



Innovative Medicines Initiative

7th Call for proposals 2012

Innovative Medicines Initiative

Version 3

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GENERAL PRINCIPLES

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership between the European Commission and EFPIA¹ driving collaboration between all relevant stakeholders including large and small biopharmaceutical and healthcare companies, regulators, academia, and patients.

The aim of IMI is to propose a coordinated approach to overcome identified research bottlenecks in the drug development process, in order to accelerate the development of safe and more effective medicines for patients, by fostering collaboration between all stakeholders such as industry, public authorities (including regulators), organisations of patients, academia and clinical centres, and enhancing Europe's competitiveness.

The revised IMI Scientific Research Agenda <http://www.imi.europa.eu/content/research-agenda> describes the research bottlenecks in the drug development process and identifies new and established research priorities correlated to at least one of the seven IMI Areas of Research Interest.

The IMI 7th Call 2012 for proposals will have 2 topics covering the following key research priorities:

- Knowledge Management (correlated to the Areas of Interest: knowledge, patient, development)
- Coping with regulatory and legal hurdles (correlated to the Area of Interest: development)

These two topics are:

- 1- Developing a framework for rapid assessment of vaccination benefit/risk in Europe
- 2- Incorporating real-life clinical data into drug development

Applicant Consortia are invited to submit expressions of interest to one of the topics.

The expressions of interest should address all aspects of the topic to which the Applicant Consortia are applying.

The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

Further information can be found under the section 'Synopsis of Call and evaluation processes'.

Before submitting an expression of interest, the various Call Documents, such as *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals, Rules for Participation, the IMI Intellectual Property Policy*, etc., shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the 7th Call 2012 launch.

Synergies and complementarities with other EU funded projects should be explored in order to avoid overlaps and duplications and to maximize European added value in health research.

¹ European Federation of Pharmaceutical Industries and Associations – www.efpia.eu

DURATION OF THE PROJECTS

The indicative duration of the project is 5 years for the first topic and 3 years for the second topic.

FUNDING OF THE PROJECTS

For this Call, the total available financial contribution from the IMI JU to participants eligible for funding will be up to the amounts that the research-based companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) will contribute as 'in kind'² contribution.

The indicative EFPIA in kind contribution will be EUR 13 million.

The indicative IMI JU contribution will be divided between the two topics as follows:

- 1- Developing a framework for rapid assessment of vaccination benefit/risk in Europe: up to EUR 5 million
- 2- Incorporating real-life clinical data into drug development: up to EUR 8 million

The Applicant Consortia shall keep in mind that the budget of each expression of interest should be adapted to the scientific goals and the expected key deliverables of the project.

SYNOPSIS OF CALL AND EVALUATION PROCESS

The IMI JU supports research activities following open and competitive Calls for proposals, independent evaluation and the conclusion of Project and Grant Agreements.

The Topics included in the 7th Call are associated with a group of pharmaceutical companies that are members of EFPIA (hereafter called the 'EFPIA Consortia') and which are committed to collaborate with public and private organisations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions to support their activities within the research projects.

The IMI JU applies a two stage Call process. In the first stage, 'Applicant Consortia' (i.e. formed by academia, small and medium sized enterprises (SMEs), patient organisations, non EFPIA companies, etc.) are invited to submit, to the IMI JU, an expression of interest (EoI) in response to a Call Topic.

In preparing their EoIs, the Applicant Consortia should carefully consider the research contribution that an EFPIA Consortium will make to a given project as well as the expectations from the Applicant Consortia, as outlined in the topic texts below.

Each EoI submitted will be reviewed by independent experts according to predefined evaluation criteria.

The Applicant Consortium with the highest ranked EoI for each topic will be invited to jointly develop a full project proposal together with the EFPIA Consortium.

For each topic, the full project proposal will then be subject to a final review by independent experts according to predefined evaluation criteria.

² In kind contribution is e.g. personnel, clinical research, equipment, consumables.

Only a full project proposal that has been favourably reviewed in the evaluation process can be selected for funding. This project will then be invited by the IMI JU to conclude a Grant Agreement governing the relationship between the selected project consortium and the IMI JU.

For full details, applicants should refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals* published on the IMI JU website www.imi.europa.eu at the launch of the 7th Call.

ELIGIBILITY TO PARTICIPATE IN PROJECTS AND TO RECEIVE FUNDING FROM THE IMI JU

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from the IMI JU are specified under the *Rules for participation* in the IMI JU collaborative projects published on the IMI JU website www.imi.europa.eu.

The IMI JU financial contribution will be based on the reimbursement of the eligible costs. The following funding rates apply to the legal entities eligible for funding: For research and technological development activities, up to 75% of the eligible costs and for other activities (including management and training activities) up to 100% of the eligible costs charged to the project are eligible for funding. For the indirect costs (overheads), the legal entities eligible for funding may opt for one of the following indirect costs methods: the actual indirect costs; or the simplified method which is a modality of the actual indirect costs for organisations which do not aggregate their indirect costs at a detailed level, but can aggregate them at the level of the legal entity; or a flat rate of 20% of total eligible direct costs (excluding subcontracting costs and the costs of resources made available by third parties which are not used on the premises of the beneficiary).

For full details, Applicant Consortia are invited to refer to the *Rules for Participation* in the IMI JU collaborative projects (www.imi.europa.eu).

The research based companies that are members of EFPIA shall not be eligible to receive financial contributions from the IMI JU.

IMI INTELLECTUAL PROPERTY POLICY

The IMI Intellectual Property Policy (IMI IP policy, www.imi.europa.eu) has been developed to be aligned with the objectives of the IMI JU to ensure knowledge creation, together with the swift dissemination and exploitation of knowledge, and fair reward for innovation.

The IMI IP Policy sets out *inter alia* basic principles regarding ownership of Background and Foreground, access rights depending on the entity and the purpose, and dissemination.

In submitting an EoI, the Applicant Consortia fully understand the principles laid out in the IMI IP policy that will apply to all research projects conducted under the IMI JU.

The IP policy does not foresee all details and does not aim to answer to all possible practical situations participants may be faced with. Flexibility is provided for participants to establish the most appropriate agreements (e.g. the project agreement) serving each individual project's objectives, and considering the wider IMI objectives.

Applicant Consortia are invited to read carefully the Guidance Note on the IMI IP Policy (www.imi.europa.eu), whose purpose is to explore ways to handle related issues and

pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

The Project Agreement is a private agreement which the participants of an IMI project conclude amongst themselves to implement the provisions of the Grant Agreement and to regulate internal issues related to work organisation and objectives for each participant, consortium governance, IP, financial and other matters.

All participants of a selected IMI project are requested to start negotiation on the project agreement between them in parallel to the preparation of the full project proposal.

The Full Consortium shall ensure that the negotiation of the project agreement is completed no later than the finalisation of the full project Description of Work.

1. DEVELOPING A FRAMEWORK FOR RAPID ASSESSMENT OF VACCINATION BENEFIT/RISK IN EUROPE

BACKGROUND

Vaccines are one of the most effective preventive public health measures, with millions of people vaccinated every year. However public distrust has been growing in recent years, fuelled by fear of safety issues and the ever fading personal knowledge of the potential detrimental effects of the prevented diseases. In some cases this has led to a decrease in vaccination uptake and subsequent outbreaks of diseases previously under control. The ability to rapidly access and evaluate information regarding both the actual benefits and risks of vaccines is needed to maintain trust from the public and to allow the Regulators and physicians to make appropriate decisions regarding vaccination strategies. For vaccines, safety concerns are often related to serious, but extremely rare events, potentially affecting only a few individuals per 100,000. But since vaccines are preventive measures given to healthy people, adverse events are far-less-to-unacceptable as opposed to drugs given to treat an already present disease. However, accurate measures of the association between vaccination and these rare events are only possible with very large sample sizes (in the order of several millions). In addition, measures of vaccine effectiveness, especially if needed over a short period of time, may only be possible with a similarly large population to observe sufficient cases of the disease and benefit offered from vaccination. Broader measures of vaccine impact on the incidence of preventable diseases, and their complications, in the general populations are also difficult to assess without a proper information system, as is the case for other measures which are critical for assessing the vaccination programs, including vaccination coverage, in different demographic or clinical groups, background rates of adverse events of special interest, and burden of the preventable diseases before and after vaccination is launched.

The increasing adoption of electronic health records in Europe, robust infectious disease surveillance systems and the widespread efforts to develop large-scale information infrastructures are quickly building a wealth of medical information, which could potentially support rapid evaluation of the impact of vaccination. Large observational databases can potentially provide in real-time, the large samples needed. However, this information is currently fragmented into geographically limited and non-standardised databases, with sometimes restricted access and/or long delays before the information is available. Furthermore, in many cases, these healthcare databases are primarily built around information regarding drug therapy and often vaccination information is absent, less accessible and/or less standardised. In addition, new analytical methods need to be developed, adapted and validated to ensure data available can be interrogated and evaluated in the most efficient and informative manner to ensure rapid delivery of robust information to allow timely decisions to be made by key decision makers.

A system for rapid detection and evaluation of safety signals for vaccines when they are first used had been pioneered in the US from 1991 (Vaccine Safety Datalink) and is in routine use for rapid cycle analysis (RCA) since 2005. Feasibility of a similar system in Europe has recently been demonstrated for the pandemic H1N1 vaccines, both (but separately) for safety (VAESCO) and effectiveness (I-MOVE). While these pilot studies were encouraging, there is clear need in Europe for a larger and more sustainable and readily available, possibly centralised, framework for combined benefit/risk measures and based on standardised, automated, and validated processes.

Beyond technical feasibility post-approval studies of vaccines are also facing multiple and possibly even harder challenges in terms of the high heterogeneity in scientific and organisational focus and interest (from infectious disease epidemiology in public health

institutes to pharmacoepidemiology in the Industry) and difficulty to reach adequate public understanding. Pilot projects in Europe (such as VAESCO and I-MOVE, both funded by the ECDC) have also highlighted an increasing issue of coordination and/or overlap between regulatory commitments by Vaccine Manufacturers and public initiatives. In their Risk Management Plans (RMP), Vaccine Manufacturers need to rely more and more on large, possibly European wide databases to which they may not be granted access, or which could already be used by public initiatives.

An infrastructure for integrated studies of post-approval benefit/risk can only be developed and sustained by a close interaction between partners from a large horizon, including regulatory agencies, public health institutes, pharmacoepidemiologists and vaccine manufacturers. While the current public initiatives have made remarkable achievements, it has also been apparent that sharing data and study results with Vaccine Manufacturers has remained an open issue. Further challenges are also expected with the introduction of the new EU legislation on Pharmacovigilance. In addition to the necessary improvement in database linkage, validation and analytical methods, there is a clear need for public/private partnership built on strong transparent governance foundations.

PROBLEM STATEMENT

Rapid vaccine benefit-risk ad-hoc assessment and continuous monitoring pose intricate challenges on both a technical and governance level. Currently no large scale, readily available centralised data infrastructure and data source exists to allow for a rapid and complete benefit-risk assessment of vaccines. In addition, there is lack of coordination and overlap of the activities employed by industry and public health initiatives on vaccine impact assessment. To allow a unified effort for vaccine benefit/risk assessment by all stakeholders involved, transparent governance rules are needed that define the roles and responsibilities of all the stakeholders. These elements combined are essential for a timely assessment of vaccination programs in order to maintain public trust, vaccine coverage and ultimately to control infectious disease.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

There are many challenges to develop and implement a sustainable framework for rapid assessment of vaccination in Europe. To be successful this will require a substantial and integrated approach utilising a large number of contributors and experts from Vaccine Manufacturers, regulatory agencies, public health institutes, healthcare organisations, academia and other key stakeholders throughout Europe. Input and support from owners of patient-level health information, experts in the linkage and use of patient-level health information, and experts in methods for measuring association of vaccine with outcomes will be essential. In addition there is a need for experienced leaders in the areas of policies, governance, regulations, ethics and communication related to public/private collaboration and to vaccination.

Academic groups and public health institutes will provide expertise, especially in developing novel methodology, privileged access to and previous experience with public health data, European-wide collaboration networks, and transparency processes (such as ENCePP). European Regulatory Agencies can bring expertise in benefit/risk assessment and knowledge and experience of the information required when faced with challenging decisions when there is uncertainty of the actual risks and benefits of a given vaccine. Vaccine manufacturers bring their experience in vaccine development, in their specific vaccines, in the challenges, expertise, best practices and standards from their own

previous studies as well as their experience in the barriers encountered in implementing their Risk Management Plans.

Particularly for vaccines unifying efforts between public and private partners in an open, transparent structure, and providing a consistent and rapid way of determining and communicating the benefit/risk of vaccination will significantly improve the public trust and the effectiveness of vaccination programs.

As described below in more details, one of the tasks of the public/private partnership in the consortium for this project will actually be to prepare the implementation of a larger and longer term infrastructure which itself can only be successful as a public/private partnership.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies will be actively sought and developed as extensively as possible with other IMI projects including EMIF, PROTECT, BioVacSafe, EHR4CR, EU2P, as well with other European projects (including GRIP and EU-ADR) and international projects such as OMOP, or any other relevant initiatives (such as I-MOVE and other large scale pathogen surveillance networks). Priority will be given to using other available infrastructures and tools, and to limiting the activities to adapting these to specificities of benefit/risk studies of vaccines. Proof-of-concept studies (see below) should be set up along these lines.

Given the importance of these potential synergies for this Call, periodic mapping of other relevant projects, along with an assessment of their actual or potential role in this vaccine project will be delivered as part of a dedicated Work Package (see below).

OVERALL OBJECTIVES

The long-term vision behind this call is an efficient and sustainable infrastructure for rapid and integrated assessment of post-approval benefit/risk of vaccines under clear governance rules meeting the common interest of all main stakeholders. The aim of this call is to pave the road towards this vision, stopping short to moving into what will be referred below as the implementation phase. This later implementation phase will need its proper funding and governance system, and cannot therefore be in itself part of this call. However it will be one of the tasks of the consortium for this call to prepare the transition to implementation as early as possible and in parallel with the other activities.

Therefore the specific and overall objective of this call is to deliver the following steps to prepare the implementation of a sustainable infrastructure accessible for all relevant stakeholders in Europe for facilitating post-approval, rapid and integrated assessment of the benefit/risk of vaccines by:

- Delivering a set of governance principles and rules that recognizes all main stakeholders
- Mapping the current synergies in existing relevant ongoing projects that provide relevant technical and methodological output and to identify any transitions needed for their application in vaccine benefit/risk assessment studies
- Proof of concept studies
- Delivering an action plan for long-term expandability and sustainability to allow transition to implementation.

EXPECTED KEY DELIVERABLES

- Reviews (white paper) to map the needs, gaps, resources, methods and processes to rapid, integrated post-approval monitoring of vaccines in Europe, reflecting the views of all main stake-holders (Regulatory agencies; public health institutes; vaccine manufacturers, general public).
- Identify synergies with existing initiatives and propose formal collaborations where relevant.
- Proof-of-concept studies to assess selected data sources, analytical methods and governance rules
- A recognised central forum to build trust between all the main stakeholders and facilitate timely agreement on the policies and governance of the new infrastructure
- Guidance for the best practices and governance for the conduct of pharmacoepidemiological studies to monitor benefit/risk of vaccines under private/public partnership
- An action plan for a sustainable framework for assessing vaccine benefit/risk, including plan for governance, funding mechanism, integration of/with other initiatives (as mapped) and supporting organisation.

CONSORTIUM

EFPIA PARTICIPANTS

GSK Biologicals, Sanofi Pasteur, Novartis Vaccines, SanofiPasteurMSD, and J&J/Crucell.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years. However the aim is also to develop an infrastructure that is sustainable for research projects beyond the life of this particular IMI call.

INDICATIVE BUDGET OF THE PROJECT

Indicative total in kind contribution from the EFPIA companies is EUR 5 million and the indicative IMI JU contribution will be up to EUR 5 million.

APPLICANT CONSORTIUM

The consortium is expected to be a multi-disciplinary body:

- to enable effective communication between key stakeholder groups (academia, regulatory agencies, public health organisations, vaccine manufacturers)
- to conduct proof-of-concept studies with challenging data collection and linkage, analytical methods, and collaborative aspects.

The consortium is expected to have an established expertise in the following areas relevant to the proposal:

- Observational Research
- Vaccine effectiveness, safety and benefit/risk studies
- Statistics and data management
- Epidemiology
- Pharmacoepidemiology

- Pharmacovigilance
- Quality and Risk Management
- Regulatory affairs
- Healthcare/data privacy ethics
- Public/private partnerships
- Health Outcomes
- Communication
- Public understanding of public health issues

The applicant consortium will also provide:

- analytical expertise to conduct analysis of existing data sets to optimise benefit/risk assessment
- relevant information, or capacity to obtain it, from public health databases as needed for the proof of concept studies
- experience and expertise in the regulatory and public health environment and/or capacity to directly engage with the key stakeholders from these environments

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The architecture below for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

Work Package 1: Governance and code of conduct for public/private partnership in studies of benefit/risk of vaccines

This work package will focus on

- mapping, assessing and documenting the current gaps and barriers, guidelines, regulations, common interests and feasibility issues for a public, private, regulatory partnership
- building a public-private consensus on best practice for post-licensure benefit/risk monitoring of (new) vaccines, outlining ways of interacting to increase transparency and trust
- developing guidance for the governance of partnership in which the roles and responsibilities of all relevant stakeholders are reflected, i.e. interaction between Vaccine Manufacturers, Public Health Institutions, and Regulatory Authorities regarding study design, data privacy, transparency, data sharing, and communication of study results. selecting, improving, adapting or establishing a code of conduct and governance system both for the proof-of-concept studies and the later implementation phase
- communicating about the project to the general public
- developing ways to improve the public understanding of vaccine benefit/risk measures and benefit/risk information coming from observational studies
- developing a clear and solid action plan for the ultimate transition from the proof-of-concept studies to exploitation, including expandability and sustainability. Consideration can be given to building up a vaccine support infrastructure as part of the ESFRI roadmap.

EFPIA Contribution : Expertise in Post-marketing monitoring, Pharmacovigilance, EU Regulatory affairs, Quality and Risk Management and government affairs; experience in

post-marketing studies in the framework of RMPs; access to databases (if/when relevant and feasible).

Work package 2: Mapping of project synergies

This work package will focus on developing synergies with other initiatives, after careful mapping, review, and selection. Specifically this assessment should address how the outputs of these projects can be transposed to the vaccine environment, where applicable, by:

- Mapping all relevant current initiatives (e.g. EHR4CR) and assessing how their output can be applied/used in the context of vaccine benefit risk assessment
- Identifying the remaining gaps to allow for vaccine benefit/risk assessments as part of the execution of the RMP or ad hoc safety assessment at time of a newly detected signal.

As part of this WP, potential partners for collaboration on execution of a (mutual) proof of concept studies in WP5 should be identified.

Work Package 3: Data sources for rapid and integrated benefit/risk analyses

- Identify databases for safety and effectiveness outcomes suitable and available for the proof-of-concept studies (see WP5)
- Identify sources of vaccine registration across EU (including any information on batch numbers), assess feasibility of linkage (see WP4)
- Organise and manage the data linkage and data extraction for the proof of concept studies and consider their interoperability
- If needed, engage database owners to provide essential data regarding vaccine usage, safety and effectiveness for the proof of concept studies
- Deliver a catalogue of databases and linkage methods to be used in the implementation phase
- Deliver a review of methods for rapid aggregation of heterogeneous data from multiple databases, with focus on vaccines (e.g., this may include a validated vaccine dictionary) and for automated case definition of adverse events of special interest, in view of their use in the implementation phase

EFPIA Contribution: Experts in observational studies

Work Package 4: Identification and/or development of methods for integrated analysis of burden of diseases, vaccination coverage and vaccine safety and effectiveness

This work package should focus on:

- the critical review, development and/or selection of methods for rapid and integrated estimation of benefit/risk in observational data, with a focus on shortening the time lag between the early safety signals and the benefit data
- testing selected method(s) in the proof-of-concept studies (see WP5)

EFPIA Contribution: experts in observational databases, vaccine safety, vaccine effectiveness and benefit/risk, and research pharmacoepidemiology

Work Package 5: Proof-of-concept studies of a framework to perform vaccine benefit/risk assessments

This work package should focus on:

- Demonstrating by proof-of-concept studies that sets of observational data can be successfully and rapidly aggregated to perform vaccine benefit/risk assessments, i.e. combinations of vaccination coverage, estimates of major safety risks, measures of the burden of the preventable disease, vaccine effectiveness, and vaccine overall impact (see WP3). Molecular epidemiology surveillance can be included but is not the main focus of the Call Topic.
- Assessing the analytical methods selected or developed by WP4
- Assessing the governance mode and code of conducts from WP1 in real public/private partnership conditions
- Assess the role of synergies with other initiatives (see WP2)
- Providing feedback and expert review from all stakeholder perspectives (public, regulatory, industry, academic) on the feasibility of future large-scale exploitation throughout the project based on the proof-of-concept studies

EFPIA Contribution: Specialists in pharmacovigilance, observational databases, vaccine effectiveness and benefit/risk, research pharmacoepidemiology and disease epidemiology expertise

Work Package 6: Project Management

This work package will address the strategy and project management encouraging regular meetings and interaction between sub-groups and teams, to coordinate the work effort.

- Each work package should have a work package leader who will be responsible for ensuring the deliverables are addressed.
- Each work package will encompass different workloads throughout the duration of the project. Progress will be monitored through regular project meetings involving all participants.

EFPIA Contribution: Overall consortium and project management

2. INCORPORATING REAL-LIFE CLINICAL DATA INTO DRUG DEVELOPMENT

BACKGROUND

Today regulatory data are generated according to guidelines based on clinical trials evidence from randomized placebo controlled trials that do not necessarily reflect the complexity of real life medical practice. On the other hand, information required for Health Technology Assessment (HTA) evaluation is related to medical practice in order to judge value for the individual and for society. These two requirements were moving further away from each other over time. The objective of the project is to look at the different possibilities to generate more relevant information for both regulatory and HTA evaluations.

Currently, assessment of benefit/risk and value of new medicines is seen as a continuing activity throughout a product's life cycle. The data available at time of initial market approval and reimbursement are supplemented by post-launch programmes, e.g. within risk management plans. Recently there has been a rapid growth in real world studies to complement clinical trial data in providing evidence for reimbursement and funding decisions at national and local levels which affect the speed and level of patient access and therefore the extent to which patients and society might benefit from new medicines.

When regulators, HTA, reimbursement agencies and other decision makers first assess new medicines, they are doing so in a context of uncertainty in benefit/risk and value over time (due to variation in health care standards and outcomes across different settings) and of increasing healthcare costs.

There are differences in the type of evidence required by regulatory bodies and HTA agencies. Currently Randomised Controlled Trials (RCTs) are primarily designed and conducted to meet the needs of regulatory bodies, and while they will continue to provide critical evidence of efficacy and safety for regulators and others, they are frequently insufficient by themselves to meet the evidentiary needs of many HTA agencies. This can result in increased uncertainty in the value of new medicines assessed by HTA agencies and healthcare decision makers at the time of new drug launches.

As a result, evidence of relative effectiveness and robust cost-effectiveness derived from real world experience in relevant local settings, is increasingly requested.

Relative Effectiveness (RE) is defined by the EU High Level Pharmaceutical Forum (2008) as: *"the extent to which an intervention does more good than harm compared to one or more alternative intervention for achieving the desired results when provided under the usual circumstances of health care practice²".* Relative effectiveness analysis is performed to inform the various stakeholders, and the scope and design of the research may be different in each case/stakeholder group.

Post-marketing effectiveness studies may be requested when reimbursement is conditional on evidence generation, and may also be incorporated into future regulatory requirements (Post Authorisation Efficacy Studies). There are two broad methodologies that are used to generate 'Real World' evidence of RE in the *post-launch* setting:

- Observational research: retrospective (database) studies and prospective non-interventional studies, providing information on the existing standards of care and practice patterns
- Pragmatic controlled trials (PCTs): designed to minimise the effect of study protocol on patient care and treatment outcomes, generally characterised by diverse study populations (approaching those encountered in routine clinical

practice), limited exclusion criteria, no blinding of treatment, and an observational style follow-up. They therefore provide a higher degree of external validity, yet maintain internal validity through the benefits of randomization.

When considering novel research approaches to relative effectiveness *pre-launch*, purely observational studies of investigational drugs are not possible. More pragmatic trials might be undertaken prior to launch, with the potential to better inform estimates of real-world RE and deliver a greater understanding of the value of new medicines to patients and health care systems with a lower degree of uncertainty at an earlier point in time. This will facilitate decision-making when considering new evidence requirements after the initial approvals.

Bringing an understanding of RE into earlier stages of R&D research will help the developers of new medicines to focus funding on therapies and disease areas where value is most likely to be delivered to patients and health care systems.

PROBLEM STATEMENT

There is an increasing recognition that pivotal RCTs demonstrating efficacy may only provide 'proof of concept' of effectiveness and value for healthcare systems. However, incorporating the additional needs of HTA agencies and other decision makers without compromising the evidence needs of regulatory agencies can be problematic, resulting in more complex clinical development programmes putting pressure on costs and efficiency.

It is important to consider when the different types of effectiveness measures used for different purposes (to inform patients, health care professionals, HTA agencies or health care policy makers) can be generated most effectively, and to develop a private/public consensus over best practice.

In making choices between the options for clinical development programmes, Pharma R&D groups need more certainty as to: the impact of development choices (e.g. adjusting pivotal RCTs or introducing additional studies focusing on developing RE evidence) on the regulatory review process; the value of different programmes to HTA bodies and other decision makers; the balance of pre-launch and post-launch effectiveness research and the coordination of post-launch assessment commitments. There is little guidance on how to incorporate alternative study designs into a development programme to optimally meet the needs of all stakeholders over time. There is a risk that novel regulatory initiatives (such as Conditional Authorisation or Adaptive Licensing) put further pressure on availability of evidence for HTA at launch.

When specifically considering introducing more pragmatic trial designs into the period before launch there are a number of research issues that need to be addressed:

- Selection of design options in the spectrum of explanatory to pragmatic
- Open-label designs and biases related to experimental drugs
- Feasibility, sample size, power and statistical analysis
- Regulatory concerns e.g. safety and equipoise
- Methods used for safety monitoring
- Choice of relevant endpoints
- Choice of alternative treatment strategies and comparators, including mixed Standard of Care (SOC) arms, comparators used off label, non-medication interventions (e.g. surgery and radiotherapy)
- Timing of study initiation relative to regulatory process
- The ability to represent 'natural' care in pre-launch trials
- Logistics such as drug supply through pharmacies

- Use of non-expert sites and investigators.

There are also outstanding questions on how best to translate and incorporate the results of such effectiveness studies in evidence reviews:

- How to generalise results from one setting/country to another
- How best to integrate data and results from different types of study
- How to use modelling to estimate effectiveness against different comparators or in health care systems with different care pathways (to those in the source effectiveness study).

NEED FOR PUBLIC-PRIVATE PARTNERSHIP

For Pharma R&D, the selection of the optimal late-development strategy for a new medicine is a complex problem, dependent on an understanding of the value frameworks and research philosophies of multiple public sector stakeholders. There is a growing scientific and educational need for Pharma R&D to better understand the principles of Health Technology Assessment and the methodological tools available to generate evidence of relative effectiveness.

At the time of the initial assessments of a new medicine, the public sector review bodies are dependent on Pharma R&D groups for the generation of meaningful data that support robust evidence-based decision making.

Development of a public-private partnership in this space will reduce barriers and stimulate sharing of insights and know-how across the relevant stakeholders. The development of a shared framework of best practice and evidence quality is essential in order to allow Pharma R&D groups to raise the relevance and quality (and therefore the credibility) of clinical and outcomes research estimating relative effectiveness at launch, provided to HTA groups and other decision makers. It will also help to reach a consensus on the appropriate balance of research pre- and post-launch. Collaboration between all stakeholders, academic groups, industry, regulators, HTA bodies, patient groups and other decision makers, is critical to develop a best practice model with an open outcome approach.

Collaboration with regulatory and reimbursement agencies would bring clear guidance on interpretation of existing policy statements and new assessment processes being developed; and it will help to assess the utility of different study design options. The agencies would benefit from the increased quality and relevance of evidence provided to them by Pharma R&D at initial assessments, and from an increased alignment of expectations for evidence generation before and after marketing authorisation.

Academic centres would bring expertise in the design and analysis of different types of clinical and outcomes studies and in evidence synthesis and modelling. Such groups would benefit from being able to work with both evidence providers and users in developing new methods and running pilot projects.

Collaboration with health care provider networks, including physicians and hospital groups, retail pharmacies and other health care professionals, would allow access to existing (routine) data collection systems and valuable insights into the efficient execution of more pragmatic study designs in their patient populations and care pathways. These providers would benefit from the increased relevance of clinical evidence to everyday clinical practice and decision making, and from the opportunity to influence both evidence providers and assessment bodies.

Patient groups provide insights into appropriate endpoints/outcomes used for assessing effectiveness, and into factors which affect the effectiveness of treatments in the real

world. Patients will benefit from any improvement in access to new medicines; from the improved relevance of evidence to their actual clinical experience; and from the opportunity to engage and influence developers and assessors of new medicines.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

There is currently a strong interest on evidence generation and assessment of relative effectiveness research at the time of marketing authorisation and afterwards, as well as on the provision of early scientific advice to pharmaceutical developers addressing HTA as well as regulatory needs.

There is an outstanding need to ensure that the different strands of research are appropriately woven together to build a public-private consensus over best practice in the timing, execution and use of observational research, pragmatic research and modelling research to support regulatory and reimbursement decision-making.

There are ongoing initiatives where synergies and complementarities should be explored to avoid duplication of efforts and bring added value, in particular EUnetHTA Joint Action 2 (2012-15); EMA (Post Authorisation Efficacy Study), GPRD, AHRQ, Tapestry, NICE/MHRA, CTTI, CMTP/GPC, NEWDIGS, CAVOMP and PCORI in the US.

There are a number of IMI projects where collaboration should be explored in particular EHR4CR, EMIF, PROTECT, as well as education and training programmes such as EU2P and EUPATI.

OVERALL OBJECTIVES

It is critical to focus the research objectives on disease areas where value is most likely to be delivered to patients and health care systems, in particular in diabetes, cardiovascular diseases, respiratory, oncology, and neurology.

- Assess existing methodologies and develop new research methodologies to be tested in pilot studies to improve quality of information generated to inform both benefit-risk and real world effectiveness at critical points in the assessment of medicines,
- Research how and at which stage Relative Effectiveness can be incorporated in R&D drug development plans,
- Identify research options, including trial designs, endpoints and outcome measures that may be used in both clinical trials and observational studies,
- Develop open tools to assess the value of new medicines which would increase the confidence and consistency of decisions that HTA bodies and other decision makers may take, affecting patient access and the ability for patients to benefit from new medicines,
- Develop training activities on relative effectiveness research, in particular on the value of new medicines to patients and providers, for a better understanding and awareness in R&D,
- Identify research issues and develop pragmatic designs to address difficulties associated with generating evidence of relative effectiveness before launch.
- Develop and pilot approaches to analyse and incorporate the results of effectiveness studies in evidence reviews to foster discussions/decisions between industry, regulatory authorities, HTA and reimbursement agencies on:
 - reasonable expectations for evidence available at launch,
 - the robustness of predictive models,
 - the value of further evidence collected after launch

EXPECTED KEY DELIVERABLES

- Analyses of:
 - the “relative effectiveness questions” of interest to patients, health care professionals and assessment bodies;
 - the scope of different relative effectiveness reviews;
 - and relevant comparators (including non-drug treatment strategies) specified by HTA agencies in different countries, and the reasons for these choices.
- Development of a decision-making framework for Pharma R&D for the systematic identification and assessment of different development strategies considering:
 - the incremental value of information from a study programme in the estimation of relative effectiveness at launch and after launch
 - technical and practical issues related to different designs
 - interaction with regulatory, HTA and other review processes
- A “toolbox” of study designs in specific disease areas categorised according to their best fit in the drug development timeline. This will facilitate R&D planning, by giving clear alternative options for evidence generation strategies:
 - Clinical trials that meet regulatory requirements for phase IIIa evidence and also address relative effectiveness questions,
 - Clinical trials that would not be suitable to address regulatory requirements, but would inform relative effectiveness questions and are feasible pre-launch IIIb studies,
 - Clinical trials and observational studies that are not feasible pre-launch but could address relative effectiveness questions as post launch studies, including regulatory and reimbursement commitments (e.g. PAES).
- A “hierarchy of evidence” for relative effectiveness to indicate to R&D and to assessors the level of robustness of different evidence used in assessing a medicine’s value in real world use:
 - Clinical trial designs and features that address factors most responsible for differences between efficacy and effectiveness, including possible trade-offs between internal/external validity and transferability,
 - Analyses which predict RE from phase II and III RCT efficacy studies alone,
 - Analyses that integrate regulatory RCTs, additional relative effectiveness trials and observational study data,
 - Analyses that predict relative effectiveness in one country from data on relative effectiveness derived in another.
- Development and validation of tools for assessing and choosing comparators (drug and non-drug strategies) to facilitate R&D decision
- Development of guidance in specific disease areas on the practical implementation of real world research methods and modeling techniques pre-launch, incorporating input from regulatory and HTA bodies
- Development of a training programme/tool for R&D on relative effectiveness for clinical development
- White papers, results of pilot studies, and scientific publications

EFPIA PARTICIPANTS

GlaxoSmithKline [lead company], Sanofi [co-lead company], Amgen, Astra Zeneca, Bayer Healthcare, Boehringer Ingelheim, Bristol Myers-Squibb, Eli-Lilly, Merck, Merck Serono, Novartis, Novo Nordisk, Roche, Takeda.

The EFPIA partners will provide:

- clinical trial and effectiveness study data sets in the disease areas
- insights regarding study RE design elements proposed in pre-launch studies
- expertise in the relevant disease areas
- expertise on modelling/analytical techniques
- expertise in outcomes research
- expertise in clinical trial design and operations
- expertise in epidemiology
- expertise in statistical analysis
- expertise in regulatory affairs
- expertise in health economics

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 3 years.

INDICATIVE BUDGET FOR THE PROJECT

Indicative total in kind contribution from the EFPIA companies is EUR 8 million and the indicative IMI JU contribution will be up to EUR 8 million.

APPLICANT CONSORTIUM

The applicant consortium should address all research objectives outlined in the call text using case studies from each of the following key disease areas: diabetes, cardiovascular disease, respiratory, oncology and neurology. The consortium may suggest additional disease areas or indications (e.g. multiple sclerosis) of particular relevance to the research objectives.

The consortium is expected to be:

- A multi-disciplinary grouping, enabling effective communication between key stakeholder groups (e.g. international academia, regulatory agencies, HTA bodies, reimbursement agencies, health care budget holders, and patient groups).
- Pan-European in nature to ensure frameworks and procedures developed through the course of the project are relevant for a broad range of European countries.

The consortium is expected to have an established expertise in the following scientific areas relevant to the proposal:

- Clinical expertise in the key disease areas
- Clinical trial expertise (design and operations, including Good Clinical Practices)
- Analytical expertise to conduct retrospective analysis of existing datasets to compare trial results; and to identify the factors that affect translation from RCT results to effectiveness outcomes
- Bayesian approaches to study planning, analysis and modelling
- Strategic simulation methodology / complex decision making analysis

- Survey and questionnaire design
- Knowledge of the regulatory and HTA requirements across Europe
- Regulatory affairs policy development
- Health care ethics and legislation
- Health Economics and Outcomes Research
- HTA expertise and/or experience in making or influencing access decisions HTA policy expertise
- Patient and carer experience and interaction with health care system, patient reported outcomes

The applicant consortium will also provide:

- access to local effectiveness databases in their countries (e.g. from sickness funds, primary care consortia, registries).

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The applicant consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The architecture below for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

Work Package 1: Developing a framework for the assessment of development strategies addressing relative effectiveness objectives

The aim of this work package is to create the decision-making framework for Pharma R&D for the systematic identification and assessment of different development strategies, considering:

- the incremental value of information from the study programme in the estimation of relative effectiveness at launch and after launch
- the technical and practical challenges of different designs
- the interaction with regulatory, HTA and other review processes.

A key desired activity is to run “strategic simulations” of different development strategies/study programme options with multiple stakeholders to predict overall impact on regulatory and HTA/reimbursement processes and decisions.

Key inputs will be:

- Clearly mapped current regulatory and reimbursement decision making processes and possible future processes
- A systematic review and analysis of:
 - the “relative effectiveness questions” of interest to patients, healthcare professionals and assessment bodies;
 - the scope of different relative effectiveness reviews;
 - and the relevant comparators (drugs and non-drug treatment strategies) specified by HTA agencies in different countries – including the reasons for these choices, and any changes emerging during a drug development timeframe.

- The outputs from WP2 and WP3 (the development strategy options, assessment of value of information and assessment of operational feasibility) and from WP4 (options for evidence synthesis and modelling)

A “toolbox” of study designs will be developed in specific disease areas categorised according to their best fit in the drug development timeline. This will facilitate R&D planning, by giving clear alternative options for evidence generation strategies.

The final framework should be structured so that a range of study designs could be identified for any disease area/indication of interest, classified into the following types:

- Clinical trials that meet regulatory requirements for phases II, IIIa evidence and also address relative effectiveness questions;
- Clinical trials that would not be suitable to address regulatory requirements, but would inform relative effectiveness questions and are feasible pre-launch IIIb studies;
- Clinical trials and observational studies that are not feasible pre-launch but could address relative effectiveness questions as post launch studies, including regulatory and reimbursement commitments (e.g. PAES).

Other deliverables should include:

- Detailed guidance on the application of real world research methods and modelling techniques pre-launch in specific disease areas including a shared assessment of the strengths and weaknesses of each approach.
- A “hierarchy of evidence” for relative effectiveness to indicate to R&D and to assessors the level of robustness of different evidence used in assessing a medicine’s value in real world use.
- An evidence-based decision tool for assessing and choosing comparators (drugs and non-drug treatment strategies).

EFPIA contribution: Provision of clinical trial and effectiveness study data, outcomes research expertise, disease area expertise, expertise in clinical trial design and operations, epidemiologists, statistical analysis expertise, regulatory affairs experts, health economics expertise.

Work Package 2: Understanding how different possible registration RCTs and IIIb studies inform the assessment of Relative Effectiveness

Identify case studies across the target disease areas where both clinical trial data and ‘real world’ data are available. Compare in pilot studies, results from Phase IIIa studies used for registration with subsequent effectiveness data, and identify factors most responsible for any differences between efficacy and effectiveness.

Expand these case studies or identify new case studies to assess how well alternative designs would improve the assessment of RE at launch: systematically identify critical drivers of real world effectiveness; describe (a “toolbox” of) research/study options that address these; assess the value of information gained (exploring differences by country); and characterise the possible studies in terms of their internal/external validity and transferability.

Identify the critical drivers of real world effectiveness for use in study design task, for example in pilot studies; consolidate data from the literature with data available from within the consortium to summarise:

- Clinically meaningful patient subgroups based on actual care pathways
- Use of drugs within defined treatment strategies
- Most relevant outcome measures /endpoints
- Critical patient and healthcare organisational factors that may drive variability of patient outcome in actual clinical practice for any given treatment strategy (efficacy to effectiveness translational factors)
- Most appropriate comparator/s (drug and non-drug treatment strategies) for key subgroups (as comparators often have an uncertain effectiveness evidence-based, a systematic review of comparator data available could be undertaken to inform recommendations for comparator selection for each case study).

EFPIA contribution: Provision of clinical trial and effectiveness data, outcomes research expertise, disease expertise, expertise in clinical trial design and operations, epidemiologists, statistical analysis expertise, regulatory affairs experts.

Work Package 3: Addressing operational aspects of conducting pragmatic clinical trial designs pre-launch

The aim of this work package is to develop a better understanding of how methodology and study designs developed and used mainly for post launch RE can be applied successfully to investigational (unlicensed) medicines, identifying potential operational solutions to key issues.

Using the combined experience of the consortium with respect to incorporating RE design elements in pre-launch studies, work should be undertaken to establish:

- a) operational barriers for this type of research and how they were or were not overcome
- b) feedback obtained from regulatory agencies, by country and by disease area.

Using the research/study options from WP2, assess different trial designs against current regulatory guidance/opinion and operational challenges; highlighting by disease/indication or country:

- Degree to which design meets HTA agencies' technical guidance
- Any conflict with regulatory guidance
- Ethical/legal issues concerning study of investigational medicines
- Operational impacts of different designs e.g.
 - study size
 - enrolment rate
 - timing of study start, duration, availability of data
 - complexity
 - investigators experience
 - patients' willingness to participate

For key issues, propose operational solutions and identify areas for further regulatory discussion (e.g. use of EHR, monitoring and safety reporting options, adaptive designs, interim reports, site training, drug supply).

EFPIA contribution: provision of insights regarding study RE design elements proposed in pre-launch studies, sharing regulatory feedback on proposed study designs, clinical operations expertise, analytical expertise.

Work Package 4: Evidence synthesis and modelling

The aim of this work package will be to address 3 key questions:

- 1) How well can Relative Effectiveness be estimated from phase II and III RCT efficacy studies alone?
- 2) How should RCTs, additional relative effectiveness studies and observational data best be integrated to address specific decision making needs of regulatory and HTA bodies at launch?
- 3) How can relative effectiveness in one country be modelled from raw data on relative effectiveness in another?

Evidence synthesis methodology should be systematically reviewed for application in specific disease areas to establish and pilot methodological approaches that may create more robust estimates of effectiveness from Phase IIIa efficacy data.

Using the same pilot data utilised in WP2, RE should be predicted in a target country by using different methods (and pilots of new methods) to model from the Phase IIIa data (and the different methodologies compared). The results should be compared with results from real world data in that country. Modelling could be performed using a) only published data, and b) detailed study datasets available from consortium members; the differences in robustness of estimates could be assessed.

This approach should then be extended to identify the uncertainty in transferring RE estimates across a range of countries, and how that uncertainty can be minimised by integrating RCT data with other study data and local data on country health care patterns. Evidence synthesis methods that may be used to combine and interpret data from different study types (e.g. pooling/meta-analysis, modelling, Bayesian models) will be summarised (including the statistical challenges) and guidance developed for their selection in different product development scenarios.

Proposed methodologies should be discussed with regulatory and HTA groups to understand any concerns they may have with the proposed approaches so that these may be addressed.

EFPIA contribution: modelling/analytical expertise, study data sets, experts in regulatory affairs

Work Package 5: Project Management and dissemination

This work package will address:

- the strategy and the governance structure which will facilitate collaboration with other ongoing initiatives in particular links with relevant governance systems (both national and European).
- the implementation of the management of the project, encouraging regular meetings and interaction between sub-groups and teams, to coordinate the work effort, communication and dissemination strategy of the project.