group's approach to identifying relevant project-related outputs and associated (potential) 'impact pathways' and short-term impacts is discussed further in section 5.

4.4. IMI's Initial Socio-economic Impact Targets

The key drivers for creating an initiative like IMI were identified in the initial 2007 Impact Assessment[4] and are summarised below:

- the overall importance of the pharmaceutical industry for Europe in terms of its economy;
- Europe's balance of trade as well as to employment and contribution to a European knowledge-based economy;
- fierce competition from US, including evidence that Europe's clusters of public private collaboration are less efficient;
- the relocation of pharmaceutical R&D to other geo-economic areas like the US and Asia;
- escalating medicines development costs and market failures in the biopharmaceutical sector;
- the need to facilitate a sea-change in the medicines development system of innovation to a more collaborative model both from R&D and regulatory aspects;
- public health concerns not being addressed.

The initial impact assessment identified three areas where IMI could have a positive influence: economic impact, health and social impact and environmental impact.

The report also included indicators categorised as short-term outcomes (2-3 years), mid-term impacts (4-5 years) and longer-term impacts (wealth and health benefits).

In the report, outcomes and benefits that could act as performance indicators relevant for assessing socio-economic impact in the short, medium and long run are outlined below:

- Short-term impact indicators: Improved scientific quality, enhanced knowledge production, network-based R&D capacity building, human resources development.
- Mid-term impact indicators: Concrete results on biomarker validation and toxicology tests, big data and shared IT infrastructures, improved knowledge transfer and communication.
- Longer-term impact indicators: Improved economic performance reflected in increased competitiveness at European level, better employment in the pharma sector and new medicines/treatments for patients.

[3] Grabovski H., Vernon J. (AEI 1981: 3-20), The determinants of research and development expenditures in the pharmaceutical industry. In helms RB (ed.) Drugs and health: Economic issues and policy objectives

[4] Gillespie I., Rosenmöller M., Tijssen R., Edquist C., Sauer F. (March 2007), The Innovative Medicines Initiative Assessment of Economical and Societal Effects

The short-term and mid-term impact indicators have been integrated into IMI's project reporting system and so have already been reported for completed projects, in project Final Reports, in IMI's Annual Activity Report and through IMI's media communications.

The added value of the socio-economic impact assessment was therefore to consider how these short-term and mid-term impacts could be expected to deliver socio-economic benefits in the longer-term.

4.5. Role of Expert Group

IMI appointed an Expert Group under the European Commission's high-level expert contract.

It has operated as an external independent evaluator to provide a qualified and objective advice on methodology, data collection and analysis of the agreed IMI1 projects. Conclusions have been arrived at independently from any influence of the IMI programme office, the European Commission and EFPIA, or from staff of the projects under review.

The IMI Programme Office has coordinated the Expert Group, which was supported by an expert rapporteur (Graeme Blackett of BiGGAR Economics) who was appointed to provide a control function in summarising the expert findings.

In addition to the context described above, the Expert Group was also guided by a number of overarching issues (see Section 2.1).

5. Methodology

5.1. Overall Approach

The overall approach to the study that was adopted by the Expert Group included four main phases.

The first phase prepared the groundwork for the impact assessment and included:

- Initial review of background documents on IMI and its objectives as well as other reference documents such as previous evaluations and bibliometric reports;
- Development of a project proforma and methodology by the Expert Group, to be used to collect and summarise information on IMI1 projects relevant to the socio-economic impact assessment (see Appendix B);
- Development of an analytical model for understanding and describing the potential pathways to impact (see Section 4.4, below);
- Preparation of a topic guide for Interviews with Project Co-ordinators and Managing Entities of each selected IMI1 project (see Appendix C).

The second phase included the review of an initial four of the IMI1 projects, specifically:

- Collation of information on the projects by the IMI Programme Office team, for the first four IMI1 projects under review, based on information held by IMI, using the project proformas;
- Review of the project proformas and other background documents on the four initial IMI1 projects by members of the Expert Group;
- Interviews with Project Co-ordinators and Managing Entities of each selected IMI1 project; and
- Preparation of a progress report, based on the review of the first four IMI1 projects reviewed.

Following completion of the progress report, a similar work programme was undertaken in the third phase of the work programme:

- Collation of information on the projects by the IMI Programme Office team, for five further IMI1 projects under review, based on information held by IMI, using the project proformas;
- Review of the project proformas and other background documents on the second batch of five IMI1 projects by members of the Expert Group; and
- Interviews with Project Co-ordinators and Managing Entities of each selected IMI1 project.

The fourth and final phase included:

- Review of all evidence gathered;
- Development of conclusions and recommendations; and
- Preparation of the socio-economic impact assessment report.

5.2. Project Proforma for Data Collection

During the planning stage of the Expert Group's work programme it became apparent that IMI had already gathered a significant volume of information on the activities and outputs of the projects supported. However, not all of that information was directly relevant to the current socio-economic impact assessment process.

A project proforma was therefore developed to identify and summarise the information on IMI1 projects that were most relevant to this socio-economic impact assessment. The project proforma was used by IMI staff to collate information for each of the selected projects, drawing on a range of documents, including Descriptions of Work reports, Project Periodic Reports, Project Newsletters, Project Final Reports, and other monitoring data held by IMI's Programme Office.

The focus of each project proforma was a summary of the evidence available on project's main outputs and whether impacts have already occurred or might be expected in the future.

A copy of the project proforma is included as Appendix B.

5.3. Interviews

While the completed project proformas contained much valuable information, the Expert Group concluded that there was additional evidence that would be useful in forming a view on actual or potential impacts. A series of interviews with each project's Project Co-ordinator and Managing Entity was undertaken.

These interviews focused on general topics regarding project outcomes and impacts, such as: the market failure and additionality rationales for the projects; the outputs achieved; how the outputs delivered may lead to impacts; and organisational/managerial lessons learned so far.

A copy of the Topic Guide for each interview is included as Appendix C.

5.4. Analytical Model – Pathways to Impact

The Expert Group recognised that the selected impact assessment process needed to be able to capture the complexities of actual practice but remain simple enough to be useful for empirical analysis and clarification of observed phenomena.

There are a number of aspects to consider in the context of the IMI projects that together provide a general model for monitoring and assessments of IMI's socio-economic impacts. These include:

- The wider European and global innovation system;
- Rationale and the added value of IMI projects;
- The medicines development process (including science, innovation and product development in medicine);
- Pathways to socio-economic impacts (the development of new medicines and improving the medicines development process);
- Final socio-economic impacts included in the impact assessment.

Each of these aspects is discussed below.

5.4.1. The Wider European and Global Innovation System

The socio-economic impact assessment recognises that the IMI projects were partially embedded in, and supported by, a European and global innovation system in pharmaceuticals. To contextualise IMI project related impacts, it is necessary to understand what the relevant features of that broader system are.

A review of the literature finds that innovations of the following kinds are reported in the material:

- organisational and process innovations (enhancing productivity);
- new features in several existing technologies, services and products (incremental innovations); and
- entirely new technologies, services and products (radical innovations).

However, it is not only the actual (final) innovations and their socio-economic impacts that are crucial. There are also intermediate outcomes and the creation or enhancement of impact pathways, which can be the basis of future innovations, and can be seen as crucial results of IMI projects with regards to their potential to achieve significant longer-term impacts. Examples might include (follow-on) research, staff trained, identification of health needs, consortia creation, entrepreneurship, increased interaction between the organisations in the innovation system, changes of rules and laws, licensing, impact on the product development process, and new policies implemented.

Such intermediate outcomes, can also be considered to be determinants of the innovation processes that make up an innovation system (Figure 5-1).

Together these activities define an innovation system characterised by a diversity of knowledge creation and utilisation processes with many interactions, pathways and feedback loops. This 'systems' view has completely replaced the traditional, stage-based 'linear' view in research, which emphasised knowledge inputs to the innovation process. Much later, and slowly, it is also replacing the linear view in innovation policy development and evaluation.

Since the ten activities listed in Figure 5-1 are the main determinants of innovation processes, they are also intermediate outcomes in innovation processes. They are steps in the process of getting final product and process innovations materialised. Therefore they can also be seen as "pathways to socio-economic impact" (to be addressed later in this section).

Figure 5-1: Determinants of Innovation Processes

I. Provision of knowledge inputs to the innovation process

Provision of R&D and, thus, creation or recombination of new knowledge, primarily in engineering, computer sciences, medicine, life sciences and natural sciences.

Competence building, e.g. through individual learning (educating and training the labour force for innovation and R&D activities) and organisational learning.

II. Demand-side activities

Formation of new product markets.

Articulation of quality requirements emanating from the demand side with regard to new products.

III. Provision of constituents for Systems of Innovation (SIs)

Creating and changing organisations needed for developing new fields of innovation. Examples include enhancing entrepreneurship to create new firms and intrapreneurship to diversify existing firms; and creating new research organisations, policy agencies, etc.

Networking through markets and other mechanisms, including interactive learning among different organisations (potentially) involved in the innovation processes. This implies integrating new knowledge elements developed in different spheres of the SI and coming from outside with elements already available in the innovating firms.

Creating and changing institutions – e.g., patent laws, tax laws, environment and safety regulations, R&D investment routines, cultural norms, etc. – that influence innovating organisations and innovation processes by providing incentives for and removing obstacles to innovation.

IV. Support services for innovating firms

Incubation activities such as providing access to facilities and administrative support for innovating efforts.

Financing of innovation processes and other activities that may facilitate commercialisation of knowledge and its adoption.

Provision of consultancy services relevant for innovation processes, e.g., technology transfer, commercial information, and legal advice.

Source: Edquist (2011)

5.4.2. Rationale and Added Value

The first IMI call for proposals, in 2008, described the aim of IMI as "to make Europe again the world leader in pharmaceutical research for the benefit of the economy and society, by removing research **bottlenecks** in the current medicines development process."

The bottlenecks were those identified as problems that affected the medicines development process and it may be noted that, at this time, the IMI call was very much influenced by a production approach rather than the systems view described in Figure 5-1.

The call identified four areas when such bottlenecks had been identified, the first three of which were included in the 2008 call, with the fourth included from 2009:

- Safety: bottlenecks related to predictivity in safety evaluation and benefit–risk assessment;
- Efficacy: bottlenecks related to predictive pharmacology, the identification and validation of biomarkers, patient recruitment and benefit–risk assessment;
- Education & training: bottlenecks related to gaps in expertise in biomedical R&D knowledge and skills, enhancing Europe's biomedical education landscape to provide maximum support in revolutionising the conventional medicines discovery and development paradigm;
- Knowledge management: bottlenecks related to gaps in information technology, providing platforms to analyse large amounts of information in an integrated and predictive way.

It may be noted that all four areas focus on knowledge inputs. While IMI's analysis of bottlenecks was based on stakeholder consultation, it provides a starting point for considering market failure.

Market failure can be said to occur when the price mechanism results in an allocation of resources that is not efficient or which society considers to be suboptimal.

There are a number of sources of market failure: (a) externalities, where there are benefits or costs to those other than the producer and consumer, (b), information asymmetries, where not all market participants have the necessary information for an efficient allocation of resources, (c) market power where for example there are barriers to entry which leads to insufficient competition, (d) public goods where usually one person's consumption does not result in a reduction in what others can consume and where people cannot be excluded from consuming the good, (e) factor immobility where, for example, labour or capital cannot easily move to where it could be efficiently used. Equality and fairness issues are also sometimes considered to be part of market failure.

While IMI's bottlenecks rationale is a useful starting point for identifying (possible) market failures, the socio-economic impact assessment also sought an understanding of what underlying cause(s) of market failures might be, so that some assessment could be made of whether the project helped to address one or more of the above-mentioned sources of those failures.

A related concept that is also useful in considering the (potential) socio-economic impacts of IMI's activities is that of **additionality**. The starting point for considering additionality is to consider what would have happened in the absence of an intervention (in this case the IMI1 projects) and so to consider only the net benefits over and above what might have been delivered anyway within the European or global medicines innovation system.

Additionality can be absolute, if something has been brought about and benefits delivered that would not have happened at all in the absence of intervention. There are also other forms of additionality, related to 'scale' (i.e., a higher level of benefits delivered), 'timing' (i.e. impacts and benefits delivered earlier), and 'quality', where benefits are of a similar scale but considered to be of a higher quality (e.g. in terms of cost effectiveness).

Two conditions shall be fulfilled for innovation policy intervention to be motivated. Public policy interventions, such as innovation policy initiatives, should be pursued only when a *problem* exists in the innovation system. The existence of a problem means that private actors in the business sector fail to achieve the objectives formulated. (Objectives are formulated in a political process.) Such a problem may concern the future. The other necessary condition for public policy intervention is that public actors must have the *ability* to solve or mitigate the problem.

Innovation policy is sometimes needed, but must not replace, duplicate, or crowd out what private actors can do. It shall supplement private action; it should only contribute to solving problems that the private actors cannot handle. Such additionality should be the rationale for public policy intervention. It is a matter of division of labour between what private and public actors do. It is a matter of effectiveness, a matter of doing the right things. These things should, of course, also be done in an efficient manner.

The socio-economic impact assessment has considered both market failures and the additionality of the outputs and impacts of each IMI1 project.

5.4.3. Medicines Development Process

As its name suggests, IMI's locus is in medicines development and so the starting point for our impact assessment model is an understanding of the medicines development process.

EFPIA estimates that the process can take 13 years from the scientific investigation into a disease that may identify potential treatments for that disease through to the availability of a medicine to patients. The key stages are summarised in Figure 5-2.

Figure 5-2: Medicines Development Process

The Medicine Development Process: The long path from petri dish to patient

It can take up to 13 years to take a medicine from its origins as a molecule to a treatment with tangible benefits for patients. A look at the many steps needed to complete this process can help explain why it is so time-consuming.

- ***Pre-discovery***: Based on a disease focus, scientists work to better understand the disease.
- ***Drug Discovery***: Researchers select a "target" such as a gene or protein, then search for a molecule, or compound, which may act on the target to alter the disease.
- ***Pre-clinical testing***: Early safety and efficacy tests are undertaken using computer models, cells and animals.
- ***Phase I Clinical Trial***: The candidate medicine is tested in people for the first time. Studies are usually conducted on a small number (20 to 100) of healthy volunteers. The dose is gradually increased during these clinical trials to allow the investigator to measure the participant's clinical response to the medicine, such as whether the medicine is sufficiently absorbed, how long the medicine remains in the bloodstream, and which dosage levels are safe and well tolerated.
- ***Phase 2 Clinical Trial***: Researchers evaluate the potential medicines efficacy in treating an illness or medical condition, in about 100 to 500 patients with the disease. In this phase, researchers work to determine the most effective dosages and the best method of delivery – for example in tablet form or by injection.
- ***Phase 3 Clinical Trial***: Researchers study the potential medicine in about 1,000 to 5,000 patients to generate data about safety, efficacy and the overall benefit-risk relationship of the medicine. Phase 3 is used to test the results of earlier trials in larger populations and gather additional information about the effectiveness and safety of the medicine. This phase generally provides the basis for the benefit-risk assessment for the new medicine and much of the core information about the medicine that will be described on the labelling.
- ***Licensing approval***: Information and results from all the studies as well as description of the medicine's manufacturing process is compiled and submitted to the regulatory agencies in order to demonstrate the safety and effectiveness of the new medicine.
- ***Health Technology Assessment***: Once it has been concluded that a medicine is safe and effective, its value and cost-effectiveness must be assessed. Health Technology Assessment (HTA) processes are used by the relevant regulatory body to assess the added-value of medicines and inform decisions on access. Depending on the given healthcare system, HTAs can be used to determine pricing, reimbursement status, and/or prescribing, for instance.
- ***Medicines available for patients***: Once a medicine is licensed for use, and pricing and reimbursement measures determined, it may be made available for patients.
- ***Post marketing studies***: Even after a drug is on the market, it is being scrutinized: post-approval or post-marketing studies are necessary to monitor a drug's long-term effects.

Source: EFPIA

In the above description it is apparent that there are many different types of research that can be included within the definition of medical research, including:

- Fundamental or basic research – generally undertaken in universities and other public research organisations, encompassing a spectrum of activity from fundamental research to pre-discovery research.
- Clinical research – generally funded and managed by industry but undertaken in partnership with clinicians, taking potential medicines through the pre-clinical and clinical trials process.
- Translational research – can be undertaken by universities and other public research organisations, but will tend to be the domain of industry, taking the results from fundamental or basic research and determining whether there is potential for a new or improve product (in this context, a new medicine).

These three bullet points capture only different kinds of research that are important determinant of medicines development. This represents a linear 'supply push' view, which has dominated for decades. It is no longer accepted in research and advanced thinking about innovation, but it is still a basis for innovation policy to a very large extent. In Section 4.4.1 we widened the perspective on the process of innovation development and presented a broader view, in terms of ten activities in innovation systems that all influence innovation processes. It is systemic and non-linear. It includes activities (determinants) not only on the supply side, but also at the demand side. It also includes the constituents of the system of innovation and support services for innovating firms as factors that influence innovation processes.

The approach to funding and project design adopted by IMI, chosen due to the problems identified in public-private interfaces of biomedical research and medicines development in Europe, has been a collaborative model with each project involving multiple universities and research organisations working with multiple companies (EFPIA member companies and SMEs). For such an innovation model to be successful it must be concerned with an area of common interest for all of those collaborating. Such a joint perspective should provide better aligned incentives for both parties to create mutually optimal outcomes.

One of the determinants of innovation processes listed in Figure 5-1 is networking. It includes interactive learning among different organisations involved in the innovation processes. That such interactive learning is a crucial source of innovation was realised in innovation research in the 1980s and it was actually a main reason why the *system* of innovation approach was developed. We will come back to the collaborative model of IMI several times in this report.

For the companies, there is likely to be limited interest in collaborating in the competitive stages of the medicines development process, that is, where companies are taking forward a specific strategic or commercial target or commercialising a new product. However, there may also be common interests in pre-competitive stages. In the context of medicines development, this pre-competitive sphere will include at least two aspects:

- The advance of scientific knowledge that will underpin the development of a range of protocols, standards, technologies and medicines; and
- The improvement to the overall process of medicines development.

The potential benefits of improvements to the development process can be set in the context of the timescales and costs that are typically associated with bringing a new medicine to the market.

Improving the 'medicines development process' may extend across a range of factors and activities summarised in Figure 5-2. Progress with regard to one or more of those activities and development stages paves the way to the (more efficient) development of new products.

A 2014 estimate by the *Tufts Centre for the Study of Drug Development*[5] put the estimated average pre-tax industry cost per new prescription medicines approval (inclusive of failures and capital costs) at $2.6 billion (€2.0 billion) and suggested that more than 80% of compounds in the portfolio of leading firms had been discontinued during the process.

While there have been some questions and challenges[6] to the methodology that such estimates are based on (including that the public sector investment in the innovation system has been accounted for), there is little doubt that the medicines development process is lengthy and expensive, and has a high 'attrition rate' (that is, target compounds that do not make it through the entire process). It is also a very complex process, since it is affected by all the ten determinants listed in Figure 5-1.

In this context, even a marginal improvement to the medicines development process, whether it was related to cost, time or attrition rates could be very valuable, since it would improve the relative cost effectiveness and productivity of the process (that is a reduction in the total value of the inputs required to generate a unit of output). This would have a direct consequence for economic performance, as much economic growth in advanced economies is associated with productivity gain emanating from process or product innovations. It could also be associated with health and health system benefits, where there are improvements in the cost effectiveness ratio when compared with previous treatments.

[5] DiMasi J. (November 2014), Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs, Study Briefing
[6] For example, Avorn J. (January 2016), The $2.6 Billion Pill – Methodologic and Policy Considerations, in The New England Journal of Medicine

In considering the scale of the impact that IMI could make it is also necessary to place the total investment in the joint undertaking in a wider context. EFPIA reports[7] total pharma R&D investment in the European economy of €30.5 billion in 2014 and the *International Federation of Pharmaceutical Manufacturers & Associations* (IFPMA) reports[8] annual global R&D investment by the sector of $137 billion (€107 billion). So, the IMI1 budget of €2 billion over the period 2008 to 2013, represents around one percent of European pharmaceutical R&D investment and just over a quarter of one percent of global pharmaceutical R&D investment over the same period.

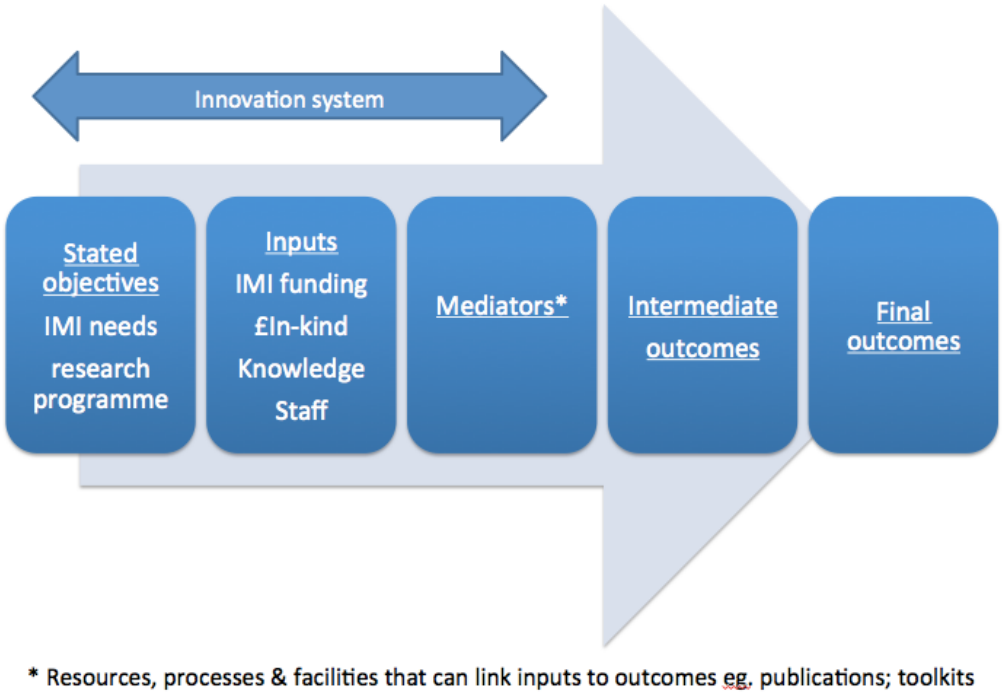
5.4.4. Pathways to Socio-economic Impact

The IMI annual reports and the project annual reviews and final reports showed that a large number of intermediate outputs were produced by the projects.

The remit of the Expert Group was to focus on socio-economic impacts and so it was necessary to understand how such reported outputs and intermediate outcomes could lead to such impacts.

While it is important to appreciate the complexity of interactions between various measures of inputs, outcomes, short-term and longer-term impacts, it is also useful to consider a simplified model of the logic chain between objectives and inputs and the final outcomes and impacts delivered (Figure 5-3).

Figure 5-3: Objectives to Final Outcomes



Source: Edquist C., Jönsson B., Payne K., Tijssen R. (2015)

5.4.5. Identifying Outcomes and Socio-economic Impacts

The starting point for reviewing the potential socio-economic impact of IMI supported projects was to consider where in the innovation process the project was acting. For example:

- Pre-clinical research;
- Training;
- Clinical research;
- Regulation and approval process;

[7] EFPIA (2015), The Pharmaceutical Industry in Figures
[8] IFPMA (2014) Facts and Figures

- Post-marketing.

The IMI annual reports, the monitoring process of the projects supported, and other reports such as IMI's bibliometric impact monitoring have gathered a broad set of high-quality information on objectives, inputs (funding, people and scientific resources) and on mediators and intermediate outcomes.

The measures of Mediators and Intermediate outcomes, include, for example:

- scientific research publications;
- impact from scientific publications (citations);
- databases of research findings;
- technical standards;
- tools for clinical research;
- animal models;
- human tissue or cell based models;
- imaging techniques;
- biobanks;
- patient cohort databases;
- biomarkers – identified and validated;
- patents;
- new product development;
- new processes;
- R&D collaborations;
- targets for medicines development;
- methods for identifying and screening targets;
- training programmes developed;
- people trained;
- guidance and recommended best practices.

Our socio-economic impact assessment has focused on these 'short-term' outcomes, while acknowledging their relevance to pathways for achieving longer-term socio-economic impacts, including:

- Medicines Development Process impacts, including:
  - Cost savings;
  - Time savings;
  - Reductions in risk;
  - Reductions in attrition rate;
  - Reduced need for animal testing;
- New Product Development, including:
  - New medicine to market;
  - Other product to market (for example, new tool);
- Industry impacts:
  - New businesses;
  - Growth of existing businesses;
- Health system benefits:

- Improved access to new treatments;
- Improved work productivity;
- More effective use of healthcare budgets or reduced costs;

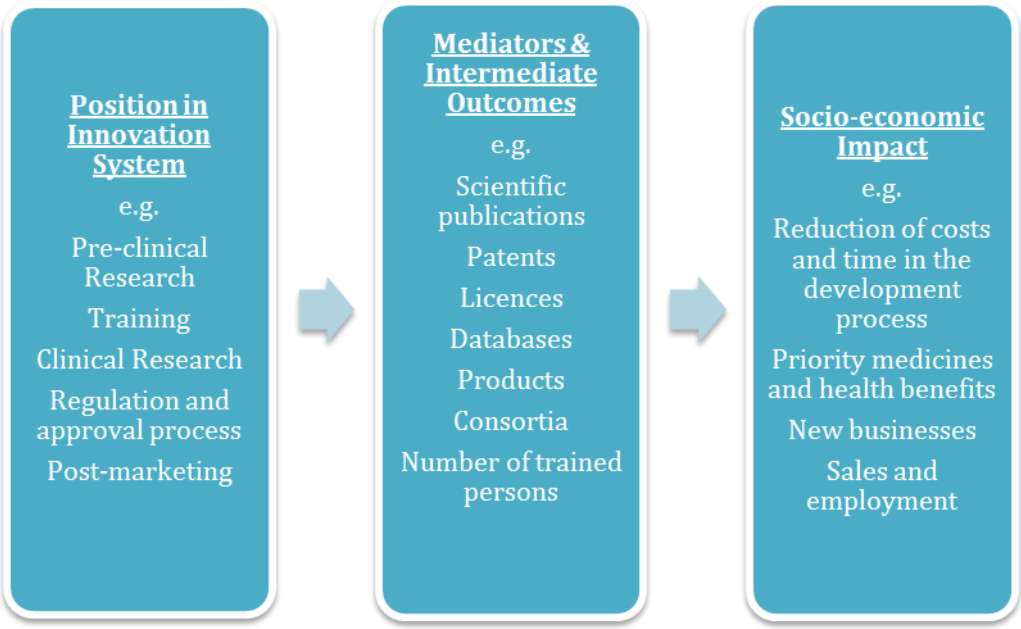
- Health benefits;
- Policy:
  - New policies implemented;
  - Regulations changed: Effect of change.

The model also recognised that, while there may be examples of new products and processes directly associated with IMI1 projects, it was more likely that the ultimate gains and benefits would be a result of improvements to the medicines development process and so the longer-term impacts would occur as a result of future productivity improvements in medicines development.

The impact assessment also sought to identify wider benefits that might continue to deliver socio-economic impacts over time by their effect on the innovation system. These could include behaviour change resulting from the projects (for example, continued collaboration between companies or between companies and academia).

Informed by the model described above, an analytical approach was developed to summarise review findings of each IMI1 project, specifically the projects' position in the innovation system, their intermediate outcomes and (potential) socio-economic impacts. The expectation of the Expert Group was that the socio-economic impacts would not yet have been delivered and so at this stage the task was to identify and describe future socio-economic impacts that could reasonably be expected. However, the intermediate outcomes should already be apparent, given that the projects reviewed for this socio-economic impact assessment had all been completed.

Figure 5-4: Analytical Approach to Summarise Findings.



6. IMIDIA

The Innovative Medicines Initiative for Diabetes (IMIDIA) project aimed to improve beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes.

A complete or relative decrease in insulin secretion by pancreatic beta-cells underlies the development of, respectively, type 1 and type 2 diabetes. These diseases impose a huge burden on welfare systems, both in Europe and in other developed and developing countries. So far, symptomatic therapeutic options for treatment of diabetes are available, but none to cure or prevent this pandemic disease. Although a considerable amount of knowledge has been gained on the function of beta-cells from animal models, knowledge of human beta-cell function, survival, and of the pathophysiological mechanisms that lead to their demise remains limited.

The scientific program aimed at delivering:

- Novel tools for the study of human beta-cell development, function and survival; their modulation by potential therapeutic compounds; and for in vivo beta-cell imaging;
- Biomarkers for the diagnosis and prognosis of beta-cell failure and for monitoring diabetes progression and treatment; and
- Knowledge on novel molecular pathways and sites that control beta-cell life & death as well as mass and function.

6.1. Position in Innovation System

IMIDIA was concerned with the development of tools and biomarkers for pre-clinical research.

6.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Werner Kramer, Sanofi-Aventis GmbH, Frankfurt, Germany

Managing Entity: Bernard Thorens, Department of Physiology & Center for Integrative Genomics, Université de Lausanne, Switzerland.

6.3. Participants

EFPIA: Sanofi-Aventis GmbH, Frankfurt/Main, Germany; Institut De Recherches Servier, Suresnes, France; AstraZeneca AB, Södertälje, Sweden; Boehringer Ingelheim International GmbH, Ingelheim, Germany; Eli Lilly Ltd., Basingstoke, United Kingdom; Novartis Pharma AG, Basel, Switzerland; Novo Nordisk A/S, Bagsvaerd, Denmark; F. Hoffmann-La Roche AG, Basel, Switzerland

Universities, Research Organisations, Public Bodies & Non-Profit: Université de Lausanne, Lausanne, Switzerland; Centre National de la Recherche Scientifique (CNRS), Paris, France; Commissariat à l' Energie Atomique, Paris, France; Imperial College of Science, Technology and Medicine, London, United Kingdom: Institut Suisse de Bioinformatique, Lausanne, Switzerland; Institut National de la Santé et de la Recherche Medicale (INSERM), Paris, France; Medizinische Hochschule Hannover, Hannover, Germany; Technische Universität Dresden, Dresden, Germany; Universita di Pisa, Pisa, Italy; Université Paris Diderot - Paris 7, Paris, France; Université de Geneve, Geneva, Switzerland; Vrije Universiteit Brussel, Brussel, Belgium

SMEs: Endocells SARL, Paris, France

6.4. Projects Inputs and Funding

The IMIDIA project received funding of €8.1 million from IMI, from a total project cost of €27.4 million and so the IMI contribution levered investment of an additional €2.41 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€8,060,760	29%
EFPIA funding	€16,940,659	62%
Other Funding	€2,445,590	9%
Total	€27,447,009	

6.5. Project Rationale and Market Failure

The project was addressing the underlying biology of a disease area, in this case diabetes. The project aimed to make progress in the pursuit of a cure for diabetes by repairing or replacing beta-cells that secrete insulin.

The project documentation did not explain the extent to which this problem can be reduced to beta-cell malfunction in type 2 diabetes. The health problems related to type 2 diabetes are mainly cardiovascular and related to the metabolic syndrome.

There was interest in this approach from EFPIA companies because other efforts to find a potential cure for diabetes have not been successful. One of the potential areas of market failure reported during the interviews was that companies were not sharing the reasons for failure and so information asymmetries arose which had the potential to lead companies to make sub-optimal decisions on where to invest.

The project also addressed one of the limits on the progress of diabetes research, the difficulty in securing the material required for research – either extract of cells from pancreas of animal subjects or deceased patients. There are differences in how beta-cells work between humans and rodents and so the limited availability of human beta-cells has hampered scientific progress.

The availability of a human beta-cell line means a new approach that can speed up science and R&D in diabetes. A collaborative effort was required to produce the human beta-cell lines; it is unlikely that one organisation could have achieved this on its own, an important area of additionality delivered by the project.

6.6. Project Achievements and Outputs

The outputs from the project, identified in the project final report included new knowledge along the following axis:

- Definition of novel conditions for isolation and in vitro culture of beta-cell precursors.
- Identification of factors required for in vivo differentiation of beta-cell precursors.
- Identification of genes modules underlying beta-cell adaptation or resistance to metabolic stress. Characterisation of the association of these gene modules with specific phenotypes or dysfunctions of glucose homeostasis.
- Initial characterisation of the role of alpha cells in beta-cell mass regulation in different metabolic conditions.
- Characterisation of genes that are differentially expressed in islets from impaired fasting glucose (pre-diabetes) patients and from type 2 diabetes patients. Association of these genes with specific aspects of beta-cell biology.
- Characterisation of novel pathways controlling beta-cell functions.

The new technical developments have generated:

- New monoclonal antibodies directed to the cell surface of human beta-cells.
- New human beta-cell lines (validated and confirmed by three EFPIA partners, allowing for medicines discovery approaches to improve beta-cell function in humans for the first time); available from the SME project partner, Endocell).
- Establishment of a unique repository of human islet transcriptomic and functional data.
- New mouse models allowing targeted gene delivery through viral transduction in beta-cells or beta-cell progenitors.
- Development of novel beta-cell imaging techniques.
- Establishment of a unique database that includes all the data generated during IMIDIA and annotated in a manner that ensures integrated analysis of all datasets as well as further integration of this database in a federated database to serve as a basis for further EU or worldwide collaboration on diabetes research and development projects.

By the time the final project report was completed, the scientific outputs included 60 publications with an average citation rate of 1.47 and 18.9% highly cited (in top 10% of papers for citations). The project reports that this has since increased to more than 90.

The additionality of the project also relates to the validation of the new research tool (the human cell line) by leading pharma companies, the establishment and enforcement of related technical standards. If one organisation working on its own was to develop a new tool then would not be a in a standard way and so would be difficult for others to validate it. This means that the tool would not be used generally across the sector and so no improvement to the overall medicines development process would have been achieved.

This validation and standardisation also applies to other outputs from the project, including the database of all results.

Another important area of additionality related to the R&D collaboration itself. No single organisation could have achieved what the group did, and IMI provided a mechanism for collaboration that had not previously taken place.

It is also important to note that the IMI role in facilitating collaboration was not only as a result of the public funding that was available. Funding was required to secure the expertise of the leading universities and research organisations in the field. However, as with the other IMI projects, the participation by industry required that a financial contribution was made.

That collaboration was valued by the participants is evidenced by the continued collaboration that is taking place, including an IMI2 project (INNODIA).

A sustainability model was developed to enable the full use and further progression of the IMIDIA data and knowledge platform for new collaborations and consortia within the IMI2 initiative as well for other collaborations. This could be an exemplar sustainability structure for other IMI projects.

The project involved eight pharma companies, cooperating on pre-competitive research. They have learned to cooperate with each other and with academia. The economic value added in this collaborative model comes from leveraging (so, for example, a company can invest €5 million, but have access to the outputs from a total €30m investment), reducing risks which would be too high for an individual company and providing a data-sharing mechanism to invest longer-term – since it is very unusual for a company to invest for 5-7 years in a area considered to be risky.

6.7. Pathways to Socio-economic Impact

The project has delivered important research outputs. About 70 scientific articles related to the data generated through IMIDIA have been published and more than 20 are in the process of being published. These inform the scientific and industrial community on the most recent progress in the knowledge of the pathophysiology of type 2 diabetes and in the treatment of the disease.

One of the important outputs is the development of a human beta-cell line that can be used by companies and academic laboratories. This standardised and verified human cell line provides a first grade model to study the biology of diabetes and can be considered as a pre-requisite for a medicines development programme.

This is a significant achievement, which was difficult and time consuming to do; researchers had been trying for years prior to the project. The human cell line is now available for use, via the SME partner in the project, Endocell.

The new cell line provides a platform for the development of medicines in a number of ways. These including new approaches to screening, development of new treatments, validation, new biomarkers and the determination of interactions between beta-cells. As a result, those involved in the project expect new novel treatments to be developed that were not possible to develop before.

While the cell line is the most striking output from the project, there has been a range of other outputs, including:

- the discovery of plasma biomarkers, that when fully validated, will provide a tool for type 2 diabetes taxonomy and the evaluation of treatments.
- the world's largest biobank of human beta-cell samples, all based on the same protocols and quality standards, a specific benefit of collaboration.
- a large database of information, that provides the basis for on-going work. The data is held and managed by the Lausanne Institute of Bioinformatics.
- progress with the imaging of the pancreas, which is important since the cells that produce insulin are scattered so difficult to see and so complex imaging techniques are need.
- The development of a systems biology approach to animal models.

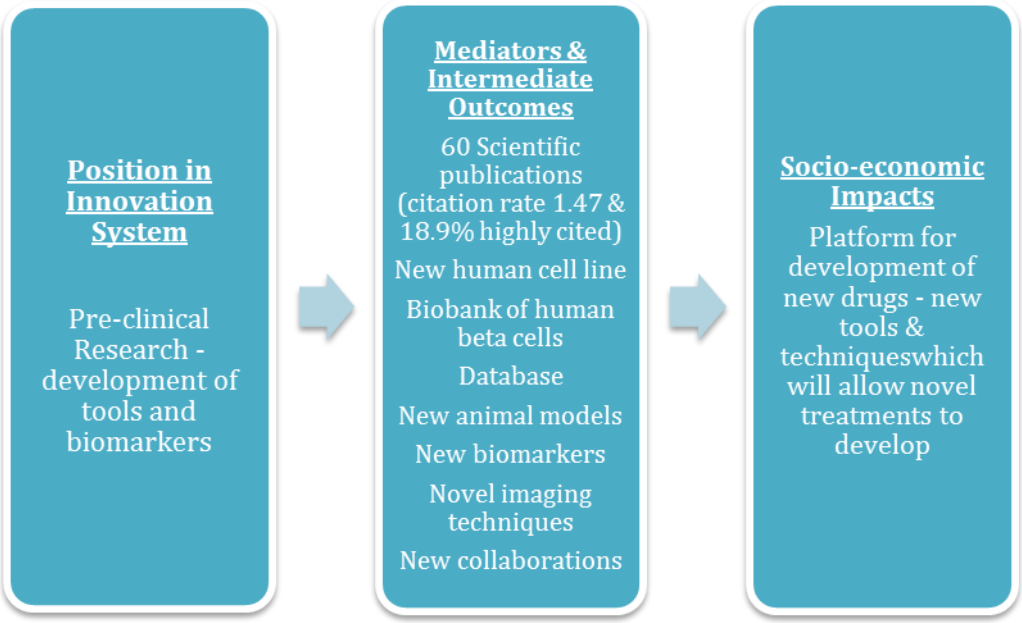
The disease is one that progresses over years, and so it takes years to observe whether potential solutions are effective. However, getting the right people together means that progress is being made, with the advancement of knowledge and the development of tools that can accelerate the progress.

While the finances and resources invested in this project were necessary to achieve the outputs and impacts, the role of IMI in bringing together the best in their field from both academic and companies seems to be one of the critical success factors. Producing valuable R&D outputs that will deliver socio-economic impacts is often about gathering and managing talented and dedicated people.

The eventual socio-economic impacts of IMIDIA will depend on the work done using the tools, talent and standards that are now available – however, without these resources and facilities it would not have been possible to undertake such work.

This project demonstrates that the nature of socio-economic impacts of the IMI interventions is not so much about product development but about improving conditions for future product development, removing barriers and shortening the timescales associated with the development of new medicines.

6.8. Summary: IMIDIA



7. MARCAR

The MARCAR project focused on biomarkers and molecular tumour classification for non-genotoxic carcinogenesis.

The efficiency of medicines development could be increased if undesired effects of candidate medicines are detected in an earlier phase of development. Therefore, the researchers in the MARCAR project searched and tested for biological clues, biomarkers, that can be used for the early detection of medicines-induced tumour formation. Biomarkers that help to predict tumour growth more accurately in a very early stage, will reduce the need for animal testing, speed up medicines development and increase medicines safety for patients.

The MARCAR project focused on non-genotoxic carcinogenesis, which is tumour formation that is not directly caused by 'writing errors' in the DNA 'text' (mutations), but by other changes in the structure of the genetic material that can alter the 'readability' of the DNA. The scientists suspected that these so-called epigenetic changes play a bigger role in the earliest stages of tumour formation than previously thought.

Therefore, the MARCAR consortium sought to further unravel the epigenetic effects, using a combination of novel and sophisticated molecular technologies. Combining their expertise in the field of biomarkers, human and rodent cancer models, imaging, molecular profiling and bioinformatics, the researchers focused on liver tumours, because it is the organ most affected by non-genotoxic carcinogenesis during the pre-clinical safety evaluations of candidate-medicines. It was anticipated that their findings would facilitate tumour identification in other organs as well, and will give better insight in the mechanisms of tumour growth, facilitating a more targeted search for safer and more effective treatments.

7.1. Position in Innovation System

The MARCAR project undertook research on medicines safety, to develop new models and tools for use in supporting pre-clinical and clinical medicines development (animal testing stage).

7.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Jonathan Moggs, Novartis Institutes for BioMedical Research, Novartis Pharma AG, Switzerland

Managing Entity: Roland Wolf, Biomedical Research Centre, University of Dundee, Scotland, UK

7.3. Participants

EFPIA: Novartis Pharma AG, Basel, Switzerland; Boehringer Ingelheim International GmbH, Germany; Bayer Schering Pharma AG, Berlin, Germany; UCB Pharma SA, Brussels, Belgium; H. Lundbeck A/S, Valby, Denmark

Universities, Research Organisations, Public Bodies & Non-profit: University of Dundee, United Kingdom; Medizinische Universität Wien, Vienna, Austria; Medical Research Council, Edinburgh, United Kingdom; Eberhard Karls Universität Tübingen, Tübingen, Germany; NMI Natural and Medical Sciences Institute, Reutlingen, Germany; Institut National de la Sante et de la Recherche Medicale, Montpellier, France

SMEs: CXR Biosciences Limited, Dundee, UK

7.4. Projects Inputs and Funding

The MARCAR project received funding of €6.0 million from IMI, from a total project cost of €13.1 million and so the IMI contribution levered investment of an additional €1.17 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€6,049,578	46%
EFPIA funding	€5,155,604	39%
Other Funding	€1,905,508	15%
Total	€13,110,690	

7.5. Project Rationale and Market Failure

There was a scientific driver for MARCAR, but one based on an area of importance for industry. The focus of MARCAR was on non-genotoxic carcinogens (medicines that can cause tumours but not through genetic damage). The problem is that gaps in scientific knowledge mean that non-genotoxic carcinogens are difficult to identify at an early stage. This means that industry may discover a problem at a late stage of the medicines development process, perhaps in late stage clinical trials.

This project addresses a typical case of market failure, where social benefits are greater than private benefits for the investigator to develop new biomarkers for early detection of cancer side effects in the medicines development process. Early detection of side effects using biomarkers will have socio-economic benefits in terms of reductions in costs for medicines development, health benefits from potential reduction in side effects for patients, and ethical benefits from less need for use of animals for safety testing.

7.6. Project Achievements and Outputs

The outputs from the project, identified in the project final report included:

1) Optimisation of tools for measurement of new biomarkers in tissue and blood, including micro-RNAs.

- Development of miniaturised assay systems that are capable of semi-quantitatively detecting more than 200 regulatory proteins (total and activated forms).
- Generation of a novel transgenic reporter model which utilises the haem oxygenase-1 promotor to drive LacZ expression in order to measure oxidative stress induced by a range of non-genotoxic carcinogens (NGCs). Almost all of the NGC's tested induced oxidative stress but to differing extents. We are currently relating the extent of oxidative stress to other cellular changes, i.e. gene expression and methylation status.
- Generation of a novel reporter model, where the glutamine synthase gene, known to be induced during NGC carcinogenesis, has been linked to multiple reporters, including those, which allow in vivo real time luminescent, MR and PET imaging.
- Development of Magnetic Resonance Imaging (MRI) protocols which allow detection of tumour lesions at a size of 1mm. This allows for non-invasive tracking of tumour progression and therapeutic responses in small animal models. Thus, the established methods are extremely valuable for the MARCAR consortium to assess tumour burden. Currently we are working on new biomarkers for non-invasive imaging of liver tumours using PET in combination with MRI.

2) Further understanding of the genetic and epigenetic effects of NGC.

- Demonstration of the relationship between dose dependent changes arising at the 5hmc mark following medicines exposure and changes in the mechanism of epigenetic regulation prior to the appearance of late stage cancer morphologies.

- Demonstration that changes at the highly dynamic 5hmC mark follow transcriptional changes in response to PB exposure and can accurately discriminate medicines exposure based on the length of dosing.
- Demonstration that the phenotype of a liver tumour in model systems is mainly driven by the genetic alteration driving tumourigenesis, and that NGCs select for a NGC class- specific geno/phenotype.
- Identification of mechanisms which can be used to understand the effects of NGC on at a metabolic level.
- Demonstration of the decisive role of the CAR nuclear receptor and Wnt signalling pathway in regulation of the non-coding RNA Gtl2/Meg3, a novel potential biomarker for NGCs that may represent reprogramming or de-differentiation to a stem cell-like state.
- Demonstration that primary human liver cells in co-culture represent a valuable in vitro system to characterise the effect of long-term exposure to prototypical compounds. Next steps will be to identify a specific gene signature for non-genotoxic carcinogenesis (NGC), compared to genotoxic carcinogen (GC) and non-carcinogen compounds (NC) in this model.
- Demonstration of gene locus- and species-specific changes in the liver cistrome in response to PB exposure.

3) Development of new bioinformatic tools for interpretation of study outcomes

- Development of a database of study results which correlates the traditional toxicity endpoints in terms of clinical chemistry and histology with new biomarkers.
- Development of a tool which facilitates the pathway-based analysis and visualization of heterogeneous cross-omics datasets, InCroMAP (http://www.cogsys.cs.uni- tuebingen.de/software/InCroMAP). The tool is extensively used by the MARCAR academic and industry partners and has been developed and published within the framework of the MARCAR project.

By the time the final project report was completed, the scientific outputs included 35 publications with an average citation rate of between 2.07 and 2.7 and 28.5% highly cited (in top 10% of papers for citations).

7.7. Pathways to Socio-economic Impact

Predicting non-genotoxic carcinogenesis in pre-clinical development is a major challenge for the development of medicines intended for long-term administration in humans. The identification of early non-genotoxic carcinogenesis mechanisms and biomarkers will provide industry and regulatory scientists with new tools for earlier decision-making, mitigation of positive carcinogenicity findings and cancer risk assessment.

MARCAR has put in place tools and methods for moving towards this goal and so has added to scientific knowledge in an area where the impacts on industry are large.

The project therefore could deliver significant long-term socio-economic impacts. If MARCAR were to contribute to the evidence base of how to assess carcinogenicity, there could be changes to the regulatory guidelines so that animal studies may not be required in certain circumstances – where it could be shown that it was scientifically obvious that a medicine may (or may not) cause tumours.

There was an important development during the project that could be significant. In 2013, the European Medicines Agency (EMA) and Food and Drug Administration (FDA) started a process of reviewing ICH S1 guidelines (those that are about carcinogenicity studies, applying to small molecule medicines that would be going into patients for 6 months or more), a process that is likely to be on-going, perhaps till 2019.

If the regulators take on board the evidence produced from MARCAR and make changes to the regulations on carcinogenicity studies (and this may be perhaps 5 years in the future), this would have a number of impacts on the medicines development process.

In terms of scale, for each medicine under development that this applied to, the impacts could be:

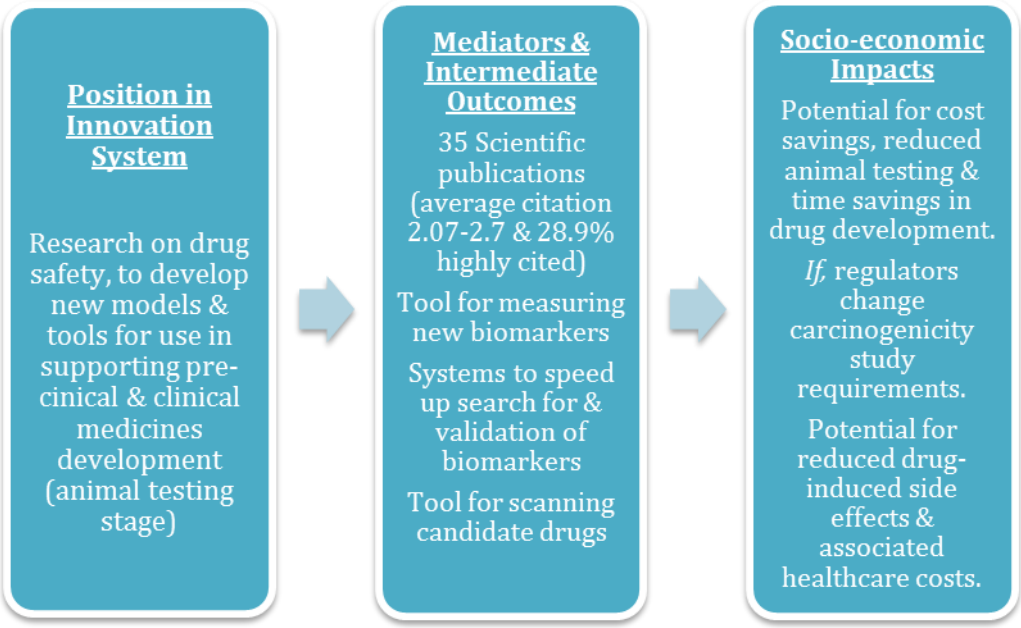
- Cost savings (in the €m's);
- Hundreds of animals not required for animal testing;

- Time savings – if a (two year plus one year planning) animal study was not required this could reduced the process by up to a year (not three years since these studies are generally undertaken in parallel with other activities).

This project shows that a complex interaction of academic research, industrial research and regulation can combine to deliver (potentially) significant effects. This complexity means that it is difficult to attribute impacts to only one part of the process, the benefit is a systematic one to the medicines development process.

The mission of MARCAR was on the implications for the medicines development process. However, the outcomes have led to interesting implications beyond this, in how chemicals (for example in the environment) might have non-genotoxic carcinogenetic effects. If this research is pursued and it leads to a better understanding then this can be used as an evidence base to avoid such chemicals in the environment or to keep them in places that they will not be harmful.

7.8. Summary: MARCAR



8. NEWMEDS

The NEWMEDS project investigated novel methods leading to new medications in depression and schizophrenia.

Despite remarkable advances in medical technologies and nearly 15,000 articles on schizophrenia and depression every year, there have been few truly innovative new medicines which have made it to the patients. There has been a tremendous explosion of new knowledge: dozens of genetic variations linked to the disease, hundreds of new molecules and mechanisms in the body identified, numerous scanning techniques distinguishing patients from healthy people, but it has been hard to translate these findings into novel therapies for patients.

Therefore, the NEWMEDS consortium aimed to develop three important missing tools to facilitate the translation of scientific findings into benefits for patients:

- A search for detectable signs of disease (biomarkers) in the DNA and the proteins of patients, in order to develop tests, based on these biomarkers, than can divide patients into subcategories of disease.
- A more precise characterisation of their disease within the biologically heterogeneous group of 'depression' or 'schizophrenia' to allow a more targeted treatment.
- In order to decrease the long time needed to test the efficacy of new treatments, the scientists sought to develop new techniques for the interpretation of brain scan images, in order to predict which candidate medicines are most likely to have a beneficial effect, in an early stage of testing on human volunteers.

Additionally, the project aimed to develop improved experimental models that mimic schizophrenia or depression in humans and develop and validate tests (such as electrical monitoring of the brain), to analyse the disease progression across species. The models and the tests will enable researchers to monitor the effects of candidate medicines in an early stage, and to identify new disease related targets for treatment in the brain.

8.1. Position in Innovation System

NEWMEDS encompassed pre-clinical testing, experimental human studies, clinical trials; new techniques, new software tools and new pre-clinical and clinical methods for medicines discovery.

8.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Tine Bryan Stensbøl, Discovery Pharmacology Research, H. Lundbeck, Copenhagen-Valby, Denmark

Managing Entity: Shitij Kapur, Institute of Psychiatry, King's College London, UK

8.3. Participants

EFPIA: H. Lundbeck A/S, Valby, Denmark; Abbott Laboratories, USA; Eli Lilly and Company Ltd, Basingstoke, UK; Janssen Pharmaceutica NV, Beerse, Belgium; Novartis Pharma AG, Basel, Switzerland; Orion Corporation, Espoo, Finland; Pfizer Limited, Sandwich, UK - Wyeth Pharmaceuticals, USA; F. Hoffmann-La Roche AG, Basel, Switzerland; Institut De Recherches Servier, Suresnes, France

Universities, Research Organisations, Public Bodies & Non-Profit: King's College London, London, UK; Karolinska Institutet, Stockholm, Sweden; University of Cambridge, Cambridge, UK; Zentralinstitut für Seelische Gesundheit, Mannheim, Germany; Agencia Estatal Consejo Superior de Investigaciones Científicas, Madrid, Spain; The University of Manchester, Manchester, UK; Bar Ilan University, Ramat Gan, Israel

SMEs: Psynova Neurotech Ltd, Cambridge, UK; Islensk Erfdagreining EHF, Reykjavik, Iceland; GABO:mi Gesellschaft für Ablauforganisation:milliarium mbH & Co KG, Munich, Germany

8.4. Projects Inputs and Funding

The NEWMEDS project received funding of €9.0 million from IMI, from a total project cost of €24.8 million and so the IMI contribution levered investment of an additional €1.77 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€ 8,986,216	36.2%
EFPIA funding	€ 13,789,412	55.5%
Other Funding	€ 2,074,047	8.3%
Total	€ 24,849,675	

8.5. Project Rationale and Market Failure

Psychiatric disorders like schizophrenia and depression are among the most serious public health threats, with increasingly large economic and social impact. According to the WHO, major depressive disorder affects between 10-20% of the global population, and depression ranks amongst the ten leading causes of disability. The WHO estimates that depression will become the second-largest global health burden by 2020. Schizophrenia, on the other hand, affects nearly 1% of the population, but because of its greatly disabling nature one in ten hospital beds in the western world are devoted to its treatment. Because it impacts almost every domain of the patient's function, and since many of its effects, particularly cognitive dysfunction, are currently untreatable it contributes to the enormous economic and social costs.

Despite the socio-economic need, the experience has been that there have been few new medicines to treat schizophrenia and depression, with the selection of targets in psychiatry driven largely by historical success (for example, monoamine-transporters and dopamine D2 receptors account for more than 90% of medicines in schizophrenia and depression).

NEWMEDS sought to identify new methods of identifying potential targets for schizophrenia and depression medicines and new models for the medicine development process.

8.6. Project Achievements and Outputs

The NEWMEDS project title could be easy to misunderstand; however, it was about new methods for developing new medicines rather than the development of new medicines.

The outputs from the project, identified in the project final report included:

- Novel insights into the biology of schizophrenia and depression.
- Standardised the application of cognitive animal models across several industrial partners – leading to development of and a standardised application of touchscreen methodology by several partners.
- Developed translational tools/platforms for medicines discovery (animal models, human imaging).
- Developed new 3 web tools (a first of its kind clinical significance calculator for assessment of potential biomarkers in psychiatry; the DupCheck tool for preventing duplicate enrolment of subjects across sponsors and therapeutic areas; a pharmacological imaging and pattern recognition toolbox).
- Standardised a PET methodology for serotonin release, and evaluated PET methodologies for non-amine transmitters.
- Rejected the hypothesis that single genetic mutations, polygenic scores or copy number variants (CNVs) can be used to stratify depression.

- Provided recommendations for the design of more efficient clinical trials including suggestions for decreasing sample size and duration in schizophrenia and depression.
- In addition, NEWMEDS assembled the largest patient level database for depression and schizophrenia that included 64 studies (34 placebo controlled studies, 30 active comparator studies) with 25,900 patients (16,105 study drug; 7,119 active comparator, 2676 placebo).
- Developed three mice models carrying copy number variants known to increase the risk in humans of developing schizophrenia. These animal models are biologically meaningful correlates of the human carriers and are being out licenced to Tachonic for public availability.
- Conducted a consensus building workshop on negative symptom studies that included academics researchers, medicines developers and regulators.

By the time the final project report was completed, the scientific outputs included 95 publications with an average citation rate of 2.83 and 28.9% highly cited (in top 10% of papers for citations).

There had been little or no history of collaboration between companies working in central nervous system research. A high level of additionality was therefore associated with IMI's role in providing a platform for the best people to work together.

In addition, this has led to the development of networks, new knowledge and new resources that participants could not have achieved on their own.

IMI has also helped change attitudes in companies that now understand that there is a pre-competitive area where there is a common interest and benefits to all from working together. This includes, for example, the design of clinical trials and the development of standards, with competition only really starting once a potential target has been identified.

8.7. Pathways to Socio-economic Impact

NEWMEDS was very much an R&D project, focusing on the early stages of the medicines development process. It clearly has generated a significant scientific output, in view of the numbers of research papers and presentations and a concomitant scientific impact (the citation impact scores are extremely high by international standards). Also in terms of media coverage and media appearances, there's quite a lot of publicity. Its output in terms of technological developments, through the PIPR Toolbox (patent applied), is also promising.

This project focused on the new medicines for psychiatric disorders like schizophrenia and depression, where progress in last decades have been limited, but the unmet medical needs are great. The potential for a large socio-economic impact is thus great, but challenges in finding new effective treatment approaches for these diseases are considerable. The case for a private-public partnership for investing in new methods for medicines development is thus very strong.

While the project cannot be linked to the introduction of a specific medicines (and was not intended to), there are important intermediate outcomes that have been documented including new medicines targets, models for validation of new targets and methods for assessing efficacy in early studies on humans.

It also contributed to knowledge about depression and schizophrenia not being one disease and identified potentially useful biomarkers.

This project focused on developing the groundwork for developing new medicines. Hence the focus was on the phase 1 of the clinical trial process but it also contributed to improved trials at phase 2 stage. This is likely to result in more effective trial designs that should reduce the chance of failure of new medicines before spending too much money.

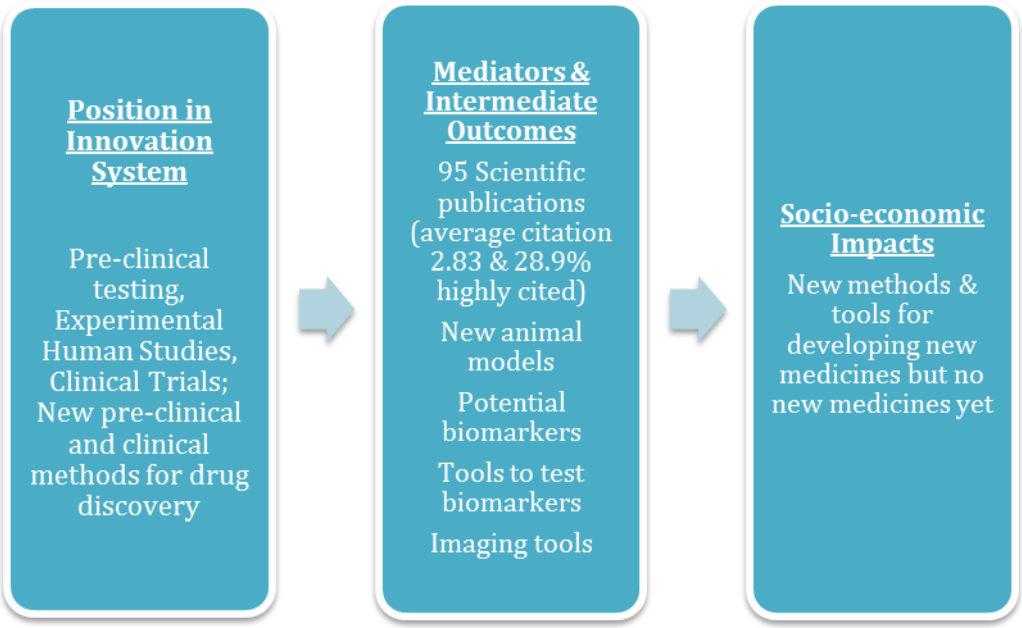
The pharma companies involved in NEWMEDS are using the new models and tools developed and they have been published so others can use them.

The touch screen technology developed and validated by partners in the NEWMEDS project is now commercially available and the new animal models have been commercialised and made available to the wider research community through vendors.

The project proposed an adjustment to the patient recruitment strategy in schizophrenia trials to be able to reduce the number of patients and length of the study, thereby significantly saving cost.

These may all realise health benefits but only if a new medicine is developed as a result; while companies involved expect this, it has not yet happened. There is also the potential to reduce medicines development costs, which would be beneficial at a societal level.

8.8. Summary: NEWMEDS



9. PharmaTrain

PharmaTrain was a pharmaceutical medicine training standard and infrastructure setting programme.

The main objective of the PharmaTrain project was to harmonise, build and implement shared standards for modular Master level programmes to improve postgraduate education in Pharmaceutical Medicine and Medicines Development Sciences. The programme was based on the Bologna credit and title system and built on the jointly developed PharmaTrain Syllabus 2010 as well as the agreed quality system and course recognition process.

The modular concept of the training programme also provided an opportunity to professionals to select courses for accredited Continuing Professional Development (CPD), as well as individualised training *à la carte*. The PharmaTrain consortium had identified six base courses and 13 master level programmes at European universities that were standardised at the same quality level. PharmaTrain has set, maintained and constantly improved the standards and quality management of the training schemes and practices for pharmaceutical professionals.

The programme aimed to encourage exchanges between the industry, regulators and academia on best teaching methodology and content, produce and promote distance e-learning programmes, and enable increased flexibility, transferability and mobility for trainees working in a mobile professional development environment, and develop a European postgraduate professional certification option in medicines development for physicians and non-physicians.

A uniform high-level training in Europe was also expected to make the medicines development process faster, safer, more economical, more tailored to patients' needs, and give Europe a global advantage in developing new innovative medicines.

9.1. Position in Innovation System

PharmaTrain was a training standard setting programme, covering all aspects of the medicines development pathway.

9.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Michael Hardman, IMED AstraZeneca, UK

Managing Entity: *Fritz Bühler,* European Federation of Courses In Pharmaceutical Medicine, Basel, Switzerland *and since 2013* Ingrid Klingman, European Federation of Courses In Pharmaceutical Medicine, Basel, Switzerland & European Forum for Good Clinical Practice, Brussels, Belgium

9.3. Participants

EFPIA: Pfizer Limited, Sandwich, UK; Bayer Schering Pharma AG, Berlin, Germany; AstraZeneca AB, Södertälje, Sweden; GlaxoSmithKline Research and Development LTD, Brentford, UK; Merck KGAA, Darmstadt, Germany; Novartis Pharma AG, Basel, Switzerland; Amgen NV, Bruxelles, Belgium; UCB Pharma SA, Brussels, Belgium; F. Hoffmann-La Roche AG, Basel, Switzerland; Novo Nordisk A/S, Bagsvaerd, Denmark; Sanofi-Aventis Recherche & Developpement, Chilly Mazarin, France; Janssen Pharmaceutica N.V., Beerse, Belgium; Laboratorios Almirall S.A., Barcelona, Spain; Laboratorios Del Dr Esteve SA, Barcelona, Spain; Orion Corporation, Espoo, Finland

Universities, Research Organisations, Public Bodies & Non-Profit: European Federation of Courses In Pharmaceutical Medicine, Basel, Switzerland (Project Co-ordinator); Universität Basel, Basel, Switzerland; International Federation of Associations of Pharmaceutical Physicians, Woerden, Netherlands; Faculty of Pharmaceutical Medicine of The Royal College of Physicians of the United Kingdom, London, United Kingdom; Pharmed, Brussels, Belgium; Semmelweis Egyetem, Budapest, Hungary; Université Claude Bernard Lyon 1, Villeurbanne, France; Cardiff University, Cardiff, United Kingdom; University of Surrey,

Guildford, United Kingdom; University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom; Hibernia College, Dublin, Ireland; The Provost Fellows & Scholars of the College of the Holy and Undivided Trinity of Queen Elizabeth Near Dublin, Dublin, Ireland; Vienna School of Clinical Research, Vienna, Austria; Universität Wien, Wien, Austria; Faculty of Medicine, University of Belgrade, Belgrade, Serbia; Universität Duisburg-Essen, Essen, Germany; PME Institute for Education in Pharmaceutical Medicine GmbH, Witten, Germany; Universitätsklinikum Freiburg, Freiburg, Germany; Université de Lausanne, Lausanne, Switzerland; Karolinska Institutet, Stockholm, Sweden; Goeteborgs Universitet, Goeteborg, Sweden; Københavns Universitet, København K, Denmark; Universite Louis Pasteur, Strasbourg, France; Universita Cattolica del Sacro Cuore, Milano, Italy; Universitat de Barcelona, Barcelona, Spain; Universitat Autonoma de Barcelona, Cerdanyola Del Valles, Spain; Universitat Pompeu Fabra, Barcelona, Spain; DIA Europe GmbH, Basel, Switzerland; European Federation for Pharmaceutical Sciences, Stockholm, Sweden; Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Swissmedic, Berne, Switzerland; European Organisation for Research and Treatment of Cancer Aisbl, Brussels, Belgium; Stichting Top Institute Pharma, Leiden, The Netherlands; European Forum for Good Clinical Practice, Brussels, Belgium; King's College London, London, United Kingdom

9.4. Projects Inputs and Funding

The PharmaTrain project received funding of €3.5 million from IMI, from a total project cost of €7.6 million and so the IMI contribution levered investment of an additional €1.17 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€3,510,300	46%
EFPIA funding	€3,489,181	46%
Other Funding	€632,047	8%
Total	€7,631,528	

9.5. Project Rationale and Market Failure

This project was a programme for creating a harmonised top quality level infrastructure for training of specialists in medicines development. While there may be arguments for public subsidies for education, the arguments for such subsidies are strongest for more basic training. For specialist training, business schools may be one example, it is usually assumed that the individual undergoing the training will also capture the benefits, and thus will be able to pay for the training with extra incomes earned. If the training infrastructure developed by PharmaTrain simply increased the earning potential of the individuals trained then the use of public funding could be questioned.

One of the bottlenecks that was being addressed was that within medicines development, the newer aspects of science (in a rapidly advancing area) were not being transferred into education and training programmes. This is because such a process takes time (so slowing down progress in improving the medicines development process). Also, the universities that have the most successful programmes have little incentive to update them, at least in the short run, since they have high demand for what they do.

The most important bottleneck addressed was that associated with the lack of harmonised content and quality standards of postgraduate Diploma and Master courses in medicines development as well as the lack of an opportunity in all EU member states for physicians and non-physicians to achieve certified specialisation in medicines development.

9.6. Project Achievements and Outputs

The outputs from the project, identified in the project final report included:

The results of PharmaTrain dedicated to quality improvement and harmonisation of training in Medicines Development, Regulatory Affairs as well as training for clinical investigators and the concept for “Specialist in

Medicines Development" was put together in the "PharmaTrain Manual Curriculum Standards and Best Practices".

The Manual was developed by almost all partners during the course of the project and included a range of appendices and guidelines.

The network and course portfolio of PharmaTrain Centres of Excellence is available on www.pharmatrain.eu. These include a jointly agreed PharmaTrain Syllabus and Curriculum in Medicines Development; a jointly agreed Syllabus and Curriculum for a Master of Regulatory Affairs; the Quality System, the concept for the new professional title "Specialist in Medicines Development" (SMD); the jointly agreed Clinical Investigator Training Concept (CLIC), as well as access to 10 e-learning compact modules. In addition, the Quality System and a Short Course recognition process aligned with www.on-course.eu, is a major achievement. The PharmaTrain Manual document, the jointly agreed curricula of 26 Elective Modules and the Good Examination Practices guide are available on the PharmaTrain website to which members of PharmaTrain Federation, former partners in IMI PharmaTrain, IMI and the general public have access.

PharmaTrain is now well known for recognising high-quality training courses in medicines development and investigator training as well as a steadily increasing network of stakeholders in this field of education and training.

Quality assurance is based on the quality criteria developed jointly by the IMI Education & Training (E&T) projects ("9 Cross Project Quality Criteria") and the SOP-based processes developed in PharmaTrain to recognise training centres and Short Courses, as the "Implementation Process of Shared Standards" and the "PharmaTrain CPD recognition and flagging request" process.

The original network of more than 20 European Universities, which grew together within PharmaTrain, was enlarged by 10 Universities from Eastern Europe (CEMDC course) and with nine Universities from non-European countries which joined the network as "Affiliates". These Universities have either already adapted the PharmaTrain content and quality standards or are working towards implementing them, to develop new courses and to participate in the network of course providers and other stakeholders.

The PharmaTrain shared standards and the cross-project quality criteria have now been implemented by 14 Universities (11 are partners in PharmaTrain and three Universities joined the network as an Affiliate (University of Aveiro in Portugal, Stellenbosch University, Cape Town, South Africa and Osaka University, Japan). These 14 Universities achieved the award of a Centre of Excellence and also started to mutually recognise ECTS and trainees.

The number of PharmaTrain approved Short Courses increased to 150 courses by successful implementation of the recognition process aligned with www.on-course.eu and led by the PharmaTrain CPD Access Panel.

PharmaTrain Federation with ca. 50 members has sustained the outputs of IMI PharmaTrain and participated in the IMI-TRAIN project.

PharmaTrain developed the content and curriculum for 14 Master and Diploma programmes and 156 single module courses.

During the duration of the PharmaTrain project, trainees included 497 students and 715 who received continued professional development. The training was delivered by the university consortium members. PharmaTrain developed the concept, shared standards and future infrastructure for education in medicines development.

The project also addressed some specific issues. For example, harmonised postgraduate training in regulatory affairs and for clinical investigators was not available and there were no training quality standards in place.

The project brought together universities and not-for-profit organisations across Europe that had some role in training for medicines development – in collaboration rather than competition – recognising that there is a common interest in establishing standards. PharmaTrain involved industry and universities in the development of those standards.

The benefit of this standardisation includes that students are reliably trained comprehensively and more mobile, there is more flexibility on what and where they can study and there is a professional, cohesive pathway toward competence development through specialisation in medicines development. The programmes are not identical but standard and so transferrable.

9.7. Pathways to Socio-economic Impact

The Expert Group noted that the scale and scope of this training project is impressive and should be seen as a good output.

The PharmaTrain programmes are designed to provide an understanding of the whole value chain in the medicines development process. So those benefitting from the training should find it easier to do their own job well, have a better knowledge of what everyone else is doing and avoid misunderstandings with people in other parts of the medicines development process.

There has been some tracking of PharmaTrain graduates in terms of stories rather than quantitative analysis – these have not been fully captured by the IMI project reporting process but are in IMI Newsletters and project process reviews.

Training is an investment in human capital, and the return on investment will be embodied in future earnings. No statistics of earnings of students before and after they completed the training program were reported, as is generally the case for evaluation of education and training programmes.

The potential socio-economic impacts of PharmaTrain could not be fully measured by tracking the career progression of those trained since the real benefits will be greater and wider – it is about improving productivity in the medicines development process more generally – and any impact on that could be much greater than career progression benefits from those trained.

Overall, the idea is that the impact of PharmaTrain will be to improve the understanding of the whole medicines development process, for all of those involved and to improve the competence of people working throughout the process. This will include pharma companies, SMEs in early stage medicines development, clinical trials companies, academics, healthcare professionals running trials etc. So, improvements to the medicines development process should, in principle, reduce timescales, reduce error rates and minimise the risk in medicines development.

However, delivering impacts depends not only on the knowledge acquisition that has been delivered by PharmaTrain, but on how that knowledge will be applied by organisations in the medicines development process.

How this is done is being addressed by the development of competency profiles for people in various medicines development roles. This is one of the responsibilities of the PharmaTrain Federation.

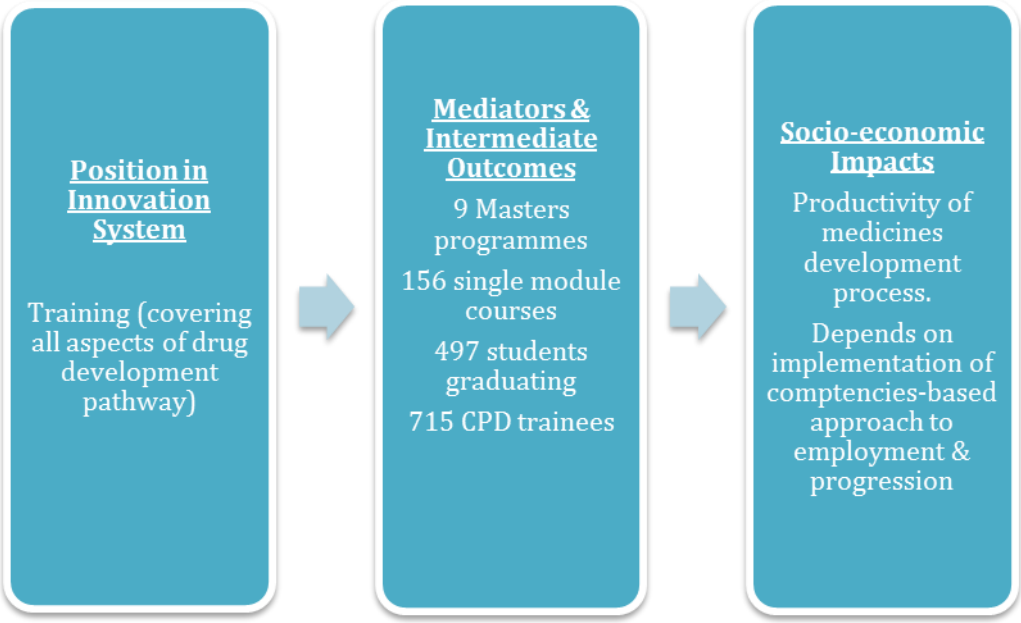
PharmaTrain Federation is a not-for-profit organisation, set up to secure the sustainability of the IMI1 PharmaTrain project. This can be seen as an indicator that there was a demand for setting up such a providers' network for these types of training courses and programs developed. The IMI programme could thus be seen as a catalyst for its development.

The full socio-economic impact of the project will to a great degree, depend on the success of the PharmaTrain Federation in taking the outputs forward.

The PharmaTrain project was an education and training project and so was quite different from the other IMI1 projects reviewed during the socio-economic impact assessment. This recognises that improvements to medicines development processes will generate socio-economic impacts that encompass more than the R&D process.

Strengthening the education and training process for medicines development in Europe should help increase investment and re-investment by pharma in Europe. It seems that PharmaTrain is generally seen as a very good programme – evidenced by the increasing involvement of partners beyond Europe – and this helps maintain Europe's reputation as a competitive location for the sector.

9.8. Summary: PharmaTrain



10. PROTECT

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium project (PROTECT) sought to enhance the monitoring of the safety of medicines.

The European Medicines Agency (EMA) coordinated the PROTECT and managed a consortium of 35 public and private participants. The aim was to enhance the monitoring of the safety of medicinal products and to contribute to better evaluation and communication of the benefit-risk profile of medicines throughout their lifecycle by developing innovative tools and methodological standards.

The PROTECT research programme was designed to address problems with the methods used in pharmacovigilance (monitoring medicines already on the market to identify adverse reactions), pharmacoepidemiology (understanding how different types of patients use and react to medicines) and benefit-risk integration and representation.

The objectives of PROTECT were: to enhance data collection directly from consumers in their native language in several countries using modern tools of communication; to improve early signal detection from spontaneous reports, electronic health records and clinical trials; to develop and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues and different data sources; to develop methods for continuous benefit-risk monitoring of medicines, by integrating and presenting data on benefits and risks from clinical trials, observational studies and spontaneous reports; and to validate various methods developed in PROTECT using different data sources in order to identify and help resolve operational difficulties linked to multi-site investigations.

10.1. Position in Innovation System

The focus of PROTECT was on post-marketing surveillance of medicines.

10.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Xavier Kurz, European Medicines Agency, Pharmacovigilance and Risk Management, London, UK

Managing Entity: Dr Anne-Marie Clemensen, Danish Medicines Agency

10.3. Participants

EFPIA: GlaxoSmithKline Research and Development LTD, Brentford, UK; Amgen NV, Brussels, Belgium; Bayer Schering Pharma AG, Berlin, Germany; AstraZeneca AB, Södertälje, Sweden; Eli Lilly and Company Limited, UK; Genzyme Europe B.V., Naarden, The Netherlands; H. Lundbeck A/S, Valby, Denmark; Merck KGaA, Darmstadt, Germany; Novartis Pharma AG, Basel, Switzerland; Novo Nordisk A/S, Bagsvaerd, Denmark; Pfizer Limited, Sandwich, United Kingdom; F. Hoffmann-La Roche AG, Basel, Switzerland; Sanofi-Aventis Research and Development, Chilly-Mazarin, France; Takeda Development Centre Europe Ltd

Universities, Research Organisations, Public Bodies & Non-profit; European Medicines Agency; Lægemiddelstyrelsen (Danish Medicines Agency), Copenhagen, Denmark; Aarhus University, Denmark; Academisch Ziekenhuis Groningen, Netherlands; Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Fundación Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain; Fundació Institut Català de Farmacologia, Barcelona, Spain; International Alliance of Patients' Organizations, London, UK; Imperial College of Science, Technology & Medicine, London, UK; Institut National de la Santé et de la Recherche Médicale, Paris, France; Ludwig-Maximilians-Universität München, München, Germany; Mario Negri Institute for Pharmacological Research, Milan, Italy; Medicines and Healthcare products Regulatory Agency, London, UK; Poznan University of Medical Sciences, Poland; Rijksuniversiteit Groningen, Groningen, The Netherlands; Stiftelsen WHO Collaborating Centre for

International Drug Monitoring, Uppsala, Sweden; University of Newcastle upon Tyne, Newcastle upon Tyne, UK; Universiteit Utrecht, Utrecht, The Netherlands; Witten/Herdecke University, Germany

SMEs: LA Santé Épidémiologie Evaluation Recherche, Paris, France; Outcome Europe Sarl, St. Prex, Switzerland

10.4. Projects Inputs and Funding

The project received funding of €11.0 million from IMI, from a total project cost of €28.6 million and so the IMI contribution levered investment of an additional €1.60 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€11,009,715	38%
EFPIA funding	€10,864,491	38%
Other Funding	€6,743,176	24%
Total	€28,617,382	

10.5. Project Rationale and Market Failure

PROTECT was designed to address important questions and problems with the methods used in pharmacovigilance and pharmacoepidemiology. One of the underlying issues leading to sub-optimal methods was that that there were a wide variety of different methods being used and these had evolved over time rather than being based on good fundamental research and robust analysis.

10.6. Project Achievements and Outputs

The project final report listed a large number of outputs and deliverables from the project, related to each of the objectives.

The main output from the project was new knowledge, on which a series of recommendations were based. These relate to both safety of medicines and the assessment and representation of the benefit-risk profile of medicinal products.

By the time the final project report was completed, there were 61 scientific publications with an average citation rate of 1.36 and 16.4% highly cited (in top 10% of papers for citations). The project reports that this has since increased to 72, including a special issue of the journal Pharmacoepidemiology and Drug Safety. The influence of publications may also be understated since an April 2014 bibliometric analysis in by Thomson Reuter of 40 articles found a citation impact of 3.91 with 37.5% highly cited papers.

In addition to the scientific publications, the methods, results and case studies on benefit-risk assessment, integration and visualisation of medicinal products have been available at a highly frequented website (http://protectbenefitrisk.eu/) and all outputs have been publicly available on the PROTECT website.

The recommendations and guidelines have also been disseminated to two main decision-making regulatory committees of the European Medicines Agency (the Pharmacovigilance Risk Assessment Committee and the Committee for Human Medicinal Products), to the European Network of Centres for Pharmacovigilance and Pharmacoepidemiology and to international scientific societies, such as the International Society of Pharmacoepidemiology, so that they can be implemented.

They have also been incorporated or reflected into guidance produced by regulators, for marketing authorisation holders and national competent authorities, for example in the latest revision of the good pharmacovigilance practice (GVP) Module VIII on Post-Authorisation Safety Studies and Module IX on signal management. Results and outputs have also been integrated in each of the annual revisions of the ENCePP Guide on Research Standards in Pharmacoepidemiology.

The main outputs from PROTECT include:

- Guidance for observational studies on medicines in several databases and several countries with common protocols. This will support the use of real world evidence for regulatory purposes by increasing consistency in findings from safety studies and revealing causes of differential drug effects.
- A comprehensive review of good detection practices has identified significant improvements to signal detection methods applied by national and international regulatory agencies and in pharmaceutical companies. This guidance was used to update methods for signal detection from EudraVigilance and will be integrated in revised regulatory guidance on signal management in 2016.
- Recommendations for benefit-risk assessment methodologies and visual representations based on real-world case examples to facilitate clear and transparent decision-making. This has led to initiatives that explore practical application of harmonised methods and the involvement of patients and the wider public in the assessment of benefits and risks of medicines.
- Exploring new methods to collect data directly from patients, including via the internet. This research included the collection of information from pregnant women via the web to better understand the safety of medicines during pregnancy.

In addition to the recorded project outputs, there was an additional benefit reported by project participants, from collaboration. Those involved appreciated the benefits of collaboration and wanted to continue working together. Networks were developed that will endure beyond the project. In particular, several research organisations are working more closely together than they did in the past and this sharing of knowledge may well deliver future benefits.

New research projects will also use the results of the project and several academic researchers are reported to be planning new research and PROTECT has been referenced as a basis for several IMI projects including GetReal, ADVANCE and ADAPT-SMART.

The PROTECT project brought together a wide range of expertise from industry, academia and regulators and this collaboration led to high quality work and acceptance of the results by different stakeholders, which facilitated the development and adoption of good practice standards.

10.7. Pathways to Socio-economic Impacts

This project fits into phase 4 of the medicines development pipeline; it is a post marketing surveillance project. The project was led by the EMA, which should mean that the findings are introduced into regulatory practice and new EMA policies. So far this has happened through revisions of good pharmacovigilance practices.

If the knowledge outputs from the project are translated into practices by regulators and by the actors in the medicines development process more generally, there will be substantial socio-economic impact.

PROTECT was based on the premise that faster approval of new medicines by the EMA and other regulators would mean earlier access to innovative medicines to patients but would also require higher confidence that on-going monitoring of potential adverse reactions is based on robust scientific methods. So the impact could occur by facilitating a speeding up of the medicines approval process, in particular, faster and better regulatory decision making on cost-benefit and on safety.

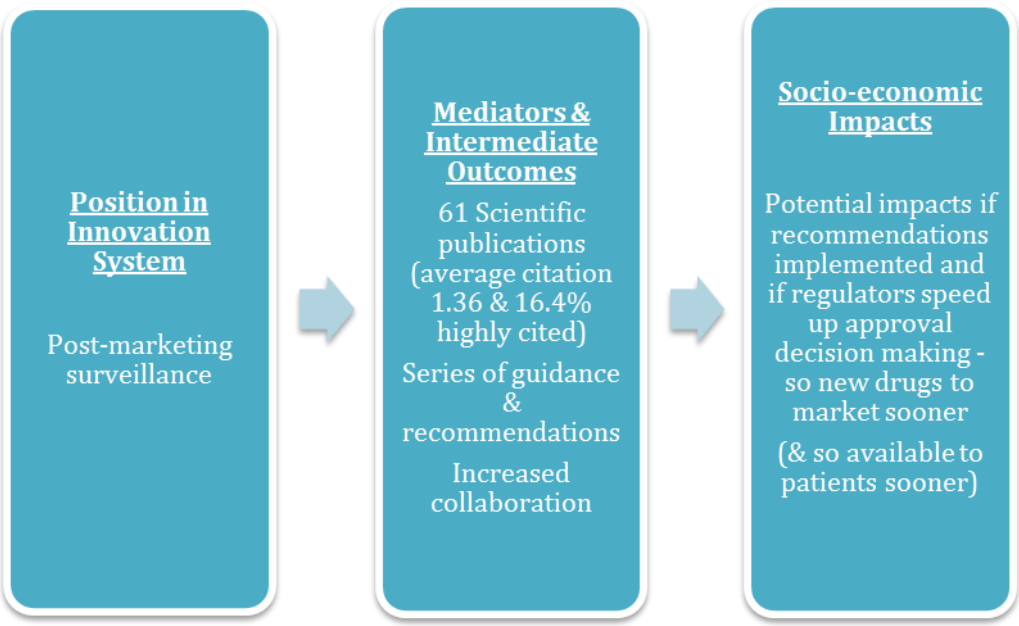
However, evaluation of the impact of PROTECT on speed and quality of regulatory decision making would require taking into account other factors. The contribution of PROTECT outputs may therefore not come to light unless specific reference is made to PROTECT publications (as has been the case for the revision of the GVP Module IX on Signal Management and of the revisions of the ENCePP Guide on research standards in pharmacoepidemiology).

Standardised protocols and methods should also mean that there is better confidence in the results of studies because the outcome differences associated with differences in method are removed or reduced.

The adoption of new methods could also decrease costs. For example, analysis of methods used for signal detection showed that all methods were equivalent, which means that the simplest, and less costly method can be used.

Such impacts depend on the PROTECT recommendations and guidance being implemented and this is expected to happen over time.

10.8. Summary: PROTECT



11. SAFE-T

The Safer and Faster Evidence-based Translation (SAFE-T) project focused on the prediction, detection and monitoring of medicines-induced injuries, in order to improve patient safety in the medicines development process.

One of the key challenges in medicines development is improvement of patient safety: many medicines side effects are not adequately predictable and often detected too late, when the risk for serious outcome is high.

The SAFE-T project worked on the development of improved tools for the prediction, detection, and monitoring of medicines-induced injuries to the kidney, the liver, and the vascular system, using markers in patients' blood and/or urine.

The ultimate goal was to identify for each of the three organ toxicities a set of safety biomarkers more specific, more sensitive and more predictive than previously available ones, and to gain regulatory acceptance for routine use of these biomarkers in medicines development.

11.1. Position in Innovation System

SAFE-T included activities relevant to all stages of medicines development from pre-clinical to clinical development, registration, and post marketing.

11.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Michael Merz, Pre-clinical Safety, Novartis Institutes for Biomedical Research, Basel, Switzerland

Managing Entity: Nicole Schneiderhan-Marra, Natural and Medical Sciences Institute, Reutlingen, Germany

11.3. Participants

EFPIA: Novartis Pharma AG, Basel, Switzerland; Laboratorios Almirall S.A., BARCELONA, Spain; Amgen, Bruxelles, Belgium; AstraZeneca AB, Södertälje, Sweden; Bayer Schering Pharma AG, Berlin, Germany; Boehringer Ingelheim International GmbH, Ingelheim, Germany; Eli Lilly And Company Limited, Basingstoke, UK; GlaxoSmithKline Research and Development LTD, Brentford, UK; Pfizer Limited, Sandwich, UK; F. Hoffmann-La Roche AG, Basel, Switzerland; Sanofi-Aventis Recherche & Development, Chilly Mazarin, France; Takeda Development Centre Europe Ltd., London, UK

Universities, Research Organisations, Public Bodies & Non-profit: Naturwissenschaftliches und Medizinisches Institut an der Universität Tübingen, Reutlingen, Germany; Charite - Universitaetsmedizin Berlin, Berlin, Germany; Assistance Publique - Hopitaux De Paris, Paris, France; Consorci Institut Català de Ciències Cardiovasculars, Barcelona, Spain; The Foundation For Medical Research Infrastructural Development And Health Services, Tel Aviv, Israel; Universitaetsklinikum Aachen, Aachen, Germany; Universität Leipzig, Leipzig, Germany; The University of Liverpool, Liverpool, UK; Universidad de Malaga, Malaga, Spain; University College Dublin, National University of Ireland, Dublin, Dublin, Ireland

SMEs: Firalis S.A.S., Huningue, France; EKF Diagnostics Limited (formerly Argutus Medical LTD, Dublin, Ireland; EDI Experimentelle und Diagnostische Immunologie GmbH, Reutlingen, Germany; Interface Europe, Bruxelles, Belgium

11.4. Projects Inputs and Funding

The project received funding of €13.9 million from IMI, from a total project cost of €31.7 million and so the IMI contribution levered investment of an additional €1.28 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€13,901,971	44%
EFPIA funding	€13,575,483	43%
Other Funding	€4,198,802	1%
Total	€31,676,256	

11.5. Project Rationale and Market Failure

SAFE-T was addressing an organisational coordination problem. Identifying, developing, and qualifying new safety biomarkers is a substantial challenge, both from a scientific and a logistic perspective. Scientifically, given the complexity of the diseases, a large number of biomarker candidates needs to be thought of and screened, using different technologies. Logistically, since the organ injuries of interest to SAFE-T are rare events, large sample sizes across a range of special patient populations are needed and they are very hard to recruit efficiently for individual companies.

It would have been possible for organisations working on their own to deal with one or two of the issues examined by the SAFE-T project but this would have had limited impact since the prediction, detection, and monitoring of medicines-induced injuries requires a comprehensive approach. The benefits from such research would be to the medicines development process itself rather than to particular medicines candidates so individual companies would have found it difficult to get a return on investment in this area.

The IMI supported SAFE-T project allowed resources and data to be pooled and so the scale of what could be done was much greater as a result of these economies of scale. IMI also provided a model for companies to interact with academics and so much faster progress could be made instead of having companies working on their own.

The anticipated outputs from the SAFE-T project, in particular new biomarkers for clinical trials would require approval from regulators such as the EMA and the FDA to be used routinely. The leaders of the project believed that such approvals were more likely to be achieved based on the work of a consortium of companies and academics research teams than by a single company.

11.6. Project Achievements and Outputs

The project sought to identify biomarkers that would indicate at an early stage whether new medicines might cause damage, to liver, kidney and cardiovascular system. The project final report concluded that SAFE-T had made a significant contribution to detect such adverse reactions as early and as specifically as possible, through the extensive characterisation of new serum, plasma and urinary biomarkers.

SAFE-T generated a vast amount of data on 105 initial biomarker candidates, of which more than 20 showed promising performance either individually or as part of marker panels. Most of these selected biomarkers will be submitted to EMA and FDA to obtain a “letter of support”, confirming the practical utility of the markers and encouraging sponsors to use them in an exploratory setting in order to generate more data that can then help to support a qualification at a later point in time.

On liver, an application has been made to FDA/EMA and may have enough evidence to get a letter of support. This should mean that companies undertake the further work required to provide the additional data needed for qualification (i.e. approval).

On the kidney, this was the area where comprehensive pre-clinical work had been done and this was taken to the level of transferring assays to human. There are promising markers here and work is on-going to get what is needed for letter of support. Submission to EMA and FDA is expected by May 2016.

On the cardio-vascular system there had been the least previous work. This proved to be a difficult area but potential biomarkers have been identified and assays established but further work will be required. Submission to EMA and FDA for a letter of support is expected by May 2016.

By the time the final project report was completed, there were 22 scientific publications with an average citation rate of 2.12 and 28.57% highly cited (in top 10% of papers for citations).

The project has also resulted in methods and resources that can be used in future research, including the strategy for clinical biomarker qualification established and tested by SAFE-T, SOPs for the validation of biomarkers assays (standard procedure & quality control), biomarker assays developed by SAFE-T SMEs, and state-of-the-art processing and storage of human biospecimens for qualification by the SAFE-T biobank, as well as a database. Samples available in SAFE-T's biobank and data available in the database cover nineteen different patient populations, and can be used for further biomarker research.

While the SAFE-T project has completed and submitted its final report, work is on-going on finalising submission to FDA/EMA for letters of support on all three areas. Discussions are on-going with consortia members and IMI on following up the project in IMI2.

11.7. Pathways to Socio-economic Impact

The project final report quoted a European Commission document[9] from 2008 that estimated that adverse medicines reactions caused an estimated 197,000 deaths per year in the EU and cost society €79 billion. While the project focused on a subset of adverse medicines reaction injuries (to kidney, liver, and vascular system), this context suggests that the socio-economic benefits from better prediction, detection, and monitoring of medicines-induced injuries could be significant.

The application of SAFE-T biomarkers in clinical trials should identify potential safety problems earlier and so stop the development process earlier, before large costs have been incurred.

If the side effects can be identified at the clinical trial stage, then the problem of having to withdraw medicines already on the market can be avoided. This can be by stopping development in the first place – or by developing the medicine but for a defined group of patients.

There may also be circumstances where knowledge about the circumstances where it is not safe to use a new medicine means that it is possible to continue the development process for use in circumstances where there is no safety concern or where that may be secondary (for example, where the damage may be a better outcome than not using the medicine).

There is also a secondary use during clinical treatment, since can be used to monitor for damage and so improve the treatment by informing the clinical decision making process on whether to continue treatment or to make changes.

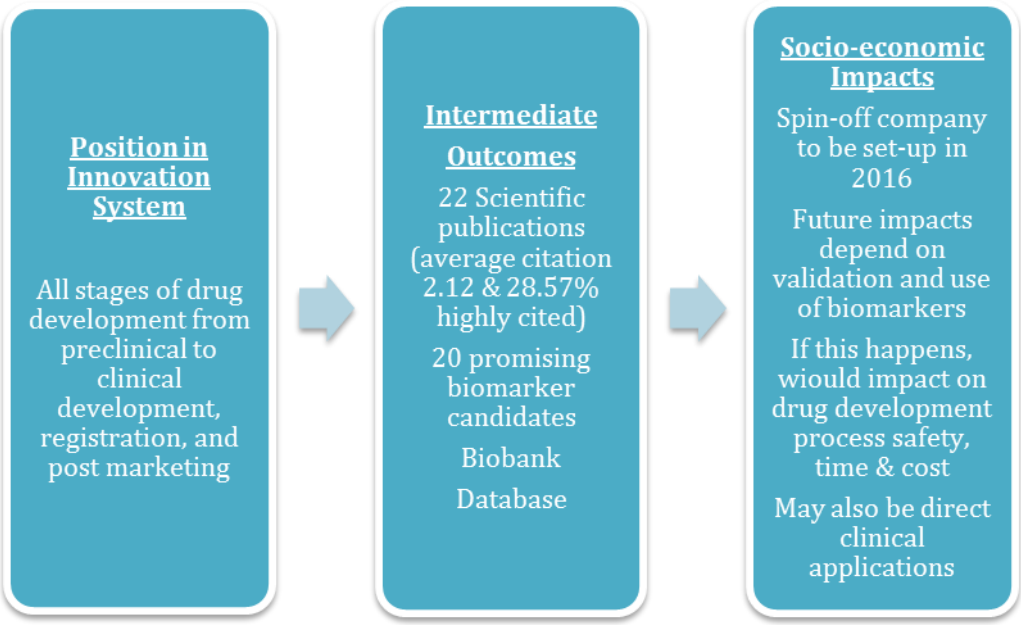
However, the SAFE-T biomarkers are not at the stage of development that they can be used routinely in clinical trials or in clinical practice. Further work will be required to apply for and received EMA and FDA approval and so socio-economic impacts are dependent on that follow-on work being done, either through future IMI supported projects or by individual companies investing further in generating the addition data required.

Follow-on topics have already been launched in IMI2 Calls 7 and 9, which are likely to lead to follow-on projects (with IMI consortia that will build on prior consortia). However, future impacts would probably be less significant, or take more time to generate, if IMI2 follow-up proposals are rejected for funding.

[9] EU commission, MEMO/08/782, 10 Nov 2008

Assay developers will be able to capitalise on the results of the consortium to develop commercial assays and establish service measurements that can be used in clinical studies and, as more data are gathered in future consortia, extend the use of the novel organ injury biomarkers to a hospital setting. One spin-off company is planned for 2016, Signatope GmbH, which will commercialise cross-species immunoassays developments from the project.

11.8. Summary: SAFE-T



12. EUROPAIN

The EUROPAIN project sought to understand chronic pain better and improve its treatment.

The EUROPAIN project aimed to improve the treatment of patients with chronic pain. The scientists searched for changes in the nervous system that contribute to pain, in order to fill the gaps in the knowledge of chronic pain. Research was undertaken to elucidate the mechanisms of pain, using novel experimental models, human volunteers and clinical data of pain patients. This included objective methods to measure pain in patients and examination of the mechanisms that are activated by placebo-medication.

The project included work to validate and qualify biomarkers for stratification and enrichment of patients into clinical trials. The scientists also examined how genetic factors, depression or anxiety, and psycho-social factors increase the risk of developing chronic pain, as well as the influence of gender on pain. By identifying the mechanisms involved in chronic pain, the EUROPAIN consortium sought to open possibilities for better treatments for patients.

12.1. Position in Innovation System

Target identification, pre-clinical, translational medicine, clinical (early and late), patient indication definitions and stratification.

12.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Märta Segerdahl, H. Lundbeck, Valby, Denmark

Managing Entity: Stephen Brendan McMahon, Kings College London, UK

12.3. Participants

EFPIA: AstraZeneca AB, Södertälje, Sweden; Boehringer Ingelheim International GmbH, Ingelheim, Germany; Eli Lilly and Company Limited, Basingstoke, United Kingdom; Grünenthal, Germany; Laboratorios del Dr Esteve SA, Barcelona, Spain; UCB Pharma SA, Brussels, Belgium; Sanofi-Aventis Recherche & Developpement, Chilly Mazarin, France; Pfizer Limited, Sandwich, UK – Wyeth Pharmaceuticals, USA

Universities, Research Organisations, Public Bodies & Non-profit: King's College London, London, United Kingdom; University College London, London, United Kingdom; University of Oxford, Oxford, United Kingdom; Imperial College of Science, Technology and Medicine, London, United Kingdom; Christian-Albrechts-Universitaet zu Kiel, Kiel, Germany; Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany; Technische Universitaet Muenchen, Muenchen, Germany; University Hospital Bergmannsheil Bochum, Bochum, Germany; Klinikum der Johann Wolfgang Goethe Universität, Frankfurt, Germany; Aarhus Universitetshospital, Aarhus Sygehus, Aarhus, Denmark; Region Hovedstaden, Hillerod, Denmark; Syddansk Universitet, Odense M, Denmark

SMEs: Neuroscience Technologies, S.L., Barcelona, Spain & Neuroscience Technologies Ltd, London, UK

12.4. Projects Inputs and Funding

The project received funding of €6.2 million from IMI, from a total project cost of €22.6 million and so the IMI contribution levered investment of an additional €2.62 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€6,229,343	28%
EFPIA funding	€11,165,740	50%
Other Funding	€5,155,000	23%
Total	€22,550,083	

12.5. Project Rationale and Market Failure

Chronic pain affects one in five European citizens and is one of the major burdens of society, both from an individual suffering perspective as well as a socioeconomic burden for society. Overall, chronic pain constitutes a major socio-economic burden also for society, with direct costs corresponding to 0.5-2% of GNP in the EU region as well as in North America (OECD 2012). More specifically, 7-8% of the general population suffer neuropathic pain. With current treatments, only one third of patients overall obtain adequate pain relief.

A 2012 OECD report put the direct cost of chronic pain at 0.5-02% of GDP in the EU, as a result of medication, disability, impacts on employability etc. so developments that reduce or better manage chronic pain can have a substantial socio-economic impact. However, those benefits will be social rather than commercial.

Existing medicines for pain tend to be generic and fairly inexpensive. So if a new medicines is developed that is more effective, but more expensive, it can be difficult to get payers to agree to use it in healthcare systems.

There is limited commercial incentive to invest in medicines to deal better with chronic pain. The problem being addressed was the need for analgesic medicines – there are not many available and many of those that are have side effects. There has been a low success rate in developing new analgesic medicines and so there was a need to improve the medicines development process in this area.

There is also the issue of whether there is a full understanding of the patient view of the extent to which pain is an area of unmet need. For example, Arthritis Research UK surveyed its members about needs and the number one issue was pain – but the research and medicines development agenda has been more focused on issues like inflammation.

12.6. Project Achievements and Outputs

There were three areas of need that were met by the project.

The first was a need for better animal models. Those that existed had shortcomings and may mislead about what would translate to the clinic. This needed a collaborative approach since all the companies were working on improving this but there was unnecessary duplication of effort in understanding what the best models might be. The project coordinated world leading centres, working on the development of detailed common protocols and all ran them in parallel. The output was an approved way of implementing models, a standardised approach for pharma to use in the future.

One of the new animal models that was an output from the EUROPAIN project dealt with the difficulty in measuring whether animal feeling pain, providing for the first time, an objective measure of pain, based on examining behaviour (burrowing). This model is already in use in medicines development by EUROPAIN participants and by companies not involved in the project. Other new models included one of diabetic polyneuropathy, for HIV drug polyneuropathy and chemotherapy induced pain. There were three new animal models validated.

The second was to find new ways of finding targets. A number of potential targets have been identified.

The third was a meta analysis of the placebo response in data from clinical trials for approved medicines. Collaboration was necessary to do this, since it allowed placebo data to be compared across trials in a consistent way.

Overall, there was a considerable volume of new knowledge. By the time the final project report was completed, there were 160 scientific publications with an average citation rate of 1.98 and 23.08% highly cited (in top 10% of papers for citations).

The project also explored the placebo response to pain control, which has implications for other areas of medicine.

The project outputs included a cohort database comprising 1,000 healthy volunteers and more than 2,300 people with neuropathic pain and biobanks.

Some of the findings from the project such as catastrophising (negative thinking) as a predictor for chronic postoperative pain and the suggestion that selective serotonin reuptake inhibitors could be used in these patients are major outputs for future use.

The project also demonstrated the benefits of collaboration between research centres, allowing for the identification and dissemination of best practice. In addition, the academics and the industry research now know and understand each other better (academic-industry, industry-industry, academic-academic) and will continue to work together. There are a number of continued collaborations already in place, including a number of academic researchers that have received further funding from pharma to look at particular issues

12.7. Pathways to Socio-economic Impact

A 2012 OECD report put the direct cost of chronic pain at 0.5-02% of GDP in the EU, as a result of medication, disability, impacts on employability etc. Around 20% of the European population suffers chronic pain and it is age related so is likely to get worse. Chronic pain has a major financial impact on business outputs in terms of both absenteeism (missed days from work) and presenteeism (reduced effectiveness while at work). So developments that reduce or better manage chronic pain can have a substantial socio-economic impact.

The outputs from the project will all act on the speed, costs and attrition rate of medicines development for chronic pain. New models and methods have increased operational excellence in pre-clinical and clinical research.

The project aimed to better understand chronic pain and improve its treatment; achieving this aim should have a substantial, long-term impact on the health and productivity of society. However, while the project has delivered a significant volume of intermediate outcomes, further work will be required to build on those to deliver socio-economic impacts.

The medicines development process will be improved as a result of the better, standardised animal model and by a range of other new knowledge. This should improve the success rate for all medicines being developed in this area. These include new tools for use in clinical trials, which will give a better understanding of how the medicines are working.

Such impacts will depend on the implementation. For example, the pharma companies have been involved in the process of developing the improved and new animal models and so are likely to use the outputs of this.

The project has also identified a number of potential targets for the development of new medicines. Some of these are being taken forward by pharma and, if the next stage is successful, will be in clinical trials in 5-10 years.

There are also some potential benefits direct to patient care. There is a better understanding of how medicines are working with patients and this will allow clinicians to focus on those who need more care. So

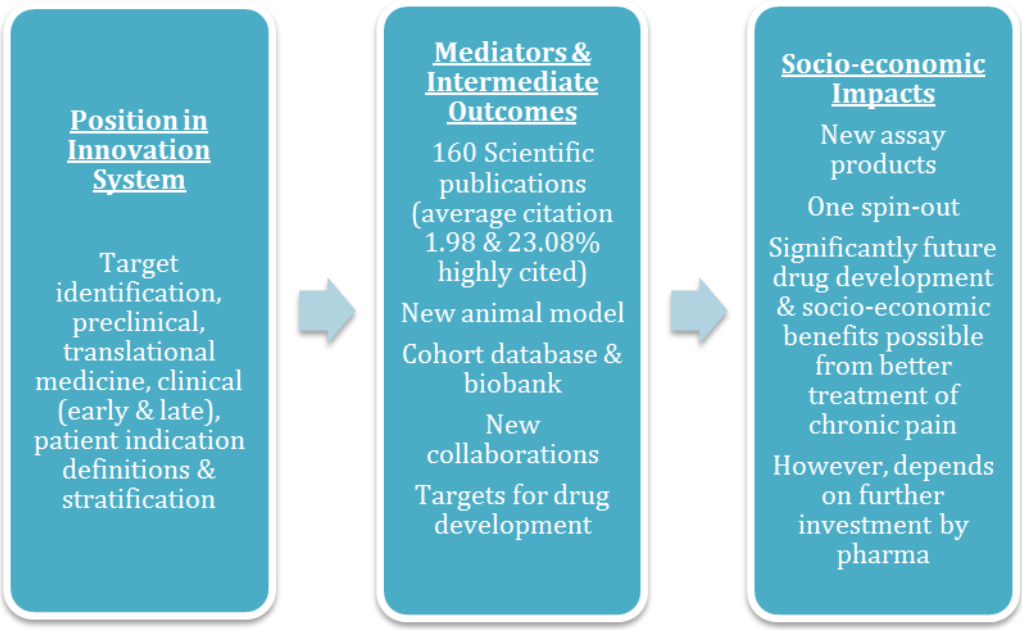
this is a benefit without additional costs – directing existing tools to better effect, focusing attention on those who need it most.

There is one specific socio-economic impact already delivered. One SME that was involved in the project had 5 employees at the start and has grown to 27 employees as a result of being involved in the project, as a result of bringing new assays to market. There has also been a spin-out company.

However, realising the potential future impact will depend on future investment in this area by pharma companies. Over the last few years, many of the larger pharma companies have either stopped investing in chronic pain or have reduced investment. So the next stage may depend on small to mid-sized pharma.

An unanticipated benefit was the understanding of fibromyalgia, a condition that some had argued was psychological rather than physical. So, while a cure was not developed, there is an important social benefit in recognising that this is a physical disease.

12.8. Summary: EUROPAIN



13. U-BIOPRED

The U-BIOPRED project focused on speeding up the development of better treatments for patients with severe asthma by identifying unbiased biomarkers for the prediction of respiratory disease outcomes.

The project addressed several knowledge gaps that make it hard to predict in the early stages of medicines development how well a new experimental medicine will work in patients. One of the major difficulties is the finding that there are many different forms of severe asthma, caused by different mechanisms of disease. Patients with different types of asthma may react differently to new or existing treatments.

The development of new treatments for individuals with severe asthma is urgently needed but hampered by lack of validated clinical and biological disease markers, underperforming of pre-clinical models, inadequate sub-phenotyping, and insufficient understanding of disease mechanisms.

The use of biomarker profiles comprised of various types of high-dimensional data, integrated with an innovative systems biology approach into distinct phenotype handprints, will enable significantly better prediction of therapeutic efficacy in severe asthma than single or even clustered biomarkers of one data type, and will identify novel targets.

The U-BIOPRED consortium brought together the leaders of the major global networks of severe asthma.

13.1. Position in Innovation System

U-BIOPRED included early stage biomarker identification (Stage 1 and Stage 2), including lead discovery and lead optimisation of specific analytes. Also included pre-clinical studies from laboratory and animal models.

13.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Peter Sterk, Academic Medical Centre, Amsterdam, Netherlands

Managing Entity: Thomas Martin, Novartis, Horsham, UK

13.3. Participants

EFPIA: Novartis Pharma AG, Basel, Switzerland; Laboratorios Almirall S.A., Barcelona, Spain; AstraZeneca AB, Södertälje, Sweden; Boehringer Ingelheim International GmbH, Ingelheim, Germany; Chiesi Farmaceutici S.p.A, Parma, Italy; GlaxoSmithKline Research and Development LTD, Brentford, UK; F. Hoffmann-La Roche AG, Basel, Switzerland; UCB Pharma SA, Brussels, Belgium; Centocor, a J&J company; Amgen NV, Brussels, Belgium; Merck Sharp & Dohme Corp, Rahway, US

Universities, Research Organisations, Public Bodies & Non-profit: Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam, Netherlands; The University of Southampton, Southampton, UK; Imperial College of Science, Technology and Medicine, London, UK; Università degli Studi di Catania, Catania, Italy; University of Rome 'Tor Vergata', Rome, Italy; Hvidovre Hospital, Hvidovre, Denmark; The Jagiellonian University Medical College, Krakow, Poland; Universität Bern, Bern, Switzerland; Semmelweis Egyetem, Budapest, Hungary; University of Manchester, Manchester, UK; Université de la Médietrranée, Aix-Marseille II, Marseille, France; Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., München, Germany; Umeå University, Umea, Sweden; Universiteit Gent, Gent, Belgium; Centre National de la Recherche Scientifique, Paris, France; Universita' Cattolica Del Sacro Cuore, Milan, Italy; Københavns Universitet (University of Copenhagen), Copenhagen, Denmark; Karolinska Institutet, Stockholm, Sweden; University of Nottingham, Nottingham, UK; Universitetet i Bergen, Bergen, Norway; Astma Fonds Longstichting, Leusden, the Netherlands; European Lung Foundation, Lausanne, Switzerland; Asthma UK, London, UK; European Federation of Asthma and Allergy Associations, Brussels, Belgium; Lega Italiana Anti Fumo – ONLUS, Catania, Italy; International Primary Care Respiratory Group, Aberdeen, UK

SMEs: Synairgen Research Limited, Southampton, UK; Aerocrine AB, Solna, Sweden; BioSci Consulting, Maasmechelen, Belgium

Other: Philips Electronics Nederland B.V., Eindhoven, the Netherlands

13.4. Projects Inputs and Funding

The project received funding of €9.9 million from IMI, from a total project cost of €26.9 million and so the IMI contribution levered investment of an additional €1.71 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€9,935,501	37%
EFPIA funding	€14,574,652	54%
Other Funding	€2,415,549	9%
Total	€26,925,702	

13.5. Project Rationale and Market Failure

The severe asthma group is only 3-8% of the total – but it accounts for half of the resources – for example, with frequent acute episodes that require hospital admissions.

From a commercial perspective, the medicines that are focused on the 92-97% of asthma patients that are not severe will be priorities for investment. However, from a healthcare cost perspective, there is a need to address the high costs of hospital admissions and other non-medicines costs associated with the severe asthma group.

There is a potential win-win for severe asthma if pharma develops medicines for severe cases; there is a market there and healthcare systems may have to pay for the treatment but they should save overall as a result of savings in other areas, such as hospital admissions.

All of the 12 or so companies that were involved had programmes looking at the severe group. But these fragmented efforts had not delivered successes or breakthroughs and so there was a need to try to understand more about the biological reasons why medicines were not working for the severe group – and to identify new targets.

The project sought to identify variation in asthma and whether it was possible to use biomarkers to identify different types of patients. The value of IMI involvement was that companies could work with academic groups to get access to wider patient populations and get samples from patients. There is particular value in getting unbiased analysis from biomedical samples from general patient populations (rather than those selected for trials). Before the project, there was a lack of big unbiased patient populations that were representative of the real world.

13.6. Project Achievements and Outputs

The IMI model of requiring everyone to work together on a single project was visionary and it turned out that there was value in sharing pre-competitive knowledge since there were common needs, for example, to identify the most relevant mechanism, find the best way to investigate tissue, develop the best mice model.

The most significant benefit was one that was not anticipated. 12 companies got together to share knowledge and discuss common problems – many of the leading scientists from companies that got together had never even met before.

The project found that asthma is a heterogeneous disease. The molecular mechanisms are very different and so require different approaches to treatment.

The project also lays the foundations for using “molecular fingerprints or handprints” as a starting point for new medicines. So the starting point would be the characterisation of patients up front – so that it is known at an early stage which patients are likely to do best.

Another development from U-BIOPRED is a method to characterise molecular fingerprints by the simple analysis of 10-15 molecules in the blood. An analytical test could be developed to take this further.

By the time the final project report was completed, there were 15 scientific publications with an average citation rate of 2.27 and 37.93% highly cited (in top 10% of papers for citations). Work is continuing on further papers including several covering the more significant new knowledge from the project.

The outputs from the project also included biological samples from a patient population that was representative of the general population. This was an important output because the project also found that the animals that had been used for research were not good enough and recommended using human tissue cell models.

The final report on U-BIOPRED also noted that many of the expected outputs had not yet been achieved at the formal close of the project. So achieving those outputs will depend on the project participants continuing to work on the project beyond the formal end date.

There also seemed to be a difference in views on the success of the project from academic and industry perspectives.

From an academic perspective the project has been successful in that it met its research objectives. It did what it set out to do: recruited patients, gathered samples, undertook analysis and found a number of pathways of interest for further research.

However, the project did not identify biomarkers or targets for medicines development. The companies recognise the scientific achievements of the project, and that there were useful outputs that could not have been achieved without the collaboration. But from their perspective there is a question of whether the outputs of commercial interest are sufficient to justify their level of investment.

13.7. Pathways to Socio-economic Impact

Improving the understanding and treatment of severe asthma has the potential to deliver significant socio-economic benefits. While the severe asthma group accounts for 3-8% of the total asthma population, it accounts for a large proportion of the healthcare costs.

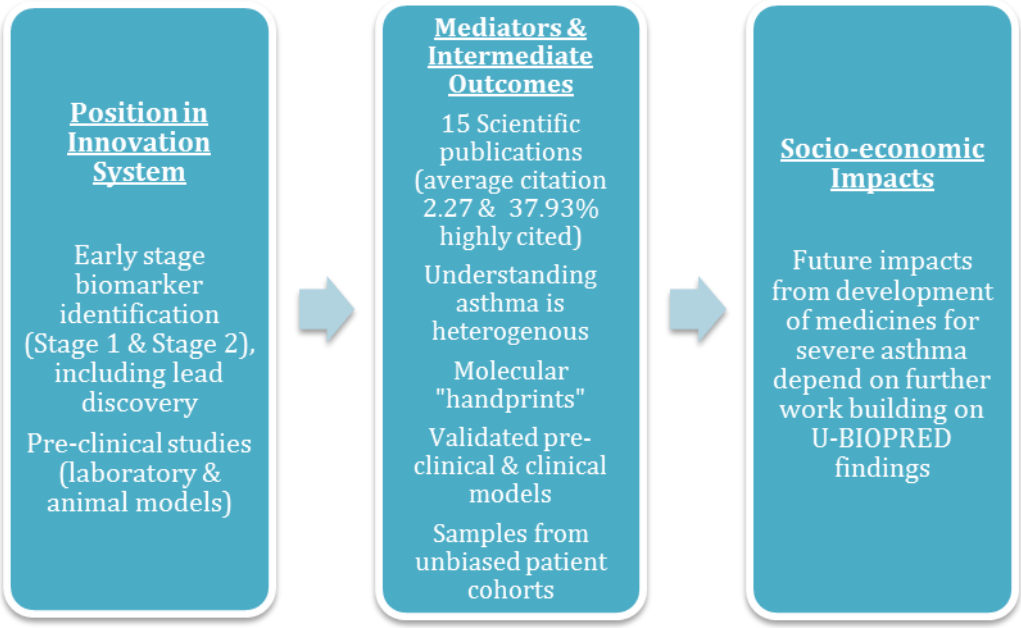
The rationale of the project was that better understanding of the mechanisms of disease and disease progression can improve the development of new medicines.

The greater understanding of asthma, including the new and separate categories identified provides an opportunity to develop more targeted medicines that are most effective for those patients with severe asthma.

At this stage work is still on-going on the final scientific outputs from the project and realising such impacts will require significantly more time and investment. The next steps will be to improve the understanding of the different mechanisms so that different treatments can be developed. Each company will need to decide how it takes forward this agenda.

However, companies are already using the preliminary U-BIOPRED fingerprints and handprints in new clinical trials and so it is likely that there will be commercial benefits from the U-BIOPRED findings.

13.8. Summary: U-BIOPRED



14. SUMMIT

The surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools (SUMMIT) project sought to identify markers for chronic diabetes complications.

There are an estimated 250 million people worldwide suffering from diabetes, and many of them develop devastating chronic complications including coronary heart disease, stroke and peripheral vascular disease, as well as microvascular disorders, leading to damage of kidneys and eyes. These complications impose an immense burden on the quality of life of the patients and account for more than ten percent of the health care costs in Europe.

However, not all patients are at equal risk for those vascular diabetic complications. In order to better predict, monitor and treat the patients at risk, the SUMMIT project sought to identify biomarkers that indicate in advance if a patient is likely to develop vascular complications.

The next step after identifying the predictive biomarkers is to demonstrate their usefulness in patient groups and do the necessary tests to make the markers acceptable by regulatory authorities such as the EMA and FDA.

Furthermore, the SUMMIT sought to identify genetic factors that make some patients more susceptible to vascular diabetic complications than others and develop novel computer simulations and models for laboratory test, in order to better predict the outcome and development of complications in human populations.

Biomarkers, models and clinical tests for the early prediction and detection of diabetic complications will be a valuable tool to speed up clinical trials with diabetic patients.

14.1. Position in Innovation System

The SUMMIT project encompassed both pre-clinical research and clinical research.

14.2. Project Co-ordinator and Managing Entity

Project Co-ordinator: Michael Mark, Boehringer Ingelheim, Biberach an der Riß, Germany

Managing Entity: Leif Groop, Lund University, Skåne University Hospital, Malmö, Sweden

14.3. Participants

EFPIA: Boehringer Ingelheim International GmbH, Ingelheim, Germany; Eli Lilly and Company Limited, Basingstoke, United Kingdom; AstraZeneca AB, Södertälje, Sweden; F. Hoffmann-La Roche AG, Basel, Switzerland; Sanofi-Aventis Deutschland GmbH, Germany; Pfizer Limited, United Kingdom

Universities, Research Organisations, Public Bodies & Non-profit: Lunds Universitet, Lund, Sweden; Karolinska Institutet, Stockholm, Sweden; Helmholtz Zentrum München Deutsches Forschungszentrum Für Gesundheit und Umwelt GmbH, München Neuherberg, Germany; Istituto Di Ricerche Farmacologiche Mario Negri, Milano, Italy; University of Cambridge, Cambridge, United Kingdom; University of Dundee, Dundee, United Kingdom; University of Exeter, Exeter, United Kingdom; Goeteborgs Universitet, Goeteborg, Sweden; Samfundet Folkhälsan I Svenska Finland RF, Helsingfors, Finland; Terveyden Ja Hyvinvoinnin Laitos - National Institute For Health And Welfare, Helsinki, Finland; Turun Yliopisto, Turku, Finland Itä-Suomen yliopisto, Kuopio, Finland; University of Oxford, Oxford, United Kingdom; Universita Degli Studi di Padova, Padova, Italy; Universita Degli Studi di Pavia, Pavia, Italy; Universita di Pisa, Pisa, Italy; Universita Cattolica del Sacro Cuore, Milano, Italy; Universita di Firenze, Italy; University of Edinburgh, Edinburgh, United Kingdom

SMEs: Biocomputing Platforms LTD OY, Espoo, Finland

14.4. Projects Inputs and Funding

The project received funding of €14.7 million from IMI, from a total project cost of €34.8 million and so the IMI contribution levered investment of an additional €1.37 for every €1 from IMI.

TYPE	Amount in €s	% total funding
IMI funding	€14,654,559	42%
EFPIA funding	€15,222,050	44%
Other Funding	€4,905,472	14%
Total	€34,782,081	

14.5. Project Rationale and Market Failure

While many companies and researchers are interested in diabetes, not surprising given the scale of the problem, generally people had been doing more of the same over time. There were things that had not been done or done only on a small scale. The IMI SUMMIT project provided an opportunity of stepping back and trying new things. This included genomics and the development of a good animal model.

Working with patients is also something that required collaboration. While pharma had the resources to invest in R&D, they did not have access to the patients.

From the perspective of pharma companies, clinical development in diabetic complications is lengthy, costly and risky process. A 10-year clinical development period is state of the art, and so it makes it a high risk area. And thousands of patients are needed for clinical trials (in order to get enough with complications). So, even a successful medicines development process will typically leave 5-7 years of a 20-year patent period, insufficient for an adequate financial return. There was a need for collaboration to see what could be done to address some of these conditions and so make development of medicines for diabetic complications commercially feasible.

In addition, the hurdles for approval have been rising in recent years – and so there was a need for new technologies to accelerate and focus the development process.

The theoretical arguments for allocating resources to this project within IMI are linked to the long-term consequences of type 2 diabetes in terms of different complications. It is not efficient to conduct clinical trials with real patient outcomes, since they would take too long and be extremely costly. The practicalities and ethical aspects of such trials also have to be considered, which adds to the argument for a surrogate endpoint in medicines development.

The case for the use of surrogate endpoints has been developed for cancer medicines in a paper by Eric Budish, Benjamin N. Roin, and Heidi Willia (AER, 2015)[10]. They investigate whether private research investments are distorted away from long-term projects. Their theoretical model highlights two potential sources of this distortion: short-termism and the fixed patent term. They analyse three potential policy responses: surrogate (non-mortality) clinical-trial endpoints, targeted R&D subsidies, and patent design. The result is a strong case for using surrogate endpoints, but with the important qualification that they correlate with real improvements in patient health.

14.6. Project Achievements and Outputs

SUMMIT developed innovative approaches to make clinical trial testing of novel medications in diabetic vascular complications faster and more efficient. The tools that were developed included imaging techniques, animal models and biomarkers.

[10] Eric Budish, Benjamin N. Roin, and Heidi Williams. Do Firms Underinvest in Long-Term Research? Evidence from Cancer Clinical Trials. American Economic Review 2015, 105(7): 2044–2085

The imaging area gave particularly important outputs because it allows for non-invasive clinical investigation and a calibration device was developed which means that imaging can now be done in a consistent way (removing inconsistencies that were due to different practices and methods). These novel imaging techniques have been patented and are being commercialised.

Progress was also made with the development of animal models. Standards were developed which meant that it was possible to compare models in a consistent way and so see which was best and so there are now better animal models than before.

There are also a number of biomarkers that are better than what was previously available to predict complications from diabetes. These have potential to be used to improve prediction of outcome, provide evidence of pathogenic pathways thus leading to potential novel medicines target identification and novel techniques and models for potential development of new medicines.

One of the areas of focus turned out not to be possible. Significant effort went into novel genetic markers that could be used to stratify patients but this failed and it was concluded that there are not genetic risk factors. This outcome will mean no further investment in this area.

By the time the final project report was completed, there were 98 scientific publications with an average citation rate of 1.78 and 18.75% highly cited (in top 10% of papers for citations).

SUMMIT research found that diabetes is more heterogeneous than the established type 1 and type 2 categorisation. Five distinct sub-groups were identified and this will have important implications because some of these are more open to complications than others.

There was a further learning process from SUMMIT – coming together to discuss problems and potential solutions was very beneficial. And this extended beyond the scope of activities covered by SUMMIT. Once these connections and relationships are developed they tend to endure.

There are continuing collaborations, both bilateral arrangements taking forward specific issues and a wider network that all participants will continue to use in future (and may come together again, in whole or part, in more formal collaborations). There is a follow-up project to SUMMIT, RHAPSODY which is more focused, on kidney disease complications from diabetes.

While the project final report has been completed, work is on-going and there will be more outputs over the next year or two, including more publications and dissemination.

A start-up company diaBRIDGE has been established in Lund, Sweden to bridge the translational gap in diabetes as a result of the output from the SUMMIT project. Other commercial developments include a mouse model developed by SUMMIT for diabetic CVD and nephropathy has been transferred to Taconic BioSciences for further exploitation, a licensing agreement for exploitation of a SUMMIT rat model is under negotiation with Janvier Labs and negotiations are on-going to further exploit the Ultrasound-based Plaque Structure Analyses (UPSA) technology developed.

14.7. Pathways to Socio-economic Impact

Diabetes is a huge healthcare issue and one that is projected to grow. The average cost of treatment for patients is €5,000 per year in terms of healthcare costs. Complications from diabetes impose an immense burden on the quality of life of the patients and account for more than 10% of health care costs in Europe.

So, if it is possible to identify those most susceptible to complications, then work on prevention, there is scope for huge healthcare savings. Better prediction in the clinic should mean better prevention.

This is a project aimed at developing surrogate endpoints for clinical trails in diabetes, that link to ultimate outcomes. However, there is no direct value in having new surrogate markers. The value comes from better treatment in clinical practice.

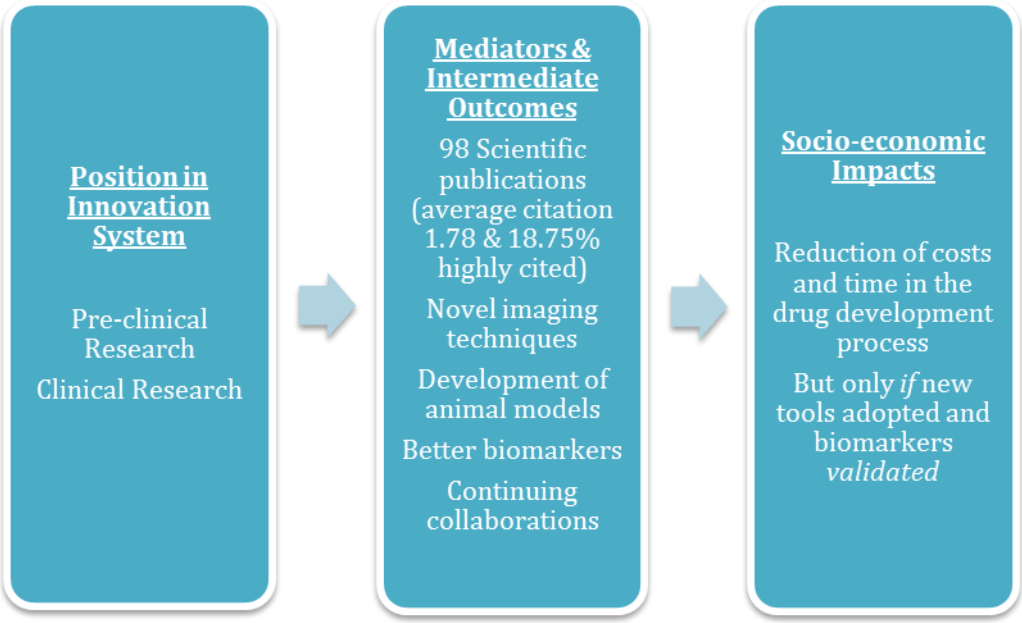
The SUMMIT project has potential for improving efficiency in the medicines development process and speed the time to market for valuable products. If it was possible to predict complications and stratify patients before trials, those trials could be much more focused. A 10% improvement in prediction would save €100m's.

However, the impact so far is difficult to assess since there is no impact on regulation reported, and the identified biomarkers are not yet validated. The process of validation is not outlined. It should be noted that there are considerable risks related to use of biomarkers and surrogate endpoints that are not validated. It is also important to notice that validation should not only be performed for assessment of efficacy in clinical trials. Payers are increasingly hesitant to accept surrogate markers as evidence of patient benefit.

For assessing the socio-economic impact of biomarkers it is important that they also are evaluated from a health economics perspective. It is understandable that this has not been included in the project, but it is of increasing importance for the future. For a review of the issues involved, see a recent paper by Oosterhoff et al (2016)[11].

There will also be an indirect benefit from the non-invasive imaging techniques. They will be less expensive, will make it easier to recruit patients and can be done in normal hospitals (rather than specialist imaging centres). So this will reduce costs in development and trials stages.

14.8. Summary: SUMMIT



[11] Marije Oosterhoff, Marloes E. van der Maas, and Lotte M. G. Steuten A Systematic Review of Health Economic Evaluations of Diagnostic Biomarkers. Appl Health Econ Health Policy (2016) 14:51–65

15. Conclusions

This chapter summarises the findings emerging from the review of nine IMI1 projects and contains the conclusions of the impact assessment.

The conclusions have been drawn based on the methodology discussed in chapter four of this report, in particular the Expert Group's model for:

- describing the position of projects in the medicine development innovation system; and
- identifying the potential pathways to impact (that is, how the project inputs and activities lead to outcomes and how such outcomes may result in socio-economic impacts, over time).

This section draws together the findings from the review of individual projects and discusses the issues that have emerged from the work programme which apply to the IMI programme more generally.

15.1. Participation

A large number of public and private sector organisations have been engaged in the collaborative IMI projects.

The education and training project reviewed involved 15 EFPIA members and 35 universities. The other eight projects reviewed involved between 5 and 14 EFPIA members, between 6 and 26 universities, research organisations, public bodies & non-profit and also had SME involvement. The projects had between 12 and 50 participants with the mean number being 27 and the median 21.

Table 15-1: Project Participant Numbers

	EFPIA	Universities etc.	SMEs (& Others)	Total
IMIDIA	8	12	1	21
MARCAR	5	6	1	12
NEWMEDS	9	7	3	19
PharmaTrain	15	35	0	50
PROTECT	14	19	2	35
SAFE-T	12	10	4	26
EUROPAIN	8	12	1	21
U-BIOPRED	11	26	4	41
SUMMIT	6	18	1	25

15.2. Investment and Leverage

The nine projects included in this initial review received funding of €82.3 million from IMI1. This levered a total investment of €104.8 million from EFPIA members and €30.5 million from other sources, giving a total investment of €217.6 million.

Table 15-2: Contributions to Projects

	IMI €	EFPIA €	Other €	Total €
IMIDIA	8,060,760	16,940,659	2,445,590	27,447,009
MARCAR	6,049,578	5,155,604	1,905,508	13,110,690
NEWMEDS	8,986,216	13,789,412	2,074,047	24,849,675
PharmaTrain	3,510,300	3,489,181	632,047	7,631,528
PROTECT	11,009,715	10,864,491	6,743,176	28,617,382
SAFE-T	13,901,971	13,575,483	4,198,802	31,575,483
EUROPAIN	6,229,343	11,165,740	5,155,000	22,550,083
U-BIOPRED	9,935,501	14,574,652	2,415,549	26,925,702
SUMMIT	14,654,559	15,222,050	4,905,472	34,782,081
Total	82,337,943	104,777,272	30,475,191	217,590,406
%	38%	48%	14%	

IMI1 covered the six year period from 2008 to 2013 and had a total budget of €2 billion, of which €1 billion came from the Health theme of the EU's Seventh Framework Programme for Research (FP7) and €1 billion came from in-kind contributions by EFPIA companies. So, the commitment from both public and private sectors to IMI was, on average €167 million per year, a combined total of €333 million per year.

The nine projects reviewed during this socio-economic impact assessment, with a total contribution from IMI of €82.3 million, therefore represent around 8% of the total for IMI1.

EFPIA members investment in R&D in Europe was €30.5 billion[12] in 2014. So the EFPIA contributions to all IMI projects was equivalent to around one third of one percent of the annual European pharma R&D investment.

It should be noted that IMI projects involve the public investment going to the universities and public bodies rather than the companies. The companies are co-investors rather than recipients of public money.

The leverage of private investment can itself to considered to be a socio-economic impact of sorts, since it indicates that the private sector saw some value in co-investing in the priorities supported by IMI1 (although there will also be an opportunity cost in that resources could have been used within the companies for other projects). The companies themselves made the decision that the potential benefits were higher spending the resources within the IMI framework rather on other activities within the innovation system.

15.3. Projects' Position in Innovation System

In order to understand how supported projects may deliver outcomes that lead to socio-economic impacts, it is first necessary to appreciate the position of the project in the innovation system.

Of the projects reviewed, one was focused on training (covering the whole medicines development process), two were focused on pre-clinical research, one on clinical research, four spanned pre-clinical and clinical research and one was focused on post-marketing (Table 15-3).

This profile is quite different from most publicly funded medical research initiatives where the focus is usually on fundamental and pre-clinical research. The IMI projects are generally closer to market, as might be expected given that they are collaborative projects involving the pharma sector.

[12] EFPIA (2015), The Pharmaceutical Industry in Figures, Key Data 2015

Table 15-3: Position in Innovation System of Reviewed Projects

	Position in Innovation System
IMIDIA	Pre-clinical Research - development of tools and biomarkers
MARCAR	Research on medicines safety, to develop new models & tools for use in clinical trials (animal testing stage)
NEWMEDS	Pre-clinical testing, Experimental Human Studies, Clinical Trials; New pre-clinical and clinical methods for medicines discovery
PharmaTrain	Training (covering all aspects of medicines development pathway)
PROTECT	Post-marketing surveillance
SAFE-T	All stages of medicines development from pre-clinical to clinical development, registration, and post marketing
EUROPAIN	Target identification, pre-clinical, translational medicine, clinical (early & late), patient indication definitions & stratification
U-BIOPRED	Early stage biomarker identification (Stage 1 & Stage 2), including lead discovery Pre-clinical studies (laboratory & animal models)
SUMMIT	Pre-clinical Research Clinical Research

15.4. Project Rationale: Market Failure and Additionality

Each project was designed to address a 'bottleneck' that had been identified. In most cases this implied some market failure. However, in future there may be merit in being more explicit about the underlying market failure and so how the project will address this and how a solution may in the longer run lead to socio-economic impact.

Rather than expressing the rationale for investment in terms of bottlenecks (which implies a linear production approach), there is merit in giving consideration to the innovation system (see Figure 5-1 in section 4) and how the proposed project may lead to socio-economic impacts (see Figure 4.3) at the project conception stage. Considering the outcomes and potential socio-economic impacts at this stage may influence the direction of the project and / or the design of the consortium.

The additionality of IMI's intervention is important; the projects should be aiming to deliver impacts that would not be possible without intervention, or not on the same scale, timescale or quality. Intervention should take place only where a problem exists in the innovation system that private actors cannot address but where public actors have the ability to solve or mitigate the problem.

Innovation policy interventions are sometimes required, but must not replace, duplicate, or crowd out what private actors can do. They should supplement private action and contribute to solving problems that the private actors cannot handle.

In most cases, the rationale for the project was that there was an area where both public and private sectors were under-investing, but where a problem could be tackled by acting in concert. The projects were envisaged as a range of activities that would improve the conditions for medicines development in Europe and remove barriers to the development of medicines and the growth of the medicines sector. However, they did not explicitly set out the additionality that would be delivered by IMI's intervention.

The projects reviewed for this impact assessment provide a number of examples of additionality and added value.

These included addressing organisational coordination problems where several organisations were working in the same area but using different methods and standards. The IMI model has enabled collaboration to establish and use the most effective methods and establish standards.

Where there have been coordination problems, there are also opportunities to remove duplication of effort, improve effectiveness and deliver economies of scale by pooling resources and expertise.

There were also examples of where the IMI model had facilitated new approaches in some disease areas where previous practices had not been delivering new medicines or where there seemed to be diminishing returns. The IMI model facilitated the collaboration that gave academic and industrial researchers the confidence to challenge previous assumptions, based on sharing experience of successful and unsuccessful research strategies and practices.

While the IMI1 calls were largely based on topics identified by EFPIA members, there were examples of projects addressing issues where there may have been market failures related to externalities, that is, where there may have been limited commercial incentives for investment since many of the potential benefits would not be captured by the private investor in terms of commercial returns. These potential positive externalities included improvements in the safety of medicines, ethical concerns (such as reducing the need for animal studies) and savings to healthcare systems (for example, where new medicines would deliver savings by reducing the need for acute healthcare).

There were also examples of investments (for example, in areas such as pain and treatments for minority patient groups), that may not have been priorities for companies but that patients and / or healthcare systems consider to be important.

15.5. Mediators & Intermediate Outcomes

Figure 5-1 in section 4 set out ten activities that are the main determinants of innovation processes, taking a systems of innovation approach. These are also intermediate outcomes in innovation processes since they are steps in the process of getting final product and process innovations materialised.

The IMI projects have delivered outcomes that are relevant to five of these ten activities. In particular the projects have facilitated *networking through markets and other mechanisms*, promoting interactive learning and the sharing of knowledge. The scientific outputs (scientific publications and new models, tools, methods, biobanks and databases) also provide evidence of the *provision of R&D* by the projects.

There are also examples of *competence building* (through both training and spreading best practice in approaches to research), *articulation of quality requirements* (in particular safety) and *creating and changing institutions* (including the provision of evidence required by regulators).

However, the scope of the IMI1 projects reviewed did not intend to deliver outcomes related to the other five determinants of innovation processes identified in Figure 5-1 in section 4, *formation of new product markets*, *creating and changing organisations*, *incubation activities*, *financing of innovation processes* and *provision of consultancy services*.

The projects reviewed had delivered a wide range of mediators and intermediate outcomes that provide a basis for future socio-economic impacts.

One of the projects (PharmaTrain) was a training project and so the intermediate outcomes were training programmes developed and individuals trained.

The other eight IMI1 projects that were reviewed all included significant research components and delivered new knowledge. One of the measures of that new knowledge was scientific publications. There were a total of 546 scientific publications across the eight projects (by the time the final project reports were completed) and these had average citation rate of between 1.36 and 2.83 and a highly cited rate (in top 10% of papers for citations) of between 18.9% and 37.9% (Table 15-4). The overall average citation rate across the eight projects was 2.01 and the overall average highly cited rate was 23.1%.

However, in many cases, the Managing Entity contacts interviewed during the impact assessment expected additional scientific publications in the year or two following the formal end date of the project. In addition, some noted that there will also be future publications which are partially based on work undertaken during the project (and partially based on follow-on research). The citation rates may also increase over time, given that many of the publications will be recently published.

Scientific publications are a common proxy measure of scientific impact in academic projects and so are a legitimate measure for the IMI projects, given the academic research input to the collaborative projects.

However, from the perspective of the industry partners, there are other, more important mediators and intermediate outcomes, those that indicate that the projects will improve the medicines development process in Europe.

Examples of the types of mediators and intermediate outcomes identified include (see Table 15-4):

- New human cell lines;
- New tools that can be used to better understand diseases and identify targets for new medicines;
- Biobanks of human tissue samples;
- Validated or potential biomarkers of diseases;
- Methods for predicting the toxicology of potential treatments;
- New animal models and humanised models;
- New approaches to identifying non-genotoxic carcinogens, which could reduce the need for animal trials in some circumstances;
- New knowledge from which new potential targets for medicines development could be identified;
- Databases of findings and of data collected but not yet fully analysed;
- Novel imaging techniques and tools;
- New guidance and best practice recommendations;
- New collaborations (this is discussed further below).

Several of the projects reported that there was on-going work beyond the project final report stage, including further analysis and the preparation of publications.

It is not clear whether this has been the result of projects failing to meet their reporting targets or whether this is additional work to that intended.

Table 15-4: Project Mediators & Intermediate Outcomes

	Mediators & Intermediate Outcomes
IMIDIA	60 Scientific publications (citation rate 1.47 & 18.9% highly cited) New human cell line, validated Biobank of human beta-cells Database New animal models New biomarkers Novel imaging techniques New collaborations
MARCAR	35 Scientific publications (average citation 2.07-2.7 & 28.9% highly cited) Tool for measuring new biomarkers Systems to speed up search for & validation of biomarkers Tool for scanning candidate medicines
NEWMEDS	95 Scientific publications (average citation 2.83 & 28.9% highly cited) New animal models Potential biomarkers Tools to test biomarkers Imaging tools New web-based tools New patient level database

PharmaTrain	Range of training programmes and standards developed including 9 Masters programmes & 156 single module courses Training delivered including 497 students graduating & 715 CPD trainees
PROTECT	61 Scientific publications (average citation 1.36 & 16.4% highly cited) Series of guidance & recommendations, providing the basis for changes in regulations & in practice Increased collaboration
SAFE-T	22 Scientific publications (average citation 2.12 & 28.6% highly cited) 20 promising biomarker candidates Biobank New methods for clinical biomarker qualification Database
EUROPAIN	160 Scientific publications (average citation 1.98 & 23.1% highly cited) Three validated animal models Cohort database Biobank New collaborations Targets for medicines development
U-BIOPRED	15 Scientific publications (average citation 2.27 & 37.9% highly cited) Understanding asthma is heterogeneous Molecular "handprints" Validated pre-clinical & clinical models Samples from unbiased patient cohorts
SUMMIT	98 Scientific publications (average citation 1.78 & 18.8% highly cited) Novel imaging techniques Development of animal models Better biomarkers Continuing collaborations

Of the measures of Mediators and Intermediate outcomes identified in section 5.4.5 almost all of the projects delivered scientific research publications, impact from scientific publications (citations) and R&D collaborations.

There were also many examples of databases of research findings, technical standards, tools for clinical research, animal models, human tissue or cell based models, imaging techniques, biobanks, patient cohort databases, biomarkers and new processes.

There were some examples in some projects of patents, new product development, targets for medicines development, methods for identifying and screening targets, training programmes developed, people trained and guidance and recommended best practices.

The above summary of mediators and intermediate outcomes associated with the projects is based on the Expert Group's review of the projects, using the information summarised in the project proforma (Appendix B) and the feedback from the interviews with Project Coordinators and Managing Entities.

Some of the mediators and intermediate outcomes have been captured by the monitoring of projects, including by the key performance indicators. However, there may have been other mediators and intermediate outcomes that have not been captured in the monitoring of projects and so may have been missed in this socio-economic impact assessment. The Expert Group's views on how IMI could revise the key performance indicators used are provided in the next chapter, Recommendations.

15.6. Socio-economic Impacts and the Medicines Development Process

Europe's innovation system, and the medicines sectoral system of innovation more specifically, are both complex knowledge utilisation systems, which involve a very large number of actors - including universities and research organisations, pharma companies, suppliers to pharma companies and clinicians.

The medicines development process can take 12 or more years from target identification to market (and use in healthcare), requiring an estimated average investment of more than €1 billion, and 5,000-10,000 candidates to be considered at the medicines discovery stage for every one that makes it to market.

Given that the average project size of the IMI1 projects reviewed was less than €25 million, it would not have been reasonable to expect the impacts to include new medicines available on the market, even if the projects had been focused on developing new products. As discussed elsewhere in this report, the focus on the projects was instead on improving the medicines development process itself.

Even a marginal improvement to the medicines development process, whether it was related to cost, time or attrition rates could be very valuable, since it would improve the efficiency and productivity of the process (that is a reduction in the total value of the inputs required to generate a unit of output). This would have a direct consequence for economic performance as much economic growth in advanced economies is associated with productivity gain. It would also be associated with health and health system benefits, since a reduction in cost would change the cost-benefit assessment of the value of medicines.

The socio-economic impacts of public sector intervention in the medicines and pharma sector and often measured in terms of long-term effects like business and associated employment benefits from new products or from improvements to the product development process and health benefits from new treatments or better healthcare.

The socio-economic impacts will mostly occur when companies then use the improved system using new approaches to identifying medicines or as a result of a less expensive, quicker or more efficient system of developing new medicines.

While IMI has existed now for 7 years, the first projects have completed within the last year or so. These projects are, by definition, pre-competitive and so one would not expect competitive activities and near-market innovations to follow soon.

Project Co-ordinators and Managing Entities were mostly confident that socio-economic benefits will occur as a result of the projects supported and that these impacts could be significant in some cases.

15.7. Socio-economic Impacts of Projects Reviewed

The socio-economic impacts associated with most of the projects reviewed were mostly related to improvements to the medicines development process rather than to the identification and development of potential new medicines.

Some socio-economic impacts had already been delivered. These tended to be where a new tool or process had been commercialised through the setting up of a new company.

Most of the socio-economic impacts will be in the future, as a result of improvements to the medicines development process for the disease area on which the project focused (Table 15-5).

The future impacts may occur as a result of some or all of the following effects on the medicines development process:

- New approach to identifying targets meaning that medicines that would not otherwise have been identified may be developed;
- Cost savings by direct improvements to the medicine development process, for example, by using a new tool that is less expensive than the previous approach;

- Time savings by direct improvements to the medicine development process, for example, by using a new tool that takes less elapsed time than the previous approach;
- Reduced need for animal testing;
- Changes to the clinical trials process that means they can be undertaken at lower cost and / or in less time;
- Providing the evidence for changes in regulations that, in turn, lead to cost and / or time savings;
- Lower risk or failure by better prediction of efficacy, safety and effectiveness.

Table 15-5: Socio-economic Impacts of Projects Reviewed

	Disease Area	Socio-economic Impacts
IMIDIA	Metabolic	Platform for development of new medicines - new tools & techniques which will allow novel treatments to develop New human cell line commercialised by SME
MARCAR	Biomarkers / Cancer/ Medicines safety	Potential for cost savings, reduced animal testing & time savings in medicines development. If, regulators change carcinogenicity study requirements. Potential for reduced medicines-induced side effects & associated healthcare costs.
NEWMEDS	Brain	Range of new methods & tools that will aid future medicines development for central nervous systems development
PharmaTrain	Education & training	Productivity of medicines development process Depends on implementation of competencies-based approach to employment & progression
PROTECT	Medicines safety	One SME set-up Potential impacts if recommendations implemented and if regulators speed up approval decision making - so new medicines to market sooner (& so available to patients sooner)
SAFE-T	Medicines safety	Spin-off company to be set-up in 2016 Future impacts depend on validation and use of biomarkers If this happens, would impact on medicines development process safety, time & cost Earlier identification of safety problems expected to reduce costs & risk in medicines development process May also be direct clinical applications
EUROPAIN	Brain	New assay products One spin-out & SME growth Significantly future medicines development & socio-economic benefits possible from better treatment of chronic pain Improvement to medicines development process acting on speed, costs & attrition rate for chronic pain treatments Patient care benefits from better understanding of existing medicines
U-BIOPRED	Lung	Future impacts from development of medicines for severe asthma depend on further work building on U-BIOPRED findings
SUMMIT	Metabolic	New product commercialised New start-up Reduction of costs and time in the medicines development process, new tools adopted and biomarkers validated

There was no evidence yet of noticeable socio-economic impacts on the health system (such as improved access to new treatments, improved work productivity or more effective use of healthcare budgets or reduced costs) or health benefits for patients. Such socio-economic impacts are possible in future, if the improvements to the medicines development process mean that new medicines come forward for approval and are accepted by health systems (the payers).

15.8. Delivering Future Socio-economic Impacts

The IMI projects may be necessary to deliver the socio-economic impacts described above but in most cases, they are not sufficient to generate impacts. In most cases, something else will need to happen, including some of the following:

- further research, building on the findings from the IMI project;
- use of tools and methods by pharma;
- following of guidance and recommendations by pharma;
- approval of regulators;
- approval of healthcare systems; and
- further investment in product development.

In some cases the actions that are necessary to build on the IMI projects to deliver socio-economic impacts will be strategies, investments and actions by companies.

In other cases, there will be a need for action from actors such as regulators, the healthcare system and policy makers. It is therefore important for the potential socio-economic impacts and the necessary follow-up actions to be identified and for this to be included within dissemination plans.

15.9. Quantifying Outcomes and Impacts

The project reports, including the final reports, were completed using an agreed template. The projects mostly reported what they had done against objectives and the extent to which they had achieved agreed project deliverables.

There was little analysis of how the project deliverables and outputs would generate benefits, either for the companies involved or for the wider public interest. Where reports did include discussion of socio-economic impacts, it tended to be quantifying the scale of the problem (e.g. the healthcare costs of the disease) rather than how the project and its outputs would address the problem.

This is not surprising since the focus of the IMI1 projects, particularly the first few that were considered in this review, tended to be on research outcomes rather than socio-economic impacts. The reports were often compiled by experience academic researchers, used to measuring end points in scientific output terms, for example, scientific papers published. Given that there was no systematic approach to gathering potential socio-economic impacts, it is possible that there are additional impacts that have not been captured in the IMI monitoring reporting system or in this socio-economic impact assessment.

15.10. Collaboration Benefits

The organisational model adopted by the IMI programme has been a collaborative model with each project involving multiple universities and research organisations working with multiple companies (EFPIA member companies and also SMEs). These collaborations and supporting facilities are unlikely to have happened without IMI-generated initiatives and investments, certainly not on the scale and scope that they did.

The IMI model has provided a platform for effective collaboration (industry-academia, industry-industry, academia-academia and in some cases extending to healthcare systems/payers, patient groups and

regulators) and in many cases it had led to the 'best of the best' in their fields being brought together to address a particular problem for the first time.

There have been many previous EU programmes that have brought academic researchers together and promoted collaboration between academic researchers and smaller companies. However, several of those interviewed during the impact assessment commented that the IMI model is the first to bring large numbers of pharma companies together, to work in collaborations with each other and with academic researchers.

The collaborations had been of a scale and on a timeframe that had encouraged long-term thinking and had been sufficient to allow significant progress to be made. Several of those interviewed during the impact assessment expressed the view that this would be possible only in Europe, with no other part of the world having the organisations required to deliver such effective collaboration.

In the projects that were reviewed, the benefits of collaboration had been demonstrated to those that participated. As a result there were many examples of continued collaboration, both formally and informally, building on the networks that had been created.

The project delivered additionality by providing a model for effective collaboration. As well as the direct outputs from the project, this also facilitated greater understanding of academic research by industry and vice versa. There was also knowledge transfer, for example, academic researchers learned about industry standards for record keeping.

The impression of the Expert Group, based on the evidence gathered, is that some of the collaborations have been more effective than others and all of those interviewed acknowledged that it took time to establish effective working relationships.

The central lesson that those interviewed offered for future is that it is important to understand that the goals and interests of each partner will be different. So, there is a need to spend time at the start of the project to understand each other and to harmonise goals.

The motivations for pharma can be described as "for profit" while the motivations for academic researchers can be described as "for knowledge". These are different motivations and so each have tended to keep the other at arms-length, preventing effective interaction. If the focus is less on conflicts of interest and more on common interest, then can find a way to effectively collaborate. Where the project leaders believed that effective collaboration had taken place, the suggestion was that the best way to identify the common interest was to consider the patient perspective.

During the course of several of the projects, there were changes in some of the companies involved, as a result of changed in research strategies. This experience does highlight the challenges that can be associated with collaboration between academic researchers, who often have long time horizons and less frequent changes in responsibilities, and industry researchers, where research strategies and individuals with responsibilities for projects can change more regularly.

However, despite such management challenges, there is no doubt that the sectors can learn from each other. For example, for many of the academics involved it was their first exposure to the commercial medicines development process. The greater understanding that has been gained about the complexities of the process will influence how academics think about problems and so will influence the future direction of research.

The IMI model has also allowed for other types of collaboration. These included a transparent model that allowed industry and regulators to work together. Such a model is necessary to make sure that there were no perceived conflicts of interest, of public interest where regulators and industry are working together.

The scale and timescale of the project may also have been important. IMI provided a framework that meant there was a stable funding environment over a period of five years, within which academia and industry could work together on a bigger challenge than can usually be taken on by either academic research funders or industry.

15.11. Wider Collaboration and Interaction with Stakeholders

Several of the projects also highlighted the importance of collaboration and interaction with a wider group of stakeholders, including healthcare systems (the payers for most medicines), patient representatives and regulators.

Several project leaders highlighted the importance of dissemination activities and recommended that future projects should invest more in this element of the project.

The involvement of a wider group of stakeholders, including the payers, must also be a consideration at the scoping stage of the project. If this is not considered, the danger is that work will be done on the development of medicines that no one is prepared to pay for.

The nature of many of the IMI consortia also provides opportunities to engage with policy making since they often involve a large number of specialists coming together and discussing the issues in consensus meetings. The output from this could provide useful insights for policy makers.

15.12. Standards and Common Protocols

One of the benefits of the collaborative model was that it allowed for standards and common protocols to be developed. There were a range of examples including research protocols, education and training standards, clinical trial standards and the validation of models using the same protocols by multiple companies.

Where companies and academic researchers (and in some cases, regulators) have collaborated in the development of standards and common protocols it is more likely that these will be subsequently adopted and that they will be adopted quickly.

15.13. Setting the R&D Agenda

While the IMI1 projects that were reviewed had been completed, there were many examples of follow-on projects. These included some IMI2 projects in which either the same collaborating participants or subsets of these had continued to work together. Given that EFPIA members have been influential in specifying the calls for proposals, this is an indicator that the IMI1 projects have had some influence on the R&D agenda in the European pharma sector.

15.14. The Profile of Europe as a Pharma Location

IMI has also delivered some structural benefits that could be important. These include raising the profile and reputation of the European medical research academic base and the pharma sector.

These benefits have occurred both directly (as a result of the outputs from the projects) and indirectly (by raising the international profile of some of the participants).

While difficult to make direct links between such profile raising and investment decisions, it seems reasonable to suppose that there will have been some contribution to retaining and attracting pharma investment and economic activity in Europe.

IMI projects have helped to demonstrate that there is a strong research base in Europe that they can work with and from which they can get value. While this will not always be enough to retain pharma activity in Europe, it is likely that it will mean there is more than there would have been if there had been no IMI.

16. Recommendations

This section sets out the recommendations of the Expert Group, based on the findings of the socio-economic impact assessment. It is recognised that the projects reviewed were amongst the first projects supported by IMI and it is understood that there have been developments in how their (potential) impacts have been considered in IMI follow-on projects. These recommendations are offered as lessons for future IMI projects.

16.1. Scope of IMI and Systems of Innovation

The focus of IMI is on the development of high value new medicines and so the potential socio-economic impacts are significant.

In order to identify and deliver such potential impacts, it is necessary to understand the innovation system as a whole and how improvements to the system might deliver socio-economic impacts.

The emphasis of the IMI1 projects reviewed tended to be on the R&D element of the medicines innovation system. The design of the projects was based largely on addressing bottlenecks identified in the medicines development process and the reporting of outcomes focused on measures of knowledge outputs such as scientific publications and new tools and methods for medicines R&D.

Rather than the linear view based on addressing bottlenecks, it is recommended that IMI should take a systems of innovation approach, considering a wider range of the determinants of innovation. This socio-economic impact assessment has proposed a model for understanding the medicines innovation system (set out in section 4). It is recommended that IMI use this model to monitor and evaluate existing projects and to inform decisions on future priorities and investments.

16.2. Project Topic Development

During this impact assessment it became apparent that potential or actual socio-economic impacts of projects had rarely been at the forefront of the minds of those involved in the projects. At the stage where the projects were being scoped out, this was done primarily on the basis of knowledge bottlenecks that had been identified. Projects addressing such bottlenecks may well deliver identifiable short-term or longer-term, but there is no guarantee that they will.

There would be considerable merit in considering potential socio-economic impacts at the project scoping stage, before IMI decisions are made on the allocation of resources.

This is not to argue that it would be possible to predict and quantify socio-economic impacts at an early stage. However, it should be possible to develop impact pathways, to identify the types of socio-economic impacts that could be delivered. Consideration of this may influence the design of projects and monitoring their progress.

The questions that should be asked at this stage would include:

- What socio-economic impacts are possible in the short-term and / or in the longer-run?
- How does that affect the project's scope and objectives?
- Which partners need to be involved?
- Where in the innovation system will the project impact?
- What output and outcome measures, and associated monitoring system, would be appropriate to identify whether progress has been made towards delivering such (anticipated) impacts?

Considering such questions at the project design should guide both the formation of consortia, and how the projects are managed to optimally achieve the objective; i.e. doing not only the right thing, but also doing things right.

That would also facilitate an ex post assessment of socio-economic impact. It is our understanding that IMI has, over time, moved in this direction.

16.3. Additionality

At the project design stage consideration should also be given to the justification for investments (both financial and in-kind). While it is recognised that IMI is a co-investment model rather than a mechanism for supporting business R&D investment, in order to prioritise the public investment it is necessary to consider why there is a need for public intervention, including questions such as:

- What is the current or anticipated market failure that is being addressed?
- How will the project's organisational model, activities, outputs or impacts address that market failure?

At the project design stage, the market failure addressed and the additionality of IMI support should be fully considered. The starting point for considering additionality is to consider what might happen in the absence of an intervention.

Consideration should be given to the additionality of each project support. Projects should be supported only when it can be shown that a problem exists in the innovation system that will not be addressed by private actors and where public actors have the *ability* to solve or mitigate the problem. So the public intervention should supplement rather than replace or duplicate private action.

16.4. Collaboration and Involving Necessary Stakeholders

The IMI model has provided a platform for effective collaboration with a number of companies and academic research teams coming together in consortia in all of the projects reviewed for this impact assessment. There were also some examples of other types of organisations being engaged including healthcare systems (the payers for most medicines), patient representatives and regulators, although these were less common.

The recommended system of innovation view and the explicit consideration of potential socio-economic impacts at the project design stage should assist in identifying the stakeholders that need to be involved and engaged. This is likely to stimulate greater involvement by other stakeholders.

Such involvement will be important in generating socio-economic impacts since business related impacts associated with the pharma sector and health benefits are not delivered as a result of the development of new medicines per se. Rather they are delivered by the availability of medicines in the healthcare system and for that it is necessary to secure approval from regulators and for the healthcare system payers to agree that the medicine should be made available.

The involvement of such stakeholders must be active rather than passive. IMI projects are not and should not become fora for discussions. The expectation would be that all stakeholders engaged in the projects should be contributing to meeting the project objectives and this will usually require contributions, either financial or in-kind.

There is also a role for a wider range of stakeholders to be engaged at the stage where IMI is making decisions on calls for new projects since healthcare systems (payers) and patient representatives may identify areas that they consider to be important, where there is market failure that needs to be addressed and the potential for significant socio-economic impacts.

16.5. Monitoring and Final Reports

Each of the projects is required to complete a final report that sets out what the project has done and achieved in some detail.

There may be merit in revising how the IMI Programme Office asks project managers to demonstrate and describe impacts (or possible impact pathways), perhaps using something like the UK's Research Excellence Framework (REF) case study model.

An IMI impact monitoring system could be partially incorporated into the mid-term of annual progress reporting, where the creation or improvement of impact pathways (designed to support or enhance longer-term impacts), is introduced as an additional key performance indicator.

16.6. Project Completion and Follow-on

The socio-economic impacts that will be achieved in future will generally require follow-on activity, on the part of project participants and / or other stakeholders.

To increase the chances that such follow-on action will be taken, part of the project completion process should be a review of the actual and potential socio-economic impacts and what needs to happen next to enhance or speed up those impacts. This should involve all of the main partners in the collaboration.

The outputs from this process should be a self assessment of the potential socio-economic impacts and an action plan, as part of a wider sustainability plan, setting out what should happen next in order to maximise the chances that such impacts will be realised in the foreseeable future.

16.7. Monitoring Progress

All IMI1 projects were monitored in terms of financial monitoring, output achievements and other performance indicators. The project management have also been asked to identify potential impacts in their reporting. However, these tended to be general descriptions and discussions that did not clarify and explain how outputs might feed through to project outcomes and later-stage impacts.

The model that has been adopted for this impact assessment could provide a conceptual and methodological basis for the future monitoring of progress in delivering socio-economic impacts. The following table sets out indicators that could be used in the IMI's monitoring and evaluation system.

Table 16-1: Project Outcomes & Outputs

Position in Innovation System	Mediators & Intermediate Outcomes	Socio-economic Impacts
▪ Pre-clinical research; ▪ Training; ▪ Clinical research; ▪ Regulation and approval process; ▪ Post-marketing.	▪ Scientific publications; ▪ Impact from scientific publications (citations); ▪ Databases of research findings; ▪ Technical standards; ▪ Tools for clinical research; ▪ Animal models; ▪ Human tissue or cell based models; ▪ Imaging techniques; ▪ Biobanks; ▪ Patient cohort databases; ▪ Biomarkers – identified and validated; ▪ Patents; ▪ New product development; ▪ New processes; ▪ R&D collaborations; ▪ Targets for medicines development; ▪ Methods for identifying and screening targets; ▪ Training programmes developed; ▪ People trained; ▪ Guidance and recommended best practices.	▪ Medicines Development Process impacts, including: ▪ Cost savings; ▪ Time savings; ▪ Reductions in risk; ▪ Reductions in attrition rate; ▪ Reduced need for animal testing; ▪ New Product Development, including: ▪ New medicine to market; ▪ Other product to market (for example, new tool); ▪ Industry impacts: ▪ New businesses; ▪ Growth of existing businesses; ▪ Health system benefits: ▪ Improved access to new treatments; ▪ Improved work productivity; ▪ More effective use of healthcare budgets or reduced costs; ▪ Health benefits: ▪ Benefits for patients; ▪ Policy: ▪ New policies implemented; ▪ Regulations changed: Effect of change.

16.8. Future Impact Assessments

The process that has been used for this impact assessment could be adopted for future assessments of IMI projects.

Expert Panel members for future impact assessments should have sufficient knowledge of medicines development to appreciate what the projects are seeking to achieve. However, to avoid conflicts of interest,

panel members should be independent experts on innovation monitoring and assessment rather than subject experts in the IMI-specific areas of science and innovation.

The project proforma and interview topic guide could be used again. However, the project proformas should take account of the proposed changes to the performance indicators, as set out above. This will make it easier for future evaluators to assess IMI's wide range of outputs and (expected) socio-economic impacts.

17. Appendix A: Project output tables

The process used during the socio-economic assessment included an initial assessment of potential impacts associated with each of the project, based on the initial review of information. The Expert Group members reviewing the projects recorded their initial views using a simple table format.

It was recognised that these were based on first impressions and in several cases it became apparent on further review and based on discussion with Project Coordinators and Managing Agents that there were often additional outcomes and impacts. The tables that were completed for each of the projects are provided below. These are intended as a record of the socio-economic assessment process and are not intended to be a final assessment of the impacts of the IMI1 projects reviewed.

17.1. IMIDIA

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☒	☐	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☒	☐	☐
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☐	☐	☒
Licenses to existing business	☒	☐	☐
New product to market	☒	☐	☐
Process of productivity gain	☐	☒	☐
Impact on product development process	☒	☐	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Follow-on Research & Consortia Established - Follow-on project INNODIA in IMI 2

New product to market - Beta-cell lines commercialised

17.2. MARCAR

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☒	☐	☐
Research Staff Trained	☐	☒	☐
Consortia Established	☒	☐	☐
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☐	☒	☐
Licenses to existing business	☐	☒	☐
New product to market	☐	☒	☐
Process of productivity gain	☐	☒	☐
Impact on product development process	☒	☐	☐

Health System Benefits	Yes	No	Maybe
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Follow-on Research & Consortia Established - Based on preliminary results developed through the MARCAR project, The University of Edinburgh were awarded a CEfic LRi grant to generate a comprehensive Epigenomic profile of liver tissue from Rat and Mouse.

Process of productivity gain - Not yet but data management systems were developed to speed up data interpretation in the search and validation of biomarkers. Furthermore, a tool was also developed to support the scanning of candidate medicines that will improve the medicines development process. Biomarkers that help to predict tumour growth more accurately at a very early stage of development will reduce the need for animal testing and speed up medicines development , both of which will lead to shorter and cheaper medicines development.

Improved Health - Not yet but significant health benefits in the near future given the increase in medicines safety for patients

Healthcare Costs - Not yet but significant cost savings in the near future given the reduction in treatment/hospitalisations for medicines-induced side effects as well as potentially cheaper medicines (due to the reduced need for animal testing and shorter and cheaper medicines development)

Workforce Health - See "Improved Health" comment above. Not yet but less side effects from medicines will mean a substantial reduction in the number of working days lost and a healthier workforce

Regulations changed - No yet but within 5 years the regulators may take on board the evidence produced from MARCAR and make changes to the regulations on carcinogenicity studies. There was an important development during the project that could be significant. In 2013, the EMA and FDA started a process of reviewing ICH S1 guidelines (those that are about carcinogenicity studies, applying to small molecule medicines that would be going into patients for 6 months or more), a process that is likely to be on-going, perhaps till 2019.

17.3. NEWMEDS

Research Impacts	Yes	No	Maybe
Follow-on Research	☒	☐	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☐	☐	☒
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☐	☒	☐
Licenses to existing business	☒	☐	☐
New product to market	☒	☐	☐
Process of productivity gain	☐	☐	☒
Impact on product development process	☒	☐	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Licenses to existing business - The mouse lines are being out licenced to Tachonic for public availability

New product to market - The touch screen technology developed and validated by partners in the NEWMEDS project is now commercially available. Furthermore, the CNV mice and the MAM-E17 mice developed by partners in the NEWMEDS project have been commercialised and made available to the wider research community through vendors.

Process of productivity gain - The project proposed an adjustment to the patient recruitment strategy in schizophrenia trials to be able to reduce the number of patients and length of the study, thereby significantly saving cost.

17.4. PharmaTrain

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☐	☒	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☐	☐	☒
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☐	☒	☐
Licenses to existing business	☐	☒	☐
New product to market	☐	☒	☐
Process of productivity gain	☐	☒	☐
Impact on product development process	☐	☒	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Follow-on Research - Follow-on project IMI-TRAIN. However, training, not research.

Consortia Established - Education and training project PharmaTrain has created the PharmaTrain Federation, which succeeds the IMI project and which is managing and continuing to develop the project 'assets' created during the IMI-funding phase

Impact on product development process - Not yet but may be the case in the future. It's certainly the long-term goal of the project.

17.5. PROTECT

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☐	☒	☐
Research Staff Trained	☐	☒	☐
Consortia Established	☐	☒	☐
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☒	☐	☐
Licenses to existing business	☐	☒	☐
New product to market	☐	☒	☐
Process of productivity gain	☐	☒	☐

Impact on product development process	☐	☒	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

New business established - Outcome Sciences, which was subsequently purchased by a larger company

17.6. SAFE-T

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☐	☐	☒
Research Staff Trained	☐	☒	☐
Consortia Established	☐	☐	☒
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☒	☐	☐
Licenses to existing business	☐	☒	☐
New product to market	☐	☐	☒
Process of productivity gain	☐	☐	☒
Impact on product development process	☐	☐	☒
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Follow-on Research - Project participants indicated interest to continue working together following the completion of SAFE-T

Research Staff Trained - No education and training programme outputs

Consortia Established - Follow-on topics already launched in Calls 7 and 9 which are likely to lead to follow-on projects

New business established - Spin-off service biotech company Signatope GmbH planned for 2016

Impact on product development process - The validation of safety biomarkers will significantly improve the monitoring of medicines induced injuries of the kidney, liver and vascular system and speed up medicines development.

17.7. EUROPAIN

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☒	☐	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☒	☐	☐

Product & Business Development	Yes	No	Maybe
New business established	☒	☐	☐
Licenses to existing business	☐	☒	☐
New product to market	☒	☐	☐
Process of productivity gain	☐	☒	☐
Impact on product development process	☒	☐	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☒
Regulations changed	☐	☒	☐

Notes:

Follow-on Research & Consortia Established - Potential Follow-on topics in Call 10 + A new H2020 project builds on output from Europain and is coordinated by Europain Partner 4 (Oxford D Bennett). It aims to further validate and qualify e.g. the µNeG and other electrophysiology measures for diagnosis and outcome/ clinical applicability in clinical development of NeuP.

New business established - 1 Spin off created between partners 6 (NT) and 27 (NTL) - see comment below

New product to market - A partner in the EUROPAIN consortium Neuroscience Technologies S.L. (based in Spain) has opened an affiliate in UK and has significantly expanded its business via commercialisation of the microneurography assays developed as part of the project activities. Several companies are using the technology in clinical development, both inside of and outside of the project.

Process of productivity gain - Tools mentioned in the comment below could potentially save costs?

Impact on product development process - Tremendous impact on product development process: Burrowing in pre-clinical development (including go/no go decisions); Microneurography for pre-clinical/ translational and clinical outcome and prediction and support of go/no go; QST as a stratification tool and inclusion biomarker in clinical trials; NGS for pre-clinical and translational assays.

17.8. U-BIOPRED

Research Impacts	Yes	No	Maybe
Follow-on Research	☐	☒	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☐	☐	☒
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☐	☒	☐
Licenses to existing business	☐	☒	☐
New product to market	☒	☐	☐
Process of productivity gain	☐	☒	☐
Impact on product development process	☐	☐	☒
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☒	☐
Healthcare Costs	☐	☒	☐
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☒	☐

Notes:

Follow-on Research - Nothing decided yet but there may be follow-on topics and projects under IMI 2

Consortia Established - Project participants will finish the remaining deliverables and indicated interest to continue working together following the completion of U-BIOPRED

New product to market - U-BIOPRED has validated various pre-clinical in vitro (PBMC, ASM, HBEC, PCLS) and in vivo (CFA/HDM) models as well as producing GMP RV16.

Impact on product development process - These validations may help determine the right medicines for the right patient and help speed up medicines development.

17.9. SUMMIT

Research Impacts	**Yes**	**No**	**Maybe**
Follow-on Research	☒	☐	☐
Research Staff Trained	☒	☐	☐
Consortia Established	☒	☐	☐
Product & Business Development	**Yes**	**No**	**Maybe**
New business established	☒	☐	☐
Licenses to existing business	☒	☐	☐
New product to market	☐	☐	☒
Process of productivity gain	☒	☐	☐
Impact on product development process	☒	☐	☐
Health System Benefits	**Yes**	**No**	**Maybe**
Improved Health	☐	☐	☒
Healthcare Costs	☐	☐	☒
Workforce Health	☐	☒	☐
Policy	**Yes**	**No**	**Maybe**
New policies implemented	☐	☒	☐
Regulations changed	☐	☐	☒

Notes:

Follow-on Research & Consortia Established - Leading partners from the 3 IMI1 diabetes projects (including SUMMIT) in the IMI Diabetes Platform have joined forces in an IMI2 project on progression of pre-diabetes (RHAPSODY). Follow up of SUMMIT.

New business established - A start-up company diaBRIDGE in Lund, Sweden was created to bridge the translational gap in diabetes as a result of the output from the SUMMIT project.

Licenses to existing business - A mouse model developed by SUMMIT for diabetic CVD and nephropathy has been transferred to Taconic BioSciences for further exploitation. In addition, a licensing agreement for exploitation of a SUMMIT rat model is under negotiation with Janvier Labs.

New product to market - Exploitation of the Ultrasound-based Plaque Structure Analyses (UPSA) technology developed in SUMMIT project by Lund University in Sweden. Negotiations are on-going with an imaging-interested party.

Impact on product development process - Industry has already shown a keen interest in the SUMMIT animal models for diabetic complications and their value for pharmaceutical research is expected to rise even more when the final results of the ENSO intervention studies become available. Implementation of the models is awaiting licensing agreement negotiations. The use of the UPSA imaging method will provide both health care professionals and industry-initiated clinical trials with an easy to use and non-invasive plaque scan approach. Also here interest is high. EFPIA partners consider the SUMMIT data, studies and results a resource for triggering and accelerating internal projects and initiate new medicines projects. These outputs have great potential but it is still too early to exactly define their final level of implementation. BCP is interested in collaboration for the commercialization of the developed prediction models.

Healthcare Costs - If UPSA is implemented, this would save cost for artery plaque assessment.

18. Appendix B: Project summary proforma

18.1. Template Framework Project

18.1.1. Summary of Impacts

To be completed by IMI and reviewed by experts

Research Impacts						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
Follow-on Research	☐	☐	☐	☐	☐	☐
Research Staff Trained	☐	☐	☐	☐	☐	☐
Consortia Established	☐	☐	☐	☐	☐	☐

Product & Business Development						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
New business established	☐	☐	☐	☐	☐	☐
Licenses to existing business	☐	☐	☐	☐	☐	☐
New product to market	☐	☐	☐	☐	☐	☐
Process of productivity gain	☐	☐	☐	☐	☐	☐
Impact on product development process	☐	☐	☐	☐	☐	☐

Health Benefits						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
Improved Health	☐	☐	☐	☐	☐	☐
Health Costs	☐	☐	☐	☐	☐	☐
Workforce Health						

Policy						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
New policies implemented	☐	☐	☐	☐	☐	☐
Regulations changed	☐	☐	☐	☐	☐	☐

Note: the analysis will consider inputs, intermediate outputs and final outcomes. The focus will be on final outcomes. However, at this stage it is necessary to collect information on inputs and intermediate outputs too, in order to ensure that nothing important is over-looked.

18.2. Innovative Medicines Initiative: Socio-economic Evaluation Framework

18.2.1. Project Details

Project acronym	Click here to enter text.
Project name	Click here to enter text.
Start date	Click here to enter a date.
End date	Click here to enter a date.
Subject/ disease area	Click here to enter text.
Project website	Click here to enter text.
Stage in drug development pathway	Click here to enter text.

Project co-ordinator	Click here to enter text.
Address	Click here to enter text.
Telephone	Click here to enter text.
Email	Click here to enter text.

Managing Entity	Click here to enter text.
Address	Click here to enter text.
Telephone	Click here to enter text.
Email	Click here to enter text.

IMI Scientific Officer	Click here to enter text.
Telephone	Click here to enter text.
Email	Click here to enter text.

TYPE	Funding committed in €s	% total funding
Universities, Research Organisations, Public Bodies & Non-profit	Click here to enter text.	Click here to enter text.
EFPIA companies	Click here to enter text.	Click here to enter text.
SMEs	Click here to enter text.	Click here to enter text.
Special Contributors i.e. other organisations participating at their own cost) (SC11s)	Click here to enter text.	Click here to enter text.
Patient organization(s)	Click here to enter text.	Click here to enter text.
Regulator(s)	Click here to enter text.	Click here to enter text.
Other	Click here to enter text.	Click here to enter text.
Source:	Click here to enter text.	

18.2.2. Value of funding input

TYPE	Amount in €s	% total funding
IMI funding (up to 75%)	Click here to enter text.	Click here to enter text.
EFPIA funding (in kind)	Click here to enter text.	Click here to enter text.
Other Funding (25%)	Click here to enter text.	Click here to enter text.
SC11 Funding	Click here to enter text.	Click here to enter text.
Total value of funding input	Click here to enter text.	Click here to enter text.
Source:	Click here to enter text.	

18.2.3. Project Objectives, Activities and Deliverables

Key project outputs
Click here to enter text.
Source: Click here to enter text.

18.2.4. Summary of Project Outcomes (note: see Project Final Reports)

Tangible outputs from project activities:
e.g. products, database, software, standards, etc Click here to enter text.
Source: Click here to enter text.

18.2.5. Short description of education and training related outputs

Courses conducted	Click here to enter text.
Trainees who completed CPD training programs	Click here to enter text.
Students graduated from different training programmes	Click here to enter text.
EFPAI take up of courses	Click here to enter text.
Teachers involved in the training programmes	Click here to enter text.
Training centres labelled "excellence"	Click here to enter text.
Countries covered by training centres	Click here to enter text.
Tangible products e.g. certification, catalogues, external partnerships formed etc	Click here to enter text.
Sustainability activities	Click here to enter text.
Other (specify)	Click here to enter text.
Source:	Click here to enter text.

18.2.6. Short description of business related outputs

Implementation of project results in industry	Click here to enter text.
Patents, copyrights or other IP rights	Click here to enter text.
Spin offs created or planned	Click here to enter text.
Buy outs, take overs	Click here to enter text.
Licensing deals with industry	Click here to enter text.
Number of additional EFPIA companies and funding attracted (after GA signature)	Click here to enter text.
Number of additional beneficiaries attracted (after GA signature)	Click here to enter text.
Additional funding sources and amounts	Click here to enter text.
Sustainability activities	Click here to enter text.
Other (specify)	Click here to enter text.
Source:	Click here to enter text.

18.2.7. Short description of dissemination of project outputs

Dissemination output	Click here to enter text.
Bibliometric output	Click here to enter text.
Number of publications	Click here to enter text.
Citations (average citation impact)	Click here to enter text.
Number of highly cited (top 10%)	Click here to enter text.
Other dissemination activities	Click here to enter text.
Source:	Click here to enter text.

18.2.8. Potential impacts of project (note: the view of the project; from Description of Project and Annual Reports)

Potential Impacts of Project (identified by Projects)
Click here to enter text.
Source: Click here to enter text.

18.3. Impacts – to be completed by expert reviewer

Note: the analysis will consider inputs, intermediate outputs and final outcomes. The focus will be on final outcomes. However, at this stage it is necessary to collect information on inputs and intermediate outputs too, in order to ensure that nothing important is over-looked.

Research Impacts						
	Yes	**No**	**Maybe**	**Already Achieved**	**Possible By 2020**	**Beyond 2020**
Follow-on Research	☐	☐	☐	☐	☐	☐
Research Staff Trained	☐	☐	☐	☐	☐	☐
Consortia Established	☐	☐	☐	☐	☐	☐

Product & Business Development						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
New business established	☐	☐	☐	☐	☐	☐
Licenses to existing business	☐	☐	☐	☐	☐	☐
New product to market	☐	☐	☐	☐	☐	☐
Process of productivity gain	☐	☐	☐	☐	☐	☐
Impact on product development process	☐	☐	☐	☐	☐	☐

Health Benefits						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
Improved Health	☐	☐	☐	☐	☐	☐
Health Costs	☐	☐	☐	☐	☐	☐
Workforce Health	☐	☐	☐	☐	☐	☐

Policy						
	Yes	No	Maybe	Already Achieved	Possible By 2020	Beyond 2020
New policies implemented	☐	☐	☐	☐	☐	☐
Regulations changed	☐	☐	☐	☐	☐	☐

For Each Impact Identified Above:

Note 1: Some of the following information may be in existing project documentation but it is anticipated that further research will be required, including interviews with project co-ordinators, managing entities and participants.

Note 2: each identified impact that has already been achieved should be 'significant' and 'robust', i.e. has occurred beyond any reasonable doubt, clearly specified in IMI documentation (or other reliable sources), and (in principle) amenable to (external) verification and auditing

Copy table below to provide one table for each impact or potential future impact identified above.

Brief description of Impact
Click here to enter text.
Geography of impact (note whether impact is local/regional, national, EU wide and/or global)
Click here to enter text.
Timescale (note when impact is likely to occur and indicate whether it has potential to increase/decrease over time)
Click here to enter text.
Risks, Obstacles and Barriers (for future impacts, what are the necessary conditions for these future impacts to occur? What is the likelihood that they will?)
Click here to enter text.
Additionality – would these impacts have been delivered anyway, in all likelihood, even if the project had not been supported by IMI? **If they would, has the project and IMI made a difference to the scale, timing or location of impacts?** **Has IMI led to changes in the direction or nature of research/activity?**
Click here to enter text.
'Market' Context for impacts (e.g. number of people effected by disease, market size for drug, health costs of existing treatment)
Click here to enter text.

Copy and paste additional tables for each impact identified.

19. Appendix C: Interview topic guide

19.1. IMI Socio-economic impacts evaluation

To help demonstrate the value of the work supported by IMI we are currently undertaking an assessment of the ***socio-economic benefits*** associated with projects that have recently been completed or are close to completion. The aim of this work is to gather views and impressions about the actual and potential benefits associated with each project over the short, medium and longer term.

During the first phase of this work a specially convened panel of experts undertook a review of the final reports produced by each project. This review identified a number of specific questions about each project, which we would now like to discuss with those responsible for delivering the projects, focusing on ***socio-economic benefits*** that have, or could be delivered.

To help with this process we have asked Graeme Blackett and Shona Glenn from BiGGAR Economics to speak to representatives from each project. The aim of these interviews will be to gather further details about each project that will help the team to evaluate the benefits it has, or is expected, to generate.

Graeme and Shona are experienced researchers in this field and will take you through a questionnaire designed to collect the additional data needed to assess immediate and potential impacts of the project's outputs and products. The interview will last for approximately 45 minutes and we would be happy to share a transcript of the interview and the final assessment report which is due in April 2016 and which will be a public IMI document.

To help you prepare for the interview we have prepared the following topic guide, which highlights the main areas we would like to discuss with you. The interviews are however intended to be semi-structured so if you believe there may be any benefits associated with your work that are not covered by the questions below please feel free to raise these with Shona and Graeme.

19.2. Interview Questions

Project Impacts and Outcomes

1. Has the project generated any of the following benefits, or would you expect it to in the future?

    a. Please describe each of the benefits (and potential benefits) associated with this project.

    b. Would these benefits have occurred if this project had not been supported? Please explain why/how.

	Description & "Additionality" of Project
Improved cooperation & knowledge transfer within the scientific community?	
Improved cooperation & knowledge transfer between the scientific community & companies?	
Improved pre-clinical models for drug development?	
Identification of new drug targets?	

Identification of novel biomarkers?	
Improved processes for clinical development and trials?	
Improvements in the training of staff?	
Policy changes?	
Changes to clinical guidelines or medical practice?	
Other?	
Other?	
Other?	

2. Do you believe that there is potential for the benefits of the project to eventually lead to socio-economic impacts?

   a. Please explain what these benefits might be.

   b. Please explain how such benefits may occur in future.

   (Note: socio-economic impacts can include new businesses and employment, health impacts and health system impacts etc.)

	Pathways to Impact
Health impacts	
Health systems impacts	
Economic impacts (businesses & employment)	

3. Was the project originally intended to address a market failure (i.e. some feature of the medicines development in system in Europe that meant there was an inefficient allocation of resources)?

   a. In the event, did the project lead to changes in these conditions or do you expect future changes to these conditions?

	Market Failure
Original market failure	
Changes to market conditions	

4. How are the results from this project being implemented by European Federation of Pharmaceutical Industries and Associations (EFPIA) companies?

Patents, copyrights or other IP rights	
Spin offs or new businesses created or planned	
Buy outs, take overs	
Licensing deals with industry	
Employment generated (in existing or new businesses)	
Other (specify)	

5. How are the results from this project being implemented by European health systems?

Improvements to productivity of health system(s)	
Changes to access to health care & health equality	
Other (specify)	

Lessons Learned and Future Expectations

6. What would your key recommendation be to help secure short-term (i.e. by 2020) socio-economic impacts from this project?

Recommendation?

7. Has the completion of this project led to any changes in the direction or nature of your current activities or objectives?

Changes?

Process Questions

8. How did IMI affect impact pathways and implementation likelihoods?

Were the expectations established for the project realistic?	
How do IMI-related IPR regimes affect impact pathways and implementation likelihoods?	

9. What were the main strengths and weaknesses of the project (thinking particularly about potential socio-economic impacts)?

Strengths – what aspects of the project have made positive impacts more likely?	
Weaknesses – what aspects of the project have been barriers to outputs or impacts?	

10. Where there any significant, unforeseen external events during the project that altered development trajectories, outcomes or impact expectations?

Nature of event	
Effect on project	

Future Monitoring

11. How should further progress of the project's outcomes and impacts be monitored over the next few years?

How should further progress be monitored?	
By whom?	

12. What are your views about designing an IMI Results Implementation Overview as a tool to monitor the development of impacts and impact pathways?

Views?

Tel +32 (0)2 221 81 81 • Fax +32 (0)2 221 81 74 | infodesk@imi.europa.eu • www.imi.europa.eu • twitter: @IMI_JU
Postal address: IMI JU • TO56 • 1049 Brussels • Belgium | Visiting address: Ave de la Toison d'Or 56-60 • 1060 Brussels • Belgium