



Innovative Medicines Initiative

**IMI2 JU Annual Work Plan 2014
as amended by the Governing Board on 17 December 2014**



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FOREWORD

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is now established as an efficient public-private partnership (PPP) that fosters high quality collaborative projects bringing together the different stakeholders involved in drug development. By consistently ensuring a fair selection of applicant consortia and facilitating agreements between the different partners, IMI JU has come to be appreciated as an effective neutral platform.

At the same time, the new challenges faced by the pharmaceutical industry and the healthcare sector at large have led IMI JU to revisit its priorities for the future. The current objective is to address the needs common to industry and society by focusing on major public health issues and ensuring a permanent dialogue with regulatory authorities and patient organisations.

This document, initially adopted by the Governing Board in December 2013, has been updated to reflect IMI2 entry into force and associated requirements and features.

In 2014, IMI JU will continue to manage its portfolio of 46 projects and will carry out the evaluation and kick-off of projects resulting from Calls for proposals launched in the second half of 2013. As running projects are progressing and maturing, specific efforts will be dedicated to document and monitor progress, notably through key performance indicators, and best exploit outputs. In parallel, IMI JU's communication activities will be further expanded by conducting outreach campaigns targeting different audiences. Furthermore, IMI JU will continue to ensure the delivery of high-quality work according to strict ethical standards, administrative and financial processes which will be continuously reviewed and adapted as needed.

IMI JU will also start implementing recommendations arising from the second interim evaluation, and most notably the following:

- A more articulate communication strategy with clear and measurable goals and objectives, addressing both the key stakeholders and a wider audience;
- Expanding the key performance indicators (KPI) framework to better demonstrate IMI impacts and socio-economic benefits;
- Further enhancing the efficiency of the Executive Office.

With an enthusiastic team fully committed to fulfil our ambitious mission, I am confident that 2014 will set the stage for a successful future!



Michel Goldman
Executive Director

1 OBJECTIVES, TRANSITION TO IMI2 JU AND KEY PERFORMANCE INDICATORS

1.1 Strategic Objectives and transition to IMI2 JU

IMI JU was set up by Regulation (EC) No 73/2008 of the Council of 20 December 2007 as one of the instruments of the European Commission's Seventh Framework Programme (FP7) for research, technological development and demonstration activities. The Joint Undertaking was entrusted with the important goal of significantly improving the efficiency, effectiveness and quality of the drug development process needed to bring innovative and safer innovative medicines to patients.

Over the past six years, IMI JU has already effectively facilitated the mobilisation of 46 public-private consortia which are delivering results of high relevance to healthcare challenges. The Joint Undertaking is recognised globally as the leading business model for PPP in healthcare, having consistently and effectively demonstrated the feasibility and added value of large, multi-stakeholder PPPs for research and development in biomedicine. IMI JU has achieved this by building trust and pioneering collaboration among a wide range of participants including the European pharmaceutical industry, academia, patient groups, regulatory and small to medium enterprises (SMEs). It has also served as a unique and neutral platform for leveraging research strengths, allowing access to other partners' expertise and for fostering open innovation across Europe in healthcare research and development.

The success of IMI JU has led to the adoption on 6 May 2014 of Regulation No 557/2014 by the Council of the European Union for the setting up Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) with a lifespan of ten years, until 31 December 2024. IMI2 JU for all intents and purposes replaces and succeeds IMI JU, and apart from implementing its own objectives under the EC's Horizon 2020 Framework Programme, it will also continue to achieve the objectives of IMI JU, including the implementation of the remaining actions and providing continued support to the research programme initiated under FP7.

The main policy objectives of both IMI JU and IMI2 JU are broadly set out in the respective Council Regulations, with the combined aims being to:

- develop and implement pre-competitive research and innovation activities of strategic importance to the European Union (EU)'s competitiveness and industrial leadership;
- address specific societal challenges;
- improve European citizens' health and wellbeing;
- pool resources and foster knowledge sharing and collaboration; and
- promote the involvement of SMEs in its activities.

The Strategic Research Agenda is the main reference for the implementation for research priorities of both IMI JU and IMI2 JU. The first annual scientific priorities for IMI2 JU for the remaining part of 2014 are summarised in Section 2. These are based on the new Strategic Research Agenda (SRA) for IMI2 JU which is publically available at <http://www.imi.europa.eu/content/imi-2#SRA>.

In addition, in the case of IMI2 JU, the Regulation also sets out how, from its establishment in 2014, the Joint Undertaking will gradually seek to contribute towards health research and development.¹ These expected outcomes will be important in the longer term as IMI2 JU implements the programme under the framework of Horizon 2020.

1.2 Annual Objectives, Key Performance Indicators and Related Targets

An updated set of annual objectives of IMI2 JU, for the remaining part of 2014, have been developed for the measurement of performance and progress in 2014, together with the associated KPIs and targets. These take into account:

- The continued implementation of actions related to IMI JU and the establishment of IMI 2 JU in 2014;
- The experience gained so far in developing KPIs, metrics and other qualitative assessment for measuring the results and achievements of IMI JU;
- The longer-term objectives and aspirations of IMI2 JU under Horizon 2020.

The 2014 annual objectives and KPIs, presented in Table 1 overleaf, are linked to the main policy objectives of IMI2 JU (established under Council Regulation 73/2008 of 20 December 2007) and IMI2 JU (replacing and succeeding IMI JU and established through Council Regulation 557/2014 of 6 May 2014) and measure performance on the following key strategic areas of the Joint Undertaking's activities, namely:

1. the coverage of the research **portfolio**, i.e. adequate implementation of the new annual scientific priorities under IMI2 JU,
2. the degree of **progress** of IMI projects in delivering pre-set results and achieving targeted **research performance** under IMI JU,
3. the impact of the IMI programme on the **regulatory framework** as well as **EU competitiveness**,
4. the level of **collaboration** and **SME participation** so far,
5. the level of **involvement of patients groups**, and
6. the overall **efficiency**, **budget execution** and **the level of awareness** of the new Programme Office (formerly known as Executive Office) covering both IMI JU and IMI2 JU.

In addition, the Programme Office will also continue to measure and track, with the assistance of external consultants and service providers, other aspects of the Joint Undertaking's 2014 performance, outputs and impact using different methods for reporting results and outcomes including qualitative assessments, periodic scoreboard and other metrics. These will continue to reflect the evolution and needs of the Joint Undertaking and its stakeholders and the longer term outputs and impact of both the IMI and IMI2

¹ According to Article 2(b), IMI2 JU will aim to:

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

programmes for the ultimate benefit of patients, as well as European competitiveness, economic growth, and advancement of science and innovation.

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Key Strategic Focus	Annual Objectives 2014	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2014 Target
		73/2008 of 20.12.2007 ²	557/2014 of 6.05.2014 ³			
Portfolio	IMI2 JU's new calls for Proposals support the implementation of the research priorities as set out in the Strategic Research Agenda and updated by the Governing Board	<ul style="list-style-type: none"> Article 2(a) and 2(b) Article 1(c) in Statutes of IMI JU 	<ul style="list-style-type: none"> Article 2(a) Article 1(b) in Statutes of IMI2 JU 	KPI 1: Target number of priority areas defined in IMI2 JU's Annual Scientific Priorities for 2014 that are addressed by IMI2 JU call for proposals launched in 2014	Extent of coverage of priority areas for 2014 as defined in Section 2 of the IMI2 JU Annual Work Plan for 2014 (updating the IMI JU Annual Implementation Plan for 2014)	KPI 1: ≥4 priority areas from IMI2 JU's Annual Scientific Priorities for 2014
Scientific Output	IMI JU projects effectively deliver and disseminate high quality outputs ⁴	<ul style="list-style-type: none"> Article 2(a) and 2(b) 	<ul style="list-style-type: none"> Article 2(a) and 2(b) 	KPI 2: Target estimated percentage of IMI JU projects that are assessed by the Programme Office as having achieved at least 100% of pre-set deliverables by the last reviewed reporting period by the end of the year	Progress for each project is calculated by the responsible IMI Scientific Officers, on the basis of cumulative achievements reported from the project start date up to the last reviewed reporting period by the end of the year	KPI 2: ≥80% of IMI JU projects
				<ul style="list-style-type: none"> Article 2(a) and 2(b) 	<ul style="list-style-type: none"> Article 2(a) and 2(b) 	<p>KPI 3: Target estimated average number of IMI publications⁵ per €10 million of total IMI JU funding requested by the projects</p> <p>KPI 4: Target to measure extent to which IMI JU's estimated average impact factor of journals in which IMI publications⁵ have been published is higher than the EU average</p> <p>KPI 5: Target to measure extent to which IMI JU's estimated citation impact of IMI publications⁵ is higher than the EU average</p> <p>KPI 6: Target to measure the extent to which IMI JU's bibliometric results compare with those of other international funding bodies</p>

² OJ L 30 of 4.2.2008

³ OJ L159 of 7.6.2014

⁴ During 2014, initial baseline data will also be collected and analysed on the number of patents resulting from IMI JU projects, particularly on the first finalised projects.

⁵ Covering all publications resulting from IMI projects from the start of IMI JU up the end of the year under review.

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Key Strategic Focus	Annual Objectives 2014	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2014 Target
		73/2008 of 20.12.2007 ²	557/2014 of 6.05.2014 ³			
Impact on regulatory framework and standardization	IMI JU projects translate key scientific discoveries into clinical practice and regulatory framework	<ul style="list-style-type: none"> Article 2 Article 1(e) in Statutes of IMI JU 	<ul style="list-style-type: none"> Article 2 Article 1(b) in Statutes of IMI2 JU 	<p>KPI 7: Target to measure the number of scientific advice and qualified opinions initiated by the IMI projects at the EMA and FDA</p> <p>KPI 8: Target to measure the number of regulatory guidelines derived from IMI projects</p> <p>KPI 9: Target to measure new standards and best practices derived from IMI projects</p>	<p>The main source of information is the annual periodic reporting, as well as close follows up of the project by the respective Scientific Officers through attendance of the project annual meetings, and other exchanges</p> <p>Each Scientific Officer will report annually during the preparation of the Annual Activity Report</p> <p>If necessary, additional complementary information may also be collected as part of an annual survey of the consortia</p> <p>For KPI 8 and KPI 9, the methodology for capturing information and the baseline data for establishing the targets will be determined in 2014-2015</p>	<p>KPI 7: ≥ 5</p> <p>KPI 8: Not applicable in 2014</p> <p>KPI 9: Not applicable in 2014</p>
Business development and sustainability	IMI JU projects increase EU competitiveness and foster innovation	<ul style="list-style-type: none"> Article 2 	<ul style="list-style-type: none"> Article 2 	<p>KPI 10: Target to measure, on average, the number of patent applications filed and/or awarded to those IMI projects which have been reimbursed at least for the third year of implementation</p> <p>KPI 11: Target to measure impact on competitiveness</p> <p>KPI 12: Target to measure the number of spin-off companies or foundations created as a result of IMI projects</p>	<p>The main source of information is the annual periodic reporting, as well as close follows up of the project by the respective Scientific Officers through attendance of the project annual meetings, and other exchanges. Each Scientific Officer will report annually during the preparation of the Annual Activity Report</p> <p>If necessary additional complementary information may also be collected as part of an annual survey of the consortia</p> <p>For KPI 11, the methodology for capturing this information from industry and other sources and the baseline data for establishing the target will be determined in 2014-2015</p>	<p>KPI 10: ≥2 patent applications per € 10 million of costs accepted and reimbursed by IMI JU. ⁶</p> <p>KPI 11: Not applicable in 2014</p> <p>KPI 12: 25% of finalised projects</p>

⁶ The calculation will be based on the total value of interim and final payments made by IMI by the end of the year under review to projects that have completed at least the third year of implementation and the total amount will be divided by the cumulative number of patents filed and/or awarded to these projects.

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Key Strategic Focus	Annual Objectives 2014	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2014 Target
		73/2008 of 20.12.2007 ²	557/2014 of 6.05.2014 ³			
SME participation	IMI JU projects promote the participation of SMEs	<ul style="list-style-type: none"> Article 2(e) 	<ul style="list-style-type: none"> Article 2(a) Article 1(c) in Statutes of IMI2 JU 	<p>KPI 13: Target percentage of participants in signed Grant Agreements that are SMEs</p> <p>KPI 14: Target percentage of overall budget for projects that has been allocated to SMEs</p>	<p>Calculation is based on the latest available data extracted from IMI applications SOFIA and QlikView. Participations in IMI JU projects may count the same organisation multiple times when the same organisation is involved in several project in line with current practice.</p> <p>All participations from the start of IMI JU up the end of the year under review are considered in this calculation</p>	<p>KPI 13: ≥20%</p> <p>KPI 14: ≥20%</p>
Patient participation	IMI JU projects promote the involvement of patient organisations	<ul style="list-style-type: none"> Article 2 	<ul style="list-style-type: none"> Article 2(a) Article 1(c) in Statutes of IMI2 JU 	<p>KPI 15: Target percentage of projects involving patients organisations as consortium partners, members of Advisory Boards, Ethical Advisory Boards or on consultancy basis for topics of relevance</p> <p>KPI 16: Target to measure impact for patients</p>	<p>Calculation is based on the latest available data extracted from IMI applications SOFIA and QlikView for the project partners</p> <p>Participations in IMI JU projects may count the same organisation multiple times when the same organisation is involved in several project in line with current practice</p> <p>If necessary, additional complementary information may also be collected as part of an annual survey of the consortia</p> <p>For KPI 16, the methodology for capturing this information and baseline data for establishing the target will be determined with the European Commission in 2014-2015</p>	<p>KPI 15: 100%</p> <p>KPI 16: Not applicable in 2014</p>
Socio-economic impact	IMI JU projects lead to job creation and increased economic activity	<ul style="list-style-type: none"> Article 2 	<ul style="list-style-type: none"> Article 2 	<p>KPI 17: Target to measure the estimated number of reported jobs created since the start of IMI JU and that can be considered as directly related to the IMI programme</p> <p>KPI 18: Target to measure additional impact on healthcare systems</p>	<p>Total number of jobs created will be reported. The data will be collected directly from the consortia via an annual survey</p> <p>For KPI 18, the methodology for capturing the information and the baseline data for establishing the target will be determined in 2014-2015</p>	<p>KPI 17: ≥ 1500</p> <p>KPI 18: Not applicable in 2014</p>

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Key Strategic Focus	Annual Objectives 2014	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2014 Target
		73/2008 of 20.12.2007 ²	557/2014 of 6.05.2014 ³			
Information, communication and dissemination	The Programme Office raises the awareness of IMI JU and IMI2 JU among all target groups	<ul style="list-style-type: none"> Article 1(g) in Statutes of IMI JU 	<ul style="list-style-type: none"> Article 1(i) in Statutes of IMI2 JU 	<p>KPI 19: Target number of average monthly visitors to the IMI website</p>	<p>Average number of monthly unique visitors as reported by Google Analytics for the year under review</p> <p>For KPI 20, the methodology for capturing the information and the baseline data for establishing the target will be determined in 2014-2015</p>	<p>KPI 19: ≥10 000</p>
				<p>KPI 20: Target to measure the performance of communication activities</p>		<p>KPI 20: Not applicable in 2014</p>
Efficiency of the Programme Office	The Programme Office meets the timeframe for Time to Grant (TTG) established by the EU for Horizon 2020	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Article 17 	<p>KPI 21: Target timeframe for TTG of 240 days</p>	<p>Comply with the timeframe set out in the Horizon 2020 Rules for Participation (Article 20.2 in Regulation (EU) No 1290/2013)</p> <p>Average Time to Grant (TTG) for a two stage evaluation is defined as the time between the deadline for the submission of a Full Project Proposal and the signature of the grant agreement. This will be calculated annually for each grant agreement signed during the year under review</p>	<p>KPI 21: ≤240 days</p>
	The Programme Office achieves high levels of performance in its annual budget execution	<ul style="list-style-type: none"> Article 1(l) in Statutes of IMI2 JU 	<ul style="list-style-type: none"> Article 1(f) in Statutes of IMI2 JU 	<p>KPI 22: Annual budget execution target for commitment appropriations of running costs</p>	<p>Extracted from annual figures compiled for IMI JU report on the budgetary and financial management</p>	<p>KPI 22: ≥95%</p>
				<p>KPI 23: Annual budget execution target for commitment appropriations of operational costs</p>		<p>KPI 23: ≥95%</p>
	The Programme Office meets the maximum time limits for expenditure operations established by the EU			<p>KPI 24: Annual budget execution target for payment appropriations of operational costs</p>		<p>KPI 24: ≥95%</p>
				<p>KPI 25: Annual Average Time to Pay (TTP) target for pre-financing payments to beneficiaries</p>	<p>Comply with time limits as established in the EU's Financial Regulation (Article 92 in Regulation (EU, EURATOM) No 966/2012)</p>	<p>KPI 25: ≤30 days</p>
				<p>KPI 26: Annual Average TTP target for interim payments to beneficiaries</p>		<p>KPI 26: ≤90 days</p>

2 SCIENTIFIC PRIORITIES FOR 2014

2.1 Introduction

The Scientific Priorities for 2014 reflect the principles of the Council Regulation on the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, specifically:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs);
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including micro, small and medium sized enterprises⁷ from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries while ensuring generally a balanced approach in terms of gender matters etc.). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The Scientific Research Agenda (SRA) for IMI2 (see <http://www.imi.europa.eu/content/imi-2>) sets out the framework that underpins the development of specific projects or research programmes to be prioritised for funding.

Twelve key health priorities have been identified on the bases of the WHO Priority Medicines Report, and it is anticipated that throughout the lifetime of IMI2, many of these health priorities will be addressed. The SRA furthermore identifies data and knowledge management as key enabling technologies and education and training and excellence in clinical trial implementation as key implementation strategies.

The SRA places the research objectives of IMI2 under four major research axes:

1. target validation and biomarker research (efficacy and safety);
2. adoption of innovative clinical trial paradigms;
3. innovative disease prevention, interception and treatment solutions;
4. patient-tailored adherence programmes.

The activities generated from the priority areas will be designed considering relevant differentiating enablers for early and effective patient access to innovative prevention and treatment solutions (Medicines Adaptive Pathway to Patients-MAPPs-⁸):

- target validation based on human biology;
- stratified medicine, precision medicine;
- innovation in clinical trials for new drugs and therapeutic modalities;

⁷ See Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 and in particular Article 1 (micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million)

⁸ Press release: European Medicines Agency launches adaptive licensing pilot project: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002046.jsp&mid=WC0b01ac058004d5c1

- data generation and interpretation (knowledge management);
- prevention, disease interception, patient adherence (incl. societal acceptance of vaccines);
- patient-centric approach – effect on medical practice and outcomes (health/disease management);
- regulatory framework (including pharmacovigilance);
- reimbursement/patient access.

Using the framework of the SRA, the 2014 Priorities for the design of the first IMI2 Call topics have been selected on the basis of their potential to foster a first set of high impact initiatives, in areas where the maximum number of stakeholders can join forces. In particular five therapeutic areas (including rare forms of diseases) and cross-cutting themes have been identified:

- 1) metabolic disorders;
- 2) neurodegeneration;
- 3) prevention and treatment of immune-mediated disease, and advancement in prophylactic and therapeutic vaccines for infectious & non-infectious diseases;
- 4) infection control including incentives for reinvestment in antimicrobials, antivirals, and vaccines;
- 5) translational safety.

In addition to these priority areas, EFPIA and/or other industries active in health care may propose further priorities under one or more of the 12 key health priorities or based on emerging needs which are identified in the Scientific Research Agenda. Topics will be selected based on the level of unmet need, the need for a public-private partnership to make a difference, the extent to which the science is capable of delivering a high impact over the next decade, and the synergies/complementarity with similar initiatives. Additional topics might also be considered according to very urgent public-health needs.

To implement these Scientific Priorities, IMI2 will initiate competitive Calls for proposals and any other necessary procedure to evaluate proposals and award funding to projects⁹. Each priority may be implemented via the launch of one or more topics, which might generate one or more multi-stakeholder projects, potentially including (or driven by) other non EFPIA industry partners, or tailor-made projects for specific stakeholder groups. These details will be further elaborated in the course of the maturation of the individual topics.

2.2 General conditions for the calls for proposals

The following general conditions shall apply to the IMI2 Calls for Proposals unless otherwise agreed in the relevant Call Conditions for the specific Call:

All proposals must conform to the conditions set out in the H2020 Rules for Participation (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>

The following general conditions shall apply to the IMI2 Calls for Proposals:

⁹ Please see Article 1 (f) and (g) of the Statutes, annexed to the IMI2 JU Council Regulation.

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation¹⁰ from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

- (a) legal entities established in a Member State or an associated country, or created under Union law; and
- (b) which fall within one of the following categories:
 - (i) micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*;
 - (ii) secondary and higher education establishments;
 - (iii) non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations.
- (c) the Joint Research Centre;
- (d) international European interest organisations.

ADMISSIBILITY CONDITIONS FOR GRANT PROPOSALS, AND RELATED REQUIREMENTS

Part B of the General Annexes¹¹ to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan.

ELIGIBILITY CRITERIA

Part C of the General Annexes to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan.

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan.

EVALUATION

Part H of the General Annexes to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan with the following exceptions:

The criteria, scoring and threshold are described in the IMI2 Evaluation Criteria¹², with the following exception: if a proposal fails to achieve the threshold for a criterion, the other criteria will not be assessed and the evaluation of the proposal will be discontinued.

¹⁰ Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking

¹¹ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-ga_en.pdf

¹² For Research and Innovation Actions, and Innovation Actions:

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/IMI2_C1_S0_Evaluation_form.pdf

For Coordination and Support Actions: [link to be added once published]

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award.¹³ The procedure for setting priority order for proposals with the same score is given in the IMI2 Evaluation Criteria. The proposals will be evaluated against the evaluation criteria (including scoring and threshold) and according to the evaluation procedure described in the call text and as defined in this annual work plan.

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to¹⁴:

- clarify the proposals and help the panel establish their final assessment and scores or
- improve the experts' understanding of the proposal.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

Information on the outcome of the evaluation (first stage) ¹⁵	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
Maximum 5 months from the date of submission to the first stage.	Maximum 5 months from the date of submission to the second stage.	Maximum 3 months from the date of informing the applicants following the second stage evaluation.

Where appropriate and duly justified, IMI 2 JU calls for proposals may follow a single or a two-stage process.

Under the single-stage process, all evaluated proposals will be ranked in one single list. Best-ranked proposals, in the framework of the available budget, will be invited to prepare a Grant Agreement.

Under the two-stage evaluation procedure, the applicant consortium of the highest ranked short proposal (stage 1) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (stage 2). The applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. Such contacts should be done in priority order, i.e. the second ranked proposal should be contacted only after failure of pre-discussions with the first ranked, and the third after the second ranked.

BUDGET FLEXIBILITY

Part I of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award.

¹³ http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/Manual_for_submission_evaluation_grant%20award_2014.06.26.pdf

¹⁴ For Calls for Proposals published after the adoption of this amended Annual Work Plan 2014.

¹⁵ This doesn't apply to IMI2 2nd Call for Proposals.

SUBMISSION TOOL

Unless otherwise stipulated in the relevant Call Conditions of the specific Call, the IMI electronic submission tool [SOFIA](#) (Submission OF Information Application) is to be used for submitting a proposal in response to a topic of the IMI2 Call; no other means of submission will be accepted. Updates of the proposals may be submitted online until the Call submission deadline. Proposals need to be formally submitted in the tool indicated in the Call text to trigger the admissibility and eligibility checks, and the peer review evaluation. Access to the IMI electronic submission tool SOFIA first requires a request to access to the tool.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2014-single-stage/1600139-essential_information_for_clinical_studies_en.pdf.

Ethical issues should be paid due attention for each of the submitted proposals.

In order to ensure excellence in Data and Knowledge Management consortia will be requested to:

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#) "). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be considered.
- 2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).
- 3) In order to make the resources included and generated by the IMI Actions discoverable for metrics and re-use, consortia will be required to disseminate a description of resources¹⁶ according to well-established metadata standards such as the Dublin Core (ISO15836).

Proposals shall contain a draft plan for the exploitation and dissemination of the results.

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, if so foreseen in the relevant Call documents, may publish at a later stage another call for proposals restricted to those projects already selected under that call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would then be entitled to open to other beneficiaries as they see fit.

The call topics to be launched are described in Annex III of this work plan. Furthermore it is foreseen to establish Strategic Advisory Groups in the areas of immunology, metabolism, neurodegeneration, translational safety, and data, Knowledge management and infections control. The contribution that EFPIA companies make to these groups represents contributions to the operational costs of the IMI2 JU.

¹⁶ Examples of Resources are (a collection of) biosamples, datasets, images, publications etc.

2.3 Metabolic disorders

Activities in this priority area should seek progress towards novel diagnostic and treatment paradigms for early onset and progression of diabetes (type 1 and type 2) and its complications, and for early diagnosis and development of novel experimental medicine approaches to safe and efficacious diabetes treatments, considering also health system sustainability of treatment intervention.

Synergies will have to be created with several ongoing EU-wide and global initiatives including ongoing IMI projects such as SUMMIT, IMIDIA and DIRECT. All these efforts are already generating large scale sequencing data, and are performing genome-wide association studies (GWAS), and metabolomic and epigenomic studies in a large number of patients to identify new targets and biomarkers for prediction of disease progression and drug response.

IMI2's activities will build on the progress made through each of these initiatives, continuing to grow the science base required to support a personalised/precision medicine approaches for diabetes.

Activities in this area planned for 2014 will focus for example on one or more of the following:

- Predictive biomarkers, targets and pathways involved in insulin resistance and disease progression in the pre-diabetic stage of the cardio-metabolic continuum should be identified. Of relevance will be early non-glucose-related biomarkers for disease initiation and progression to complications and renal failure, and cardiovascular mechanisms as independent risk factors for type 2 diabetes.
- Tools and methods for the monitoring of key markers of glucose metabolism and diabetes complications using nanotechnologies should be defined.
- Data should be generated to allow a molecular definition of diagnosis criteria, and the determination of the best time point for pharmacological intervention to prevent disease progression to overt diabetes and complications.
- The interactions of immune cells (T-cells) with pancreatic β -cells should be defined, and the development of early predictive biomarkers for the immunodestruction of β -cells should be sought. This should lead to a better understanding of common and rarer immune mechanisms in type 1 diabetes and other auto-immune diseases, paving the way towards a molecular taxonomy of type 1 diabetes.
- Reliable and generally accepted outcome parameters and clinical trial designs for immune therapy in type 1 diabetes patients should be established. This might include comparative experimental clinical trials with different immune-modulatory drugs for a tailor-made, immune-modulating therapy of type 1 diabetes, and the definition of the safety and efficacy parameters, regulatory rules and a roadmap for immune-modulating therapy in newly-diagnosed type 1 diabetes patients.

2.4 Neurodegeneration

Given the healthcare burden that neurodegenerative diseases pose, together with the current disinvestment by major pharmaceutical companies, joint and urgent action from public and private sectors is essential.

The focus will be on the early and correct diagnosis of neurodegenerative diseases, the development of more preventative treatment approaches, the development of innovative patient focused endpoints, trial designs, and simulation and analytical approaches to devise new clinical trial paradigms both pre-and post-marketing. This will be critical to assess outcomes (good and bad) in small patient populations, thus balancing the needs for regulation (efficacy/safety) and HTA (Health Assessment Agencies) agencies (effectiveness/safety), as well as the risk and cost for pharmaceutical companies while responding to the urgent patient needs in this area.

A framework for scaling the collection of biomarker and clinical data is already in place, at least for some neurodegenerative conditions, with successful implementation of worldwide efforts such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). These include IMI's EMIF-AD project, the Joint Programme – Neurodegenerative Disease Research (JPND), the Centre of Excellence Network (CoEN) and UK Dementias Platform supported by the UK's Medical Research Council (MRC) and the German Centre for Neurodegenerative diseases (DZNE) and others. Any new activities undertaken in IMI2 will collaborate with such initiatives and data resources available from academia across Europe to ensure synergies are maximised, and efforts are not duplicated.

Furthermore, important learnings should be generated by tackling alternative neurodegenerative and aging-related diseases with a high societal burden such as ophthalmic indications.

Activities in this area foreseen for 2014 will focus among other possible neurodegenerative conditions for example on one or more of the below:

- Age-related macular degeneration (AMD) is a serious neurodegenerative condition and leading cause of progressive blindness in patients of middle age and older. Outcome measures, biomarkers and composite endpoints that may be used in efficacy and safety trials for AMD, should be identified, and validation and regulatory agreement in principle should be sought;
- Health economic models and ways of monitoring therapy for AMD after marketing authorisation is granted should also be developed.

2.5 Prevention and treatment of immune-mediated disease

Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. Activities should seek to identify therapeutic opportunities and design and implement clinical strategies, which will transform the diagnosis and management of autoimmune diseases.

The proposed work will build on the knowledge base and infrastructure present within the EU from ongoing research-based initiatives e.g. Eumusc.net, EMEUNET, EUSTAR, ERS/ELF, ECCO, BILAG, EUVAS and Euro Lupus OMERACT, as well as relevant IMI projects (BTCURE, PRECISESADS), which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders in order to guide better patient treatments.

For some conditions, like multiple sclerosis (MS), while disease modifying therapies have been available for 20 years, there has been limited progress in evaluating the real world outcomes and impact of treatment. Similarly there is a limited amount of long term data to support the impact of the approved therapeutic approaches in terms of disability and quality of life.

There are efforts at national and international levels to capture real world data, however up to now there have been only limited efforts to improve, expand and link up this data in a way that would enable the use of real world evidence to develop tools to guide health professionals in how and when to use treatments and support their management decisions to optimise outcomes (personalised medicine).

Activities in this area foreseen for 2014 will focus for example on one or more of the below:

- Database efforts across Europe should be further expanded and coordinated leading to a European knowledge platform in MS and its treatment. This should aim to expand and enhance the collection of real world MS data in Europe, explore the use of real world data in innovative regulatory pathways, and develop models for disease risk assessment for better decision making;
- Tools and measures to assist in personalised medicine decision making should be developed and advanced. These should include magnetic resonance imaging (MRI) and other techniques for assessment of brain function, patient reported outcomes (PROs), cognition, adherence, and clinical measures. This will require also developing relevant education in MS with specialist certification courses for healthcare professionals (nurses, neurologists, radiologists, etc.) and pharmaceutical industry professionals.

2.6 Infection control including incentives for reinvestment in antimicrobials, antivirals, and vaccines

Vaccination is one of the most valuable and cost-effective public health measures to prevent and control the spread of viral/bacterial infectious diseases responsible for high mortality and morbidity. It saves at least three million lives every year globally. Changes in society both nationally and internationally have led to the need for research & development on vaccines to address the changing risks and immunological characteristics of the whole lifespan. This requires innovative solutions to understand and measure the maturation of the immune system, and to tackle emerging/unmet medical needs. Research is also needed to better understand drivers underpinning inconsistent utilisation of available immunisation measures, as a rise in the numbers of people hesitating to use vaccines undermines individual and societal public health and exacerbates the challenges of maintaining the financial sustainability of healthcare systems. Furthermore this is a priority area where research to reduce the use of experimental animals is highly relevant.

In the field of vaccines a number of large research infrastructures already exists such as CIMT/CIC (T-cell Immunity), and EU-funded OPTIMALVAC/EMVDA (malaria vaccines) and TRANSVAC (vaccines in general) among others. This provides an excellent opportunity to drive collaboration between these existing initiatives, bringing together industry and public research organisations and maximising synergies. The benefits could be even further enhanced by linking to other European infrastructures such as biobanks and IT infrastructures.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- Alternative approaches to the current animal tests required for lot release testing of established vaccines have been under development in both the public and private sectors for years, and some progress has been made. However, validation of these methods by comparison with the immunisation-challenge potency tests has been very difficult, time consuming and not always successful, for, amongst other reasons, the poor reproducibility of the in vivo tests. Therefore, the development of analytical methods, in vitro models demonstrating functionality of immune responses, and bioinformatics, to generate a set of consistency tests that will allow improved monitoring of vaccine quality during production and final formulation should be sought.

2.7 Translational safety

There is still a critical need for tools and methods that will facilitate the monitoring of safety issues, contributing to the safety of patients beyond the launch of new products. A better understanding of toxicological findings for human risk assessment has to be built for example via a retrospective review of clinical side effects and their relationship to non-clinical safety data. Better preclinical models representing human biology for predicting safety issues, and understanding the molecular causes underlying it, are needed to reduce attrition in the development of novel drugs and enable the development of safety biomarkers for the management of risks in humans.

Activities in the area will build on progress and success from the portfolio of IMI projects on safety, from other relevant European and global initiatives to create synergies (e.g. US Critical Path Institute and NIH driven projects) and from data management initiatives.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- The concordance of toxicity of pharmaceuticals in humans and in animals should be re-assessed. While an extensive arsenal of biomarkers for renal and hepatic safety has been already generated, during clinical studies and particularly during early or adaptive licensing it will be important to monitor early for changes and trends in those biomarkers;
- Identification and/or further validation of known and suggested new safety biomarkers representing different types of molecules, e.g. proteins and enzymes, but also nucleic-acids, might also be sought. One goal will be the characterisation of biomarkers which are easily translatable across preclinical species and human patients. A further goal will be the search for/evaluation of biomarkers for organs other than the liver and kidney, e.g. heart, pancreas, gastro-intestinal tract, brain etc;
- A key component of these activities might be the development of devices to automatically monitor for metabolic changes while being minimally invasive, and the use of contemporary communication technology to aggregate/monitor information in real time. The use of automated biomarkers will also be used in combination with the knowledge management work to understand and optimise real world medicine use more broadly. Points of care for automated safety monitoring will help minimise and provide early detection of drug-drug interactions and unanticipated consequence of treating patients with multiple conditions;
- New platforms should be developed reflecting human organ physiology (e.g. 3D, or organ-on-chip models, single cell-type or co-culture) to predict toxicity and safety during early drug development. In particular, liver, renal and cardiac safety might be studied using induced pluripotent stem (iPS) cells from subjects with a variety of phenotypes to understand better which patient subpopulations are at risk from rare safety issues. These models will be validated based on existing compound libraries and safety databases. Assessment of such new models will include evaluation of the limitations of such models with respect to *in vivo* organ function, which thereby will define their applicability;
- Molecular targets and pathways (through e.g. integrated ‘omics’ approaches) underlying toxic phenotypes of drugs failed for safety reasons should be identified. One goal will be the development of *in vitro* models representing these pathways which can be employed in early safety testing. This should lead to a reduced and refined use of animals, including the possibility for better prediction of suitable toxicology species;

- Since toxicological phenotypes are the result of both the hazard and the dose, a further activity should include the evaluation and optimisation of existing or new toxicokinetic models with the aim of predicting adaptive and adverse changes based on *in vitro* assay results and modelled exposure data. Of relevance may also be studies of the pharmacokinetic interactions caused by mechanism-based, time-dependent and metabolite-mediated inhibition of drug metabolism and transport as well as relevant pharmacogenetic studies. This will be important to anticipate and study adverse drug interactions, understand variability in the metabolism and disposition of drugs and their metabolites, and guide future revisions of regulatory guidance on drug-drug interaction studies;
- A systematic annotation of observed toxic phenotypes, and the integration of various types of both newly generated and already available data into existing data management structures should be also achieved, with potential consolidation into fewer database formats to allow flexible public and private use.

2.8 Other Priorities derived from the SRA: 1- Psychiatric diseases

More than a quarter of all Europeans are estimated to experience at least one form of mental disorder during their lives. Although several treatments are available, positive response is limited, and for most mental disorders, treatment algorithms are based on trial and error.

Activities are needed for a better understanding of the disease biology and potential biomarkers of psychiatric disorders, which will be the key to increasing rates of diagnosis and treatment success, and to the development of more targeted medicines. Attention should be paid to new techniques for the functional assessment of the human brain.

Activities will build on early successes and progress in ongoing IMI projects (NEWMEDS and EU-AIMS) and will seek synergies with other national, European and global initiatives on mental health.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- A systematic analysis of genetic and environmental factors contributing to different psychiatric disorder categories in a trans-diagnostic way should be considered. This should be the basis for (back)-translational work, taking advantage of new instruments of research and patient characterisation, to allow the establishment of trajectories for the development of psychiatric disorders;
- A taxonomy which better reflects the neurobiological mechanisms of psychiatric disorders and is better suited for developing new and efficacious drugs to treat mental disorders should be developed. This activity will link to ongoing projects on disease taxonomy already implemented by IMI;
- A framework for translation of research on clinically relevant neuropsychiatric endo-phenotypes for regulatory agencies should also be built;
- This might also include the development of surrogate endpoints and markers for efficacy and patient stratification, and for identification of endo-phenotypes of potentially disruptive disorders in 'at-risk' patients.

2.9 Other Priorities derived from the SRA: 2- Respiratory diseases

Despite improvements in the way respiratory diseases are managed, they continue to pose a significant burden on patients and healthcare systems. Unlike asthma and other allergic respiratory diseases, chronic obstructive pulmonary disease (COPD) remains a relatively poorly understood disease despite one person dying of COPD every 10 seconds, more than breast and lung cancer combined.

IMI2 activities will have to seek synergy with ongoing initiatives such as The COPD Foundation Biomarker Qualification Consortium, the UK Technology Strategy Board funded ERICA or the Industry-funded ARCADE and ECLIPSE cohort studies, among others. Furthermore the initiatives will build on current relevant activities in IMI (e.g.PROactive).

Activities in this area planned for 2014 will focus for example on one or more of the below:

- A better understanding of what aspects of COPD heterogeneity are relevant for patient-based risk assessment and stratification should be delivered. This should consider an impact on therapeutic strategies and patient management in real life clinical practice. This might include the identification of alterations of pathway regulation associated with poor patient prognosis;
- Rules for subject-specific health risk assessment and patient-oriented stratification with impact on healthcare management (both preventive and therapeutic) should be generated;
- Knowledge acquired by the project should be transferred to clinical practice through well-defined validation strategies and implemented as a fully deployed integrated care scenario;
- The optimisation of the interactions between pharmacological and non-pharmacological interventions in COPD patients might also be relevant;
- The exploration of potential re-orientations of the use of existing drugs for the design of novel therapeutic approaches (i.e. antioxidant therapies) might be also included.

2.10 Other Priorities derived from the SRA: 3 Enabling Technologies and Excellence in Data Management

The increasing volume (terabytes/patient), diversity (clinical, GWAS/RNASeq, eHR, 'omic', cytometry, imaging, pharmacology, pharmacovigilance etc.) and velocity (e.g. real time telemetric monitoring of patients, social media feeds, etc.) of biomedical data create significant opportunities for healthcare R&D. However, common data standards, as well as robust data production and knowledge management (KM) solutions and services will be essential if the full value of these data sets is to be realised in the development of innovative precision medicines.

Furthermore, as healthcare delivery systems change, clinical trials move to more adaptive designs, new monitoring devices become more sophisticated and "live" patient interactions through mobile enabled, social media technology, are implemented, there will be a need to engage with the IT sector. This will be necessary to collaborate on the development of novel enabling technologies and adaptive therapies to facilitate the efficient capture and interrogation of these data sets to ensure effective healthcare practices for patients.

The IMI2 activities will expand upon work from existing IMI projects including EMIF¹⁷, eTRIKS and EHR4CR as well as other FP7 projects in the area of electronic health records, and will require coordination/collaboration with European biomedical research infrastructures through the European Strategy Forum on Research Infrastructures (ESFRI). They will also take into account policies and guidelines for data gathering and sharing from relevant international initiatives such as the International Rare Diseases Research Consortium, International Human Cancer Genome Consortium and the Global Alliance for Chronic Diseases.

Ethical Legal and Social Aspects (ELSA), will have to be carefully considered and developed as part of all research activities in this area.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- Building on EMIF, a comprehensive, large scale, usable and accessible database should be developed that in the long term will link genotype, clinical and phenotype data for any individual (diseased or non-diseased). This will be essential to maximise opportunities to understand disease. This project will include the generation and coordination of a pan-European, controlled access database (data safe haven) for qualified genetic and health record/patient-level phenotype information to provide longevity and accessibility to data for 1-3 pilot disease areas beyond those already tackled by EMIF.
- Real-time identification of behavioural and physiological patterns that culminate in disease relapse is of great importance: early detection and communication of "red flags" to both patients and providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory. This element is particularly critical in the context of patient compliance/adherence and need to develop interventions to reduce the incidence of non-adherence with prescribed medicines. Achieving this objective might involve among others that:

¹⁷ The European Medical Information Framework (EMIF) programme was established as part of the 4th IMI Call, as an IMI project composed of the EMIF-Platform (the data and technical part) and 2 research topics (in metabolics and Alzheimer's disease).

- a) the science of using biosignatures to characterise disease and predict changes in disease state through a series of observational studies is developed and validated;
- b) innovation and development of novel biosensors and the associated knowledge management technology is stimulated;
- c) the understanding of the regulatory pathways for using remote assessment in healthcare is enhanced;
- d) standards for Information exchange that enable seamless integration of sensor, data capture, data management, & analysis technologies are developed;
- e) an open source reference platform is created to enable the collection, storage and analysis of remote assessment data.

3 MANAGEMENT OF CALLS AND PROJECTS

3.1 Activities related to Proposals Evaluation and Grant Negotiation

Key activities in 2014 will comprise the evaluation of Expressions of Interest and/or Full Project Proposals submitted for the topics of Calls 9, 10 and 11, launched in Q4 2013. Furthermore, proposals submitted to the third ENSO Call will be evaluated.

The first calls of IMI2 will be launched to implement the 2014 Scientific Priorities. It is expected that at least 2 Calls for proposals will be launched covering at least 4 topics. Details are set out in Annex III.

Besides the launch of competitive Calls for proposals, IMI JU will explore any other necessary procedure to evaluate proposals and award funding to projects.

Timelines for completion of the evaluation process and of negotiation will be kept as lean as possible with the aim of completing signature of the Grant Agreements for Calls 9 projects by Q2 2014, for Call 10 projects by Q3 2014 and for Call 11 projects by Q4 2014.

To maximise efficiency of the calls management, the IMI JU will continuously explore and implement simplification and improvement processes while maintaining the highest standards of the evaluation process.

3.2 Activities to support and monitor on-going projects

46 on-going and currently in preparation projects generated from Calls 1-8 will be running at different stages of their life cycle in 2014. IMI JU will continue to provide support and advice to the consortia, including on amendments to Grant Agreements. In addition, 4 new projects from Calls 9, 1 from Call 10, should start in 2014, as well as 8 projects from Call 11.

An overview of the project support and monitoring activities for 2014 is provided in the table below (status of projects as forecasted for 1st January 2014).

IMI Calls	Number of IMI projects						
	on-going	starting in 2014	1 st year	Interim/scientific reviews	post-interim review phase	final year	submitting annual reports & financial statements
1	15				15	12 ¹⁸	15
2	8			2 ¹⁹	7	1	8
3	7			7			7
4	7			1 ²⁰			7
5	1						1
6	2						2
7	2		2				2
8	4*		4	1			4*

¹⁸ Based on a justified demand one project U-BIOPRED has been granted a 1 year extension to finalise the activities.

¹⁹ The project DDMORE will undergo a supplementary scientific review upon request of the interim reviewers.

²⁰ The project EMIF will undergo a 1st scientific review.

*Of the 5 topics in Call 8, ND4BB 1C (the "Innovative Trial Design & Clinical Development" subtopic) will become part of the Call 6 COMBACTE project.

IMI Calls	Number of IMI projects						
	on-going	starting in 2014	1 st year	Interim/ scientific reviews	post-interim review phase	final year	submitting annual reports & financial statements
9		4					
10		1					
11		8					

Figure 1

12 out of 15 of the projects generated from **Call 1** will complete the final year of activities in 2014 and 8 of the mentioned 12 will submit their final activity reports.

The 8 projects generated from **Call 2** will enter their fourth year of activities. For one of these projects, OpenPHACTS, a budget neutral 6 months extension of the project period was granted in 2013 and thus 2014 will be the final year of activities, with also submission of the final activity report. Quick-Concept, the latest starting project from Call 2, will undergo an interim review. The project DDMORE will undergo a supplementary scientific review upon request of the interim reviewers.

The 7 projects generated from **Call 3** will enter their third year of activities in 2014, with all of them due for their interim review.

6 out of 7 **Call 4** projects will enter their third year of activities in the Q4 2014.

The Project EMIF from Call 4 will enter its second year of activities and it will be due for its first year scientific review as recommended by the expert panel during the Call 4 Stage 2 evaluation.

The **Call 5** European Lead Factory project and the first two projects part of the New Drugs for Bad Bugs (ND4BB) platform launched in **Call 6** will all enter their second year of activities, while the projects generated from **Calls 7 to 11** will all be in their first year of activities.

A key task will be to continue maximising efficiency, facilitating, optimising, and monitoring the implementation of all these projects and seeking feedback for continuous improvement to IMI JU operations. To this end, further workshops to provide guidance on the financial and administrative aspects of the projects to the EFPIA coordinators, non-EFPIA partners and to beneficiaries will continue in 2014.

Furthermore, **interactions between projects** and sharing of best practices (including on sustainability plans) will be promoted by organising joint and cross-projects meetings and/or using various other channels (e.g. the IMI Group on LinkedIn).

Activities are expected in particular in the following areas:

- Diabetes Research: further collaboration and data sharing will be facilitated by the memorandum of understanding and specific agreements signed in 2013 between SUMMIT, IMIDIA and DIRECT projects;
- Neuroscience: activities will be organized to facilitate links between the Call 1 projects and those generated from later calls (e.g. EMIF-AD and AETIONOMY);
- Knowledge Management (KM): a cross projects meeting between KM projects will be organized. Activities will be developed to foster implementation and development of standards for clinical data (CDISC and CFAST) as well as non-clinical data. Furthermore, 2014 should mark the finalisation of a Code for use of health data in collaborative scientific research projects developed collaboratively across projects, in particular the KM projects;
- Antimicrobial resistance: activities are planned to boost integration of projects under the ND4BB programme. To this effect, dedicated meetings will be organised in 2014 for ND4BB projects and, more widely, for other initiatives active in the fight against antimicrobial resistance.

- Stem Cells and iPS Cells Research and Banking: IMI JU will facilitate in 2014 a networking event with ongoing European funded stem cell initiatives including STEMBANCC from Call 4, EU AIMS Call 3, MIP-DILI Call 3, and EBISC Call 8, for which the ultimate goal is the establishment of a European Induced Pluripotent Stem Cell Bank. Such event will aim at facilitating the interaction between the different consortia, explore new ways of collaboration and ultimately maximise European added value in health research in this area.

With regard to sustainability plans of IMI projects, IMI JU will also:

- explore any other necessary procedure to evaluate proposals and award funding to on-going projects; and
- launch a tender procedure to make available the necessary legal and financial expertise and support to projects.

3.3 Monitoring and analysis of projects' results

A combination of internal management information systems, external databases, periodic reports on the projects, independent evaluations and, if necessary, commissioned studies and surveys will be used to measure the progress and identify significant achievements of IMI projects.

In order to continuously and effectively monitor IMI projects and the overall program there is a need to develop an online platform that would allow for customisable, real-time analytics on all project outputs beyond publications; such as progress reports, data repositories, Standard Operating Procedures, standards, templates. Due to the high demand for customisation IMI Programme Office will have to resource to external collaboration on this matter to best design such a monitoring tool and explore the feasibility of interlinks with any existing systems.

In 2014 the collaboration with Thomson Reuters will continue to allow the analysis of the IMI project outputs in terms of publications and collaboration among IMI researchers.

Furthermore, IMI JU will explore possible expansions (e.g. through a tender procedure) of the KUL case study carried out in 2013 on IP and business outcomes of six IMI projects, notably by including a macroeconomic perspective.

Exploitation of results

In 2013, a pilot study analysis of project results was undertaken by KU Leuven on a small selection of IMI projects with a focus on IP and business opportunities. The results offered a basis for designing means to optimise the exploitation of IP and value generated in a number of selected IMI projects.

In 2014, the analysis will extend to other areas of focus not necessarily directly linked to IP and commercial exploitation but key to ensure that the impact of IMI projects can be maximised and that the results are sustainable, can be considered in the development of new medicines and maybe taken up in the decision-making process. To that end, IMI launched a tender for an Exploitation of results platform in August 2013. Activities to build the platform started late 2013 and will initially last 9 months. The platform should help maximise the translation of project outputs into standard of care (new practices and processes leading to improved healthcare), by bringing together all key and representative stakeholders, including the clinical community (e.g. clinicians, physicians, nurses, pharmacists), and patients in a discussion forum ('Think tank').

Such a multi-stakeholder Exploitation of Results Forum should be responsible for the following:

- Analysing IMI project outputs;

- Addressing legal, ethical, institutional opportunities and limitations for uptake of such outputs in the current regulatory/legal/institutional framework;
- Defining the uptake route and workable processes and formulate recommendations to be implemented by the relevant stakeholders/organisations to support delivering improved treatment options to society.

Intellectual Property

IMI JU will continue providing information, training and guidance on the handling of IP-related issues from the launch of Calls for proposals to the implementation phases of IMI projects.

To that end, the IMI JU will:

- continue regular communication in order to further improve knowledge and understanding of IMI IP policies to all stakeholders;
- provide SMEs with simple and practical information through the dedicated webpage;
- maintain its IP Helpdesk;
- get feedback from participants and stakeholders on the implementation of the IP policies;
- provide support during the consortium agreement negotiations to ensure compliance with the IMI IP policies and right balance between the participants while maintaining tight timelines;
- participate in Info Day meetings and in events organised at European level on IP management and best practices.

In addition, IMI JU will develop an IP Guidance Note in relation with the IMI2 rules. The purpose of this guidance note is to describe the IMI2 rules concerning Intellectual Property (IP) in contrast to IMI1 policy, to highlight the flexibility provided therein, and by doing so to explore ways to handle IP related issues and pitfalls that participants may encounter during the preparation and completion phases of the grant agreement and the negotiation phase of the consortium agreement.

Finally, IMI JU will explore ways or possibility of closer collaborations with the IPR-Helpdesk managed by the European Commission's Executive Agency for Small and Medium-sized Enterprises (EASME), and with policy guidance provided by the European Commission's Enterprise and Industry Directorate-General.

3.4 Stakeholders' engagement and external collaborations

Patients

Based on the Governing Board's strategy to improve patient involvement at IMI, the IMI JU will invest in improving the patients and lay community understanding of what IMI delivers and how it might impact their lives. This will be achieved through various actions that include the development of a patient-dedicated section on IMI's website, translating outputs from IMI projects into lay language, specific sessions with patients' involvement in IMI stakeholder forum, and the organisation of dedicated patient meetings. This also follows on from the June 2013 pilot patient group meeting, with two Patient Focus Meetings to be held in 2014: one session on diabetes, as requested by the Juvenile Diabetes Research Foundation (JDRF), and the second one around overall challenges facing patients regardless of the disease they are suffering from.

Efforts will also be made to improve the way IMI draws on the patients' expertise by involving patients into defining and executing IMI projects. This has already been implemented in Calls 9-11 by including sections dedicated to patient involvement in call topic texts for relevant projects. In addition, patient input will be sought more systematically in scientific challenge workshops as well as where appropriate in evaluation process. This way patients involvement at all levels will be ensured.

Finally, IMI aims to provide a forum for discussion and interaction between patients and other stakeholders, in particular scientists, to help collaboratively determine the best way to actively involve

patients in research. This will be done via workshops where best practices would be exchanged between IMI projects as well as other initiatives.

Regulators

The strengthening of the relations with regulatory agencies including EMA, FDA and PDMA will continue in 2014 to ensure that IMI projects benefit from the Regulators' input. As IMI projects start delivering tangible results, engagement with Regulators is important to facilitate their translation into the regulatory practice, with the aim to enhance the efficiency of the development and the registration of medicinal products. IMI will therefore continue raising awareness of the IMI projects through early liaison with the Regulators in the context of qualification advice/opinions procedures.

In addition, joint meetings and teleconferences will be organised in conjunction with EFPIA and the European Commission to further discuss the impact of the IMI projects in the regulatory environment. Experiences and lesson learnt will continue to be shared with other initiatives (e.g. C-Path, NIH) to better explore synergies.

Small and Medium Size Enterprises

Based on past activities IMI JU has been successful in encouraging SME participation in IMI Calls. As of the end of September 2013, 15.4% of the successful applicants to IMI were SMEs. Furthermore, SMEs that have successfully applied have been allocated 22.5% of the IMI budget for the projects launched. To build on this success, IMI JU will continue to work with its founding members and other stakeholders to increase support for SMEs and increase SME participation in its projects. IMI JU will achieve this through the provision of targeted support and guidance disseminated through the dedicated helpdesk and IMI website.

The IMI Programme Office will host and attend meetings specifically aimed at involving the SME sector. It will also undertake activities to increase liaison with both individual SMEs and European umbrella organisations that support the SME sector at the regional, national and international level.

To provide further support to SMEs, IMI will increase its efforts in communicating information on sources of funding available within IMI projects but also more widely within European Institutions and bodies, both public and private. It is envisaged that a series of networking events will be held to discuss business funding opportunities for SMEs with life science venture capitalists, representatives from EFPIA investment units and representatives of the European Commission.

CDISC

The collaboration with the Clinical Data Interchange Standards Consortium (CDISC) will continue in 2014 for the benefit of IMI JU beneficiaries, in particular with the training activities by CDISC offered to partners of IMI consortia. In order to further facilitate implementation of data standards, in-depth trainings on CDISC standards (CDASH²¹, SDTM²², ADAM²³, SEND²⁴) and any other applicable, as well as a consultancy session will be organized for the projects. The standards developed in the context of IMI projects will continue to be discussed in the context of CDISC standards. The latter will be enhanced with taking part in the Scientific Advisory Committee of the Coalition for Accelerating Standards and Therapies (CFAST), a joint partnership between CDISC and Critical Path Institute created to accelerate clinical research and medical product development by developing and maintaining data standards, tools, and methods for conducting research in therapeutic areas that are important to public health.

²¹ Clinical Data Acquisition Standards Harmonization

²² Study Data Tabulation Model

²³ Analysis Data Model

²⁴ Standard for Exchange of Nonclinical Data

C-PATH Institute

The fruitful collaboration of 2013 with C-Path Institute will continue in 2014, notably with a second joint IMI & C-Path meeting scheduled in Q4 of 2014. The objective remains to foster synergy in areas of common interest such as modeling and simulation, and to maintain collaborations between specific projects and research areas as follows:

- SAFE-T and PSTC for pre-clinical safety;
- IMI Portfolio of Alzheimer’s Projects and CAMD;
- PreDICT-TB and CPTR for tuberculosis research.

IMI and C-Path Institute will work together for synergies and alignment and will seek to avoid duplication of efforts in these programmes. Collaboration will also focus on the data standard space with a view to ensure consistent remapping of respective data sets to enable leveraging the data on both sides.

Furthermore, collaboration in the area of anti-microbial resistance will start in 2014.

FNIH Biomarker Consortium

Collaboration will be enhanced, in particular between EU-AIMS project and FNIH Biomarkers Consortium’s Autism Initiative to align initiatives in particular for biobanking and clinical research aspects.

4 COMMUNICATION AND EVENTS

4.1 Communication objectives

The IMI Communication and External Relations Strategy for 2014 will focus on the following objectives:

- Promote the launch of IMI2 and raise awareness levels and perception of IMI among all target groups;
- Attract the best researchers from relevant target groups to apply for funding under the first IMI2 Calls;
- Increase engagement of patients and SMEs in IMI's activities.

4.2 Key audiences

- Academic researchers – convince them of the excellence and applicability of research coming out of IMI projects and encourage them to apply for funding;
- Industry (both pharmaceutical and other, e.g. biomedical imaging, medical information technology, diagnostics, animal health) – convince them that IMI is a forum that allows them to share risks and move forwards, especially in the most challenging disease areas;
- Small and medium-sized enterprises (SMEs) – convince them that IMI provides opportunities to not only receive funding, but to work with networks of the leading experts in their area;
- Patient groups – engage them in IMI's activities, and inform them that IMI is speeding up the development of better, safer drugs;
- Regulatory authorities and payers – further engage them in IMI's activities, so that the novel tools developed by IMI projects can be formally validated as rapidly as possible;
- Policy makers and opinion leaders – convince them that a public-private partnership is an essential component of the health research and innovation landscape, delivering results that would not be possible through other programmes;
- General public – inform them that IMI is speeding up the development of better, safer medicines including for diseases that affect a large proportion of the population.

4.3 Key messages

Top level messages

- IMI is evolving, with an even stronger focus on the needs of patients and society
- IMI delivers breakthroughs that are having an impact on drug research and development and, ultimately, patients' lives
- In terms of both budget and scope, IMI is the world's biggest public-private partnership in the life sciences
- IMI accelerates the development of, and patient access to, new treatments, especially in areas where treatments are lacking / where the impact of a disease on society is particularly high
- By acting as a neutral broker, IMI facilitates collaboration and enables joint investments to tackle challenges that are too big for any one company, organisation or country to tackle alone

Messages for potential applicants on IMI2

- EUR3.276 billion budget for period 2014-2024 makes IMI the world's largest public-private partnership (PPP) in life sciences
- IMI now has simpler funding and reporting rules (funding rates and reporting rules aligned with Horizon 2020, protection for beneficiaries under H2020 Guarantee Fund)

- Funding for all non-profit organisations (not just research-based organisations)
- Funding for mid-sized companies (i.e. annual turnover of up to €500 million)
- Companies from other industries (e.g. biomedical imaging, medical information technology, diagnostic industries, animal health industries) can contribute in-kind (so contributions matched by IMI funding)
- Stronger focus on needs of patient and society
- Increased emphasis on improving patient access to innovative medicines (in addition to medicines development)

Messages for the pharmaceutical industry

- IMI is an attractive instrument to implement collaborative programmes involving industrial and non-industrial partners
- IMI provides incentives for innovation in particularly challenging / high risk areas
- IMI delivers tools and instruments to improve pharmaceutical R&D and speed up patient access to new treatments
- IMI shapes a new image of the pharmaceutical industry
- IMI trains a new generation of industrial scientists and regulators as well as current professionals

Messages for other industries

- IMI welcomes the participation of companies from a broad range of healthcare-related sectors
- IMI is an attractive instrument to implement collaborative programmes involving industrial and non-industrial partners

Messages for academic researchers

- IMI now has simpler funding and reporting rules
- IMI offers unique opportunities to translate breakthrough discoveries into clinically useful tools and products through open innovation networks
- IMI projects are generating scientifically excellent results
- IMI is creating new training schemes designed to address specific unmet needs identified by affected individuals/carers
- IMI has a flexible intellectual property (IP) policy that brings many benefits

Messages for SMEs and mid-sized companies

- IMI now has simpler funding and reporting rules
- IMI supports small and medium-sized enterprises and mid-sized companies engaged in drug development and innovation
- IMI has a flexible intellectual property (IP) policy that brings many benefits

Messages for patients and their families and carers

- IMI projects are focused on patients' needs and interests
- Patients are encouraged to participating in IMI's activities, e.g. by participating in IMI projects and committees

Messages for policymakers

- IMI implements EU policies
- IMI contributes to improving European citizens' quality of life
- IMI creates/maintains jobs and contributes to the competitiveness of the pharmaceutical sector in Europe
- IMI has a flexible intellectual property (IP) policy that brings many benefits
- IMI projects are generating scientifically excellent results

Messages for regulators and payers

- IMI is developing tools to facilitate (innovative) drug approval by regulatory authorities and payers
- Through IMI, regulators and payers can have direct contact with collaborative consortia as opposed to individual research groups or institutes

Messages for general public

- IMI is developing new treatments for diseases where there is a high, unmet societal need
- IMI is contributing to improved medicine and vaccine safety
- IMI creates/maintains jobs and contributes to the competitiveness of the pharmaceutical sector in Europe

4.4 IMI2 launch activities

Activities related to the launch of IMI2 are:

- Update of communication strategy, including key messages and corporate identity
- Draft new texts / slides / infographics explaining IMI: general text, governance, rules & procedures, especially 'what's new'
- Update relevant web pages
- Develop new promotional materials (leaflets, posters)
- Contribute to JTI-2 launch event on 9 July (including with press release)
- Organise webinars to present new rules and procedures and topics of first Call (July)
- Organise a launch dinner to raise awareness of the launch of IMI2 among key stakeholders such as policymakers (September)
- Organise Info Day to present new rules and procedures and topics of first and second Call, and to facilitate networking (September)
- Support STATES REPRESENTATIVES GROUP members and NATIONAL CONTACT POINTSs in organisation of national events.

4.5 Increasing the engagement of patients and SMEs in IMI's activities

Patients and carers have an important role to play in research. Throughout 2013, the IMI made significant efforts to reach out to patients and explore ways of boosting their involvement in IMI projects. This initiative was warmly welcomed by patients and projects alike, and will continue in 2014, with further events and materials dedicated to patients. IMI has a dedicated scientific officer working on outreach to patient groups, and the communications team works closely with her to develop messages and materials relevant to the patient community.

IMI has made great strides in its efforts to reach out to SMEs, and they now receive 18.4% of IMI's budget and account for 15% of all recipients of IMI funding (for the projects under the first eight Calls for proposal). Under IMI2, in line with Horizon 2020, IMI will be expected to ensure 20% of its budget goes to SMEs. IMI has a scientific officer dedicated to relations with SMEs, and this has helped to cement IMI's relations with SME umbrella organisations. In liaison with the scientific team, the Communications Team will continue to develop messages and materials relevant to the SME community, including SME 'success stories'.

4.6 IMI's Corporate Identity

The launch of IMI2 provides an opportunity to refresh the IMI corporate identity, including the visual elements. A new visual identity will also help to reinforce the message that IMI's activities have a renewed focus. To this end, a mission, vision and values have been drafted and our graphic designer will draw on these to develop a revised visual identity that will encompass the logo, other design elements, colours, images, and templates. The draft mission, vision and values are as follows. These will be finalised in collaboration with EFPIA and the European Commission.

Mission

The Innovative Medicines Initiative (IMI) is a partnership between the European Union and the European pharmaceutical industry. IMI facilitates collaboration in research to advance the development of, and accelerate patient access to, innovative medicines for the health and wellbeing of all, especially in areas of unmet medical need.

Vision

Improved health for all thanks to a vibrant, competitive medicines development community in Europe.

Values

Integrity - We always act with integrity and are transparent in our dealings with our projects, stakeholders and society. We take our role as a neutral facilitator seriously, and endeavour to treat all stakeholders and project partners fairly.

Adaptability - While maintaining a focus on the needs of patients, we ensure our work is in line with the latest developments in the fast-moving world of medicines research and development, and where possible adapt our way of working to take account of IMI's evolution.

Collaboration - Collaboration is key to IMI's success. Our projects work because they involve collaboration between experts from different sectors and different countries. Among our staff and committees, we value diversity and our strong team spirit. We also seek out collaboration with like-minded organisations around the world.

Efficiency - Our funding comes from the public purse and the pharmaceutical industry, and we work hard to manage these funds as efficiently as possible.

Passion - We are passionate about our work and ensuring the results of our projects benefit patients and society.

4.7 Communication channels

IMI will continue to develop the following channels in support of its communication goals:

- Events (both IMI and external)
- Website
- Newsletter
- Social media (LinkedIn, Twitter)
- Multipliers (IMI founding members, members of advisory bodies (States Representatives Group, Scientific Committee, IMI Programme Office and staff, , , National Contact Points, relevant umbrella groups / associations, IMI projects, organisations partnered by IMI, e.g. through a Memorandum of Understanding)
- Media (general and specialist, mainly in Europe but also international)

- Direct mailings
- Publications
- Direct contacts with opinion leaders

4.8 Media outreach

In recent years, IMI has enjoyed increased positive visibility in key general and specialist media. In 2014, IMI will work to ensure this trend continues by maintaining links with key journalists, issuing regular press releases, organising press interviews, and inviting media to IMI events. IMI will also maintain close contacts with its projects to ensure a steady flow of success stories that can be used to illustrate IMI’s key messages when communicating with the media.

In addition, IMI will continue to work with a public relations agency, Media Consulta, to further develop its work in this important area. Specifically, Media Consulta will provide support in the following areas:

- General communications advice
- Media monitoring
- Assistance keeping media database up to date
- Handling logistics of media attendance at IMI events (invitations, travel, follow-up, etc.)

The Executive Office will also remain alert to issues that could damage IMI’s reputation, and respond accordingly, for example by preparing briefings or sets of questions and answers. In order to strengthen IMI’s in-house capabilities in this area, IMI will organise, through Media Consulta, a one-day crisis communications course for all senior management, the communication team, and a member of the legal team. IMI will also organise general media training for staff members who would benefit from this.

4.9 Key events planned in 2014

Event	Date - Place	Target audience	Objective
IMI Investing in Excellence - SME networking event	18 February Brussels, Belgium	SMEs, venture capitalists, policymakers, industry	Spotlight IMI SMEs, promote involvement of SMEs in IMI
DIA EuroMeeting	25-27 March Vienna, Austria	Researchers, industry	Raise awareness of IMI
IMI-JDRF Diabetes Patient Focus Meeting	20 May Brussels, Belgium	Patients, researchers, research-funding organisations	Gain patient input on research needs for diabetes
IMI Stakeholder Forum	21 May Brussels, Belgium	Policy makers, researchers, patients	Raise awareness of IMI
Launch of renewed JTIs	9 July Brussels, Belgium	Policy makers, press, other key stakeholders	Raise awareness of IMI & promote 1 st Call
Webinars on IMI2 – Call 1 topics	July / September Online	Potential applicants	Encourage experts to apply for funding
Webinars on IMI2 rules & procedures	July / September Online	Potential applicants	Encourage experts to apply for funding
National IMI2 Info Days	Summer / Autumn	Potential applicants	Encourage experts to

Event	Date - Place	Target audience	Objective
(organised by States Representatives Group)			apply for funding
IMI2 launch dinner	September Brussels, Belgium	Policymakers, opinion leaders, patient groups, other stakeholders	Raise awareness of the launch of IMI2
IMI2 Info Day	September Brussels, Belgium	Potential applicants	Encourage experts to apply for funding
Webinars on IMI2 – Call 2 topics (tbc)	Autumn Online	Potential applicants	Encourage experts to apply for funding
Webinars on IMI2 rules & procedures (tbc)	Autumn Online	Potential applicants	Encourage experts to apply for funding
Workshop on adaptive clinical trials	Autumn tbc	Patients, researchers, industry	Engage patients in debate on alternative trial designs
IMI – C-Path joint event	3 December Washington DC, US	Policymakers, opinion leaders, researchers, industry, patient groups	Promote debate on PPPs
Italian presidency event (tbc)	2 nd half of year Italy	Policy makers, researchers, patients	Raise awareness of IMI

Figure 2

4.10 Resources

IMI2 Office

The IMI Communications Team comprises three people and takes the lead in setting IMI's Communication Strategy and overseeing its implementation. The Communications Team also supports the many other groups of people who communicate on IMI. Other IMI staff contribute to IMI's communication activities in a variety of ways.

- Providing news from the projects for use in communications
- Providing expertise on important issues
- Promoting IMI via presentations and scientific articles
- Identifying speakers for IMI events
- Maintaining personal links with opinion leaders and key stakeholder representatives
- Providing technical support (e.g. the IT team liaises with the contractors responsible for the technical side of the website and newsletter content management systems)
- Providing administrative support (e.g. at events)

In addition, two Scientific Officers lead IMI's outreach work for two important stakeholder groups, namely SMEs and patients – the Communications Team supports them in this work, for example by organising events and developing materials. The Executive Director also plays an important role in these activities.

IMI2 Stakeholders

EFPIA and the European Commission regularly promote IMI through their own communication channels.

Members of IMI's States Representatives Group, Scientific Committee, and Governing Board all act as IMI ambassadors, presenting and representing IMI in a variety of situations. In addition, the Governing Board provides regular feedback on IMI's communication plans and activities.

Other stakeholders

National Contact Points, relevant umbrella groups such as scientific societies and patient organisations help to promote IMI.

4.11 Analysing the impact of IMI communication activities

IMI will continue to monitor the impact of its communication activities as follows:

Website – number of visits, visitors, and page views per month

Social media – number of Twitter followers, number of members in IMI LinkedIn group

Press coverage – number, geographical spread and tonality of articles

Events – feedback from participants (gathered via online survey)

In addition to this, in 2014 IMI will carry out a survey of key stakeholders across Europe to gather a broad view of awareness levels and perception of IMI. This will be carried by YouGov via IMI's contract with Media Consulta. The results of this survey will help IMI to further refine its key messages and activities.

5 MANAGEMENT OF THE EXECUTIVE OFFICE

Building on 2013 achievements, a key strategic action for 2014 will be to further consolidate IMI2 JU's Programme Office as a strong and creative organisation, notably in preparation for the transition to IMI2.

5.1 Support to Governance bodies

The IMI2 JU will continue to provide support in 2014 to its Governing Board, the Scientific Committee, the States Representatives Group and the Stakeholders' Forum and their working groups.

The Governing Board gathers representatives of IMI2 JU founding members. It has the responsibility for overseeing the operations of the IMI2 JU and the implementation of its activities. It will meet at least twice in 2014, in addition to monthly teleconferences between the Chair, Vice-Chair and IMI office senior management. The first IMI2 Governing Board is due to meet on 2 July 2014.

The Scientific Committee is an advisory body to the Governing Board. It will meet at least twice in 2014 with a partially renewed membership. The composition will be reviewed on the basis of criteria set out in IMI2 Regulation.

The IMI States Representatives Group will be consulted on the Call texts and will receive the evaluation outputs. At least two meetings of the States Representatives Group are foreseen for 2014.

In addition, as part of the new governance features of IMI2, Strategic Advisory Groups to the Governing Board (called Strategic Governing Groups) will be established in different thematic areas with the primary aim to make the process of topic development and gathering industry commitment more transparent, effective and strategic. Relevant areas identified are:

- Immunology;
- Diabetes and metabolic disorders;
- Neurodegeneration;
- Translational safety;
- Data and Knowledge management.

Continuous attention will be given to enhance communication with these bodies and seek and feedback on any significant IMI activities and developments, including on the future of IMI. In addition, these bodies will be increasingly called upon advising on how best to exploit IMI projects outputs, enhance cross-projects' collaboration as well as explore synergies with similar or complementary activities at national level.

The collaborative platforms for supporting the Governing Board, the Scientific Committee and the States Representatives Group will be maintained and updated both from a content and operations point of view.

In addition, communication on IMI achievements will continue to be available through QlikView, a specific tool that generates statistics and data.

5.2 Budget and Finance

Draft Budget Plan 2014

The draft annual budget plan for 2014 approved by the Governing Board in December 2013 has been increased by the amount covering needs of IMI2.

Commitment appropriations (in EUR)	
Running costs	8,880,000
*Operational costs	213,533,700

Figure 3

*Excluding amounts carried over from 2013

Payment appropriations (in EUR)	
Running costs	8,880,000
*Operational costs	161,187,993

Figure 4

*Excluding amounts carried over from 2013

Budget for running costs (in EUR)	
Title 1 – costs related to IMI staff	
Salaries, missions, training and recruitment costs	4,855,000
Title 2 – running costs of the IMI JU office	
Office equipment, IT and telecommunications, external communication and events, audit, formal meetings and expenditure in connection with research activities (experts, workshops, meetings and events targeting the IMI projects).	4,025,000

Figure 5

The budget forecast for **running costs** in 2014 is increased by EUR 980,000 compared to the draft that covered only IMI1 to cover needs of IMI2 in terms of additional staff, office space and furniture, IT costs and costs of evaluations of projects launched under IMI2.

As regards **operational expenditure**, whilst payment appropriation is only increased by EUR 733,257 representing the amount carried over from 2013 based on the Decision of the Governing Board in January 2014, the commitment appropriation is being increased by EUR 213,533,700 which will be used for Calls for proposals launched under IMI2. In addition to this, EUR 880,903 representing the amount carried over from 2013 was entered in the budget increasing commitment appropriation available for 2014. The bank interest is not budgeted at this stage. The amount of bank interest yielded in 2014 will be entered in the budget 2015.

Preliminary Draft Budget 2015

The preliminary annual budget plan for 2015, together with the staff establishment plan, is set out in Annex II.

In a nutshell, the driving elements are the following:

- A total of EUR 185,741,743 in payment appropriations is planned to cover payments of cost claims of Calls 1 to 10 launched under IMI1 and pre-financing of first calls launched under IMI2.
- EUR 217,593,567 is foreseen in commitment appropriations for Calls for proposal launched under IMI2.

Total appropriations for running costs are foreseen at EUR 8,881,400. The increase is related to the needs of IMI2.

Financial Management

During 2014, the finance team will continue with its day to day activities of initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, and analysis of periodic reports and negotiations of financial and administrative parts of projects. These activities will be conducted in a timely manner that will be monitored through corporate KPIs, in particular payment times and budget execution.

Best practice and highest quality standards will be ensured through the availability of a Manual of Financial Procedures that is under regular revision. In addition, knowledge dissemination will be further developed through the development of further guidance and the tenure of several financial workshops, in particular targeting beneficiaries, with the aim to reduce errors in financial reporting.

5.3 Human Resources

Together with well-defined workflows and processes, human resources management is at the heart of IMI's Programme Office organisational efficiency, namely through:

- Adequate recruitments and staff performance assessment;
- A balanced workload allocation and clear teams coordination;
- Learning and development opportunities;
- A clear organisational culture and open communication;
- Inter-JU cooperation.

2014 Staffing level

In 2014, 9 work contracts have been extended until 31 December 2017, the end of the organisation's life under IMI1 legal framework. The renewal of a work contract is based on both the business need and the staff member performance appraisal.

Since 2012, IMI has reached the authorised ceiling of 36 staff members, of which 29 temporary agents and 7 contract agents. The total headcount remained identical in 2013 despite a growing workload. In 2014, IMI2 will grow up to 41 staff members, with 5 authorised additional staff (4 Temporary Agents, and 1 Contract Agent) under IMI2. Of these additional posts, 2 have been earmarked for priority recruitment in the fields of science and communication with a view to rapidly address additional activities and workload linked to IMI2 set up. Further details are available in sections 3 and 4.10.

As stated in the amended EU budget for 2014 and in the legislative Financial Statement annexed to the European Commission draft proposal setting up IMI2, the IMI Programme Office should keep on growing until it reaches a total of 49 staff members in 2017. This extension will call in 2015 for an adaptation of the organisation chart.

Learning and professional development opportunities for better efficiency and staff retention

The IMI JU's organisational efficiency is also the result of a rational learning and development policy. This policy relies on internal as well as external trainings in order to keep staff members up-to-date mainly on:

- IT skills on tools such as Word, Excel, MS Project or ABAC, the European Commission's financial IT tool, and on any IT tool developed by IMI;
- Scientific knowledge (Drug Development cycle, Medicines regulations or more specific topics linked to research area);

- Legal context: IP recent case law, financial regulations, audit rules, staff regulations, etc.;
- Communication: communication strategy, social media, public speaking, languages, etc.

All training actions are oriented towards greater flexibility and reactivity of staff (ability to back-up an absent colleague, good understanding of the work context, etc.).

IMI is faced with an inherent risk of high turnover which can be explained by short term contracts offered by a time-limited organisation. This risk points to the importance of stabilising IMI's workforce, which is critical in view of the increase in workload foreseen in 2014. The problem of staff retention is critical for an organisation of this size and remains a key challenge for HR in 2014. This requires maintaining a stimulating and motivating work environment.

A new staff regulation in 2014 but still the same internal culture and open internal communication

In 2014, one of IMI's HR objectives will be to implement the new Staff Regulation of the EU's civil service which entered into force on 1 January 2014. Changes include an increase of working time to 40 hours weekly and a reduction of some leave entitlements. The Governing Board will accordingly adopt IMI's implementing rules in line with the EU new Staff Regulations.

IMI JU will ensure a smooth transition for staff. It will first have to identify:

- Implementing rules from the European Commission to be adopted by analogy by IMI's Governing Board;
- Implementing rules to be redrafted before adoption by IMI's Governing Board in order to take into account the specificities of a Joint Undertaking. Most of the time, the size of the Executive Office explains the need to adapt the text.

If, 9 months after the European Commission has issued an Implementing rule, no action is taken from IMI's side (adoption by analogy, redrafting or opt-out), this Implementing Rule will automatically apply to IMI. In order to be able to implement a rule quicker, and in order to benefit from the input from its Staff Committee, IMI JU will limit this adoption by default to texts that:

- only brings small and/or technical changes;
- cannot be amended (e.g. rules on pensions etc.);
- don't require to be quickly implemented.

Since its autonomy IMI's Office has developed its own identity and work culture. This work culture is based on an open internal communication, ensuring that all staff members do share the same understanding of IMI's overall objectives and priorities. A consistent service-oriented culture has progressively arisen among staff members while maintaining compliance with the EU legal and regulatory framework and the highest ethical as well as integrity principles and rules.

Further efficiency and savings through inter-JU cooperation

In 2013, IMI continued to explore and encourage all flexible arrangements, including close collaboration with other Joint Undertakings, and mechanisms of pooling expertise for specific time-bound tasks. In 2014, IMI will be willing to go further notably through common calls for tender, common recruitment procedures (setting-up of common reserve lists for administrative positions), common approach on implementing rules, etc.

5.4 Information and Communication Technology

IMI ICT strategic objective is to deliver value to the business and to be a key enabler of new business initiatives with the goal of supporting and shaping the present and future of IMI. ICT applications and infrastructure aim at making all IMI processes simpler and more efficient.

The following table sets out an overview of ICT developments and activities planned in 2014.

IMI Core Business	
SOFIA (Submission OF Information Application)	<ul style="list-style-type: none"> – Electronic Signature (Q2) – Monitoring system for EFPIA In-Kind Contribution cap (Q1) – Ex-post Audit (Q2) – Interim Reviews (Q3) – Enhancements for Experts management (Q3)
ICT Internal Support	
DORA (Document Repository Application)	<ul style="list-style-type: none"> – Process flow for invoices approval (Q3)
ISA (Information System for Absences)	<ul style="list-style-type: none"> – Adapt for new staff regulations (Q1)
eMA (electronic Missions Application)	<ul style="list-style-type: none"> – New platform for managing the missions requests and expenses claims (Q2)
IMI Intranet	<ul style="list-style-type: none"> – Maintenance (continuous improvements)
ICT Tenders	
File, email and Print Servers plus support services	<ul style="list-style-type: none"> – Current FWC finishing in Q4 2014. New joint tender.
sTesta	<ul style="list-style-type: none"> – Current EC FWC renewed till next year. For 2014 a different supplier already selected by the European Commission.
Internet	<ul style="list-style-type: none"> – Current FWC finishing in Q4 2014. New joint tender.
Software development	<ul style="list-style-type: none"> – Current FWC finishing in Q4 2014. New tender.
Other IMI Business tools	
Support to Governance Bodies (Governing Board, Scientific Committee, States Representatives Group)	<ul style="list-style-type: none"> – Maintenance (continuous improvements)
PST (Partner Search Tool)	
Events Registration Tool (IMI and JTIs platforms)	
IMI website	

Figure 6

Support to IMI Core Business

The management of current IMI Calls and Projects plus related processes is done electronically via an integrated IT System: SOFIA (Submission of Information Application) and QlikView - a statistics and KPI monitoring module, with a variety of tailor-made dashboards, enabling the analysis of scientific and financial data in SOFIA.

Due to the increased workload derived also from the Calls launched in 2013 it is of vital importance to achieve completeness of SOFIA. Therefore 2014 developments will be as follow:

- Electronic Signature (Q2)

The financial statements and adjustments are already submitted to IMI electronically but the printing step for blue print signature is still required. In view of a paperless grant management in IMI the electronic signature for the electronic-only transmission of financial statements (Form C) and adjustments will be developed.

- Monitoring system for EFPIA In-Kind Contribution cap (Q1)

We will implement a monitoring system to allow easy verification that EFPIA non-EU In-Kind contributions remain within the caps defined by Special Clauses 13A and 13B.

- Ex-post Audit (Q2)

In 2014 it is envisaged to finalise the development of this module to support the ex-post audit sampling, implementation, analysis and follow-up.

- Interim Reviews (Q3)

EoI, FPP and ENSO evaluations are already managed via SOFIA. For 2014 it is envisaged to integrate in SOFIA the management of the Project Interim Reviews also, increasing efficiency and facilitating the capture of the output from project activities.

- Enhancements for Experts management (Q3)

In view of a paperless Call management it is envisaged to have in SOFIA the electronic-only administration of Experts including the appointment management.

Support to other IMI Business Tools

IMI has well established collaborative platforms to provide support to the Governance Bodies, namely the Governing Board, the Scientific Committee and the States Representatives Group. In 2014 such platforms will have continuous improvements whenever needed.

Regarding the Partner Search Tool (PST) in 2014 it is envisaged to enhance further its usability for coordinators and partners to team up.

The events registration tool has been extended to also help the management of events shared by other Joint Undertakings. Continuous improvements for the IMI events registration tool are envisaged to be implemented during 2014, such as a pre-event networking module and a workshop module.

ICT Tenders

2014 will be a demanding year concerning IT tenders as all Framework Contracts will be finishing. This also implies several planning and coordination of possible systems' handovers, should contracts be awarded to new operators.

ICT Internal Support

Further efficiency gains in the operations of the Office will be sought through improvements of IT systems. Key actions will include:

- Improvements to common file and email servers with other Joint Undertakings;
- Further development of DORA (DOcument Repository Application), the IMI JU's electronic document management system enabling full electronic processing, storage and fast retrieval of all official IMI documents, to manage the process flow for invoices approval;
- ISA (Information System for Absences) will be adapted to the new EU Staff Regulations;
- A new platform will be developed: eMA (electronic Missions Application) to manage the complete missions work flow, from the request up to expenses claim.

Following a request from other Joint Undertakings located in the same premises, in order to best exploit synergies towards enhanced efficiency and cost-effectiveness, IMI will make available its internal HR and other administrative IT applications for their own use.

In addition, staff portable laptops and printers shall be upgraded for the majority as they turn 3 years of usage.

5.5 Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI JU will allocate funds to procure the necessary services and supplies. In order to make tender and contract management as effective and cost-efficient as possible, IMI makes use as much as possible of multi-annual framework contracts and inter-institutional tenders. All essential framework contracts IMI is using will be running beyond 2014 with the exception of the IT and telephony services framework contracts mentioned below.

The most important contracts to be concluded in 2014²⁵ are the renewals of the framework contracts for IT support services; telephony infrastructure and support services; and software development. The call for tenders will be launched in Q1. IMI is tendering for the contracts in a single tender jointly with four other Joint Undertakings located in the same building and sharing the same ICT infrastructure²⁶.

As regards communication, in Q3 2013 IMI has expressed its interest to join a tender procedure carried out by European Commission's DG RTD for a framework contract for events' organisation. Therefore IMI has reversed its plan to launch its own procedure for a similar contract. For public relations consultancy, IMI intends to conclude a specific contract in 2014 under the framework contract of DG RTD.

On the operational side in 2013, IMI - concluded a contract for consultancy services to establish a platform to study the optimisation of exploitation of IMI's project results. This contract is likely to be renewed in 2014, a possibility foreseen in the original tender.

Furthermore, IMI JU will explore possible expansions of the KUL case study carried out in 2013 on IP and business outcomes of six IMI projects, notably by including a macroeconomic perspective.

Concerning the activities to support and monitor IMI projects, IMI JU will launch a tender procedure to provide projects with the necessary legal and financial expertise and support to explore and implement sustainability plans.

²⁵ I.e. tenders for contracts with a value exceeding €130,000, which is the statutory limit for publication of the tender in the S series of the Official Journal. In addition, IMI uses negotiated procedures for low-value contracts below this statutory threshold.

²⁶ ARTEMIS JU, Clean Sky JU, ENIAC JU and FCH JU.

5.6 Data protection and access to documents

Data protection

In 2014, IMI JU will continue to ensure that personal data are protected and that Regulation (EC) No 45/2001 is complied with. Key actions for 2014 will include:

- Raising awareness with the IMI JU Staff: the IMI Data Protection Officer will invest time in informing the staff in particular in relation to the implementation of the accountability principle and to the follow-up of the new thematic guidelines issued by the European Data Protection Supervisor;
- Finalising procedures internally for handling notifications related to standard administrative procedures or addressing new processing operations;
- Follow-up on developments and implementation of the revised EU legal framework for data protection, alongside a continuous analysis of the impact of technological developments on personal data protection, especially those connected to the Internet.

Access to documents

IMI will also continue to address requests for access to IMI documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and output closer to the public.

The objectives of actions in this field will continue, as a means to strengthen public confidence in IMI by giving the opportunity to the public to monitor its work. In addition, this will bring additional benefits such as improving public awareness of IMI activities and processes as well as stimulating the interaction on key issues and on the future of IMI.

6 INTERNAL CONTROL AND AUDIT ENVIRONMENT

IMI JU has in place an integrated management system of governance structures, internal controls and risk management procedures to plan and implement its strategic and operational goals and objectives. In addition, the organisation relies on a combination of internal and external audits, ex-post audits, performance measurement tools, continuous improvement initiatives and independent expert reviews to monitor and ensure that IMI JU remains efficient, effective and compliant with all relevant regulations, rules and procedures. The existing internal control and audit set-up and arrangements take into account the nature and objectives of the public-private partnership as well as its size and organisational needs.

IMI JU will continue to build on the experience and lessons learned from the past four years as well as respond and adapt to new challenges and developments. It will implement and enhance its established internal control measures, ensuring in the process that all critical risks are appropriately mitigated; key priorities are achieved; legal and regulatory requirements are complied with; and stakeholders' expectations are met. The annual risk assessment exercise carried out by the Executive Office in the second semester of 2013 signalled the need to take specific measures in 2014 to adequately manage the risks resulting from the envisaged transitional change to reflect Horizon 2020 objectives, obligations and *modus operandi*, as well as to mitigate the risk that IMI JU may continue to detect an average 'error rate' that is higher than the 2% threshold set for the programme.

More specifically, throughout 2014, management will pro-actively assess and ascertain the robustness of internal controls and ensure overall compliance with rules and procedures. This will be achieved mainly through the:

- Review, coordination and follow up of the annual action plan for the implementation of IMI JU's internal control standards (ICS);
- Maintenance of a systematic risk management process in the annual planning and the conduct of an annual risk assessment exercise;
- Identification and prioritisation of the ICSs that need to be improved taking also in consideration the recommendations resulting from internal and external audits;
- On-going self-assessment and reporting on IMI JU's formal compliance with the ICS and on the effectiveness of the ICS put in place.

The following ICSs will be therefore prioritised for the year 2014:

ICS 3,²⁷ ICS 7²⁸ and ICS 10²⁹

Particular attention will be given to the impact of new challenges and developments on the organisation structure as well as on staff allocation and business continuity. This is crucial in order to ensure that the structure and resources in IMI JU continue to meet evolving organisational objectives and needs.

ICS 5

Objective and Performance Indicators: Management will ensure that annual goals and objectives as well as key performance indicators are updated to reflect changing strategic priorities.

ICS 8

Processes and procedures: Management will take measures to safeguard the integrity and maturity of IMI JU's internal control system as the organisation evolves to respond to new challenges and developments.

²⁷ Staff allocation and flexibility

²⁸ Operational structure

²⁹ Business continuity

Ex-Post Audits of beneficiaries and EFPIA companies

Throughout 2014, the Executive Office will carry on with the implementation of the Ex-post Audit Strategy adopted in 2010 to ensure the legality and regularity of the operational expenditure. This strategy complements ex-ante controls embedded in IMI JU's management processes and includes the correction of any amounts found to have been paid in excess. Errors of a systematic nature will also continue to be extended to cover unaudited financial statements ('Forms C') of the same participants.

Representative and, if necessary, risk-based audits of beneficiaries will be launched during the year to cover new cost claims received and validated by IMI JU since the last audited period. In parallel, independent reviews of submitted certificates of in-kind methodology as well as audits of accepted declarations of in-kind contributions by EFPIA companies will also be continued and followed-up.

Internal and External Audit

In 2014, the Internal Audit Service of the European Commission (IAS) and the Internal Audit Capability (IAC) of IMI JU will continue to implement the coordinated multi-annual audit strategy for 2012-2014. These activities will include the provision of independent, objective assurance as well as consulting engagements on various aspects of IMI JU's processes and activities.

In parallel, during the year, the European Court of Auditors will audit and report on the reliability of IMI JU's 2013 Annual Accounts as well as the legality and regularity of the underlying transactions.

Anti-fraud strategy

In 2014, IMI JU will prepare and implement a comprehensive anti-fraud strategy in line with the European Commission Anti-Fraud Strategy (COM(2011)376) applicable to its services and also extended to agencies and other EU bodies.

Anti-fraud measures are part of sound financial management required under the EU Financial Regulation. In essence, the anti-fraud strategy will outline specific objectives and pro-active actions for fraud protection and detection within the existing internal control system with the aim of further protecting IMI JU's financial interests, its compliance with ethical values and the protection of the JU's reputation. The strategy will cover the following features:

- preventive measures against fraud, corruption and any other illegal activities;
- carrying out effective checks;
- recovering amounts wrongly paid and
- imposing effective, proportionate and dissuasive administrative and financial penalties where appropriate.

**ANNEX I - DRAFT BUDGET 2014, INCLUDING STAFF ESTABLISHMENT PLAN 2014
(version 27/06/2014)**

STATEMENT OF REVENUE				
Heading Revenue		Financial year 2014		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	EU contribution	217 973 700	165 627 993	Commitment appropriations include EUR 4,440,000 for running costs and EUR 213,533,700 for operational costs. Payment appropriations include running costs of EUR 4,440,000 and operational costs of EUR 161,187,993.
	Title 1 - Total	217 973 700	165 627 993	
20	EFPIA contribution	4 440 000	4 440 000	EFPIA contribution to IMI JU running costs
	Title 2 - Total	4 440 000	4 440 000	
C2	Title 3 - Total	880 903	733 257	
	Total EU (operational and running costs) and EFPIA (running costs) contribution	223 294 603	170 801 250	
STATEMENT OF EXPENDITURE				
Heading Title 1		Financial year 2014		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	4 370 000	4 370 000	Salaries
12	Staff recruitment - miscellaneous expenditure	25 000	25 000	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190 000	190 000	Mission expenses
14	Sociomedical structure	250 000	250 000	Other staff costs: training, language classes, medical service, interim staff
17	Entertainment and representation	20 000	20 000	Representation, receptions and internal meetings (EC/EFPIA)
	Title 1 - Total	4 855 000	4 855 000	
Heading Title 2		Financial year 2014		Comments
Chapter		Commitment Appropriations (CA)	Payment Appropriations (PA)	
20	Office building and associated costs	590 000	590 000	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	583 000	583 000	IT purchases, software licences, software development, IMI website
22	Office equipment (movable property and associated costs)	145 000	145 000	Purchases and rental of office equipment, maintenance and repair
23	Current administrative expenditure	130 000	130 000	Office supply, literature, subscriptions, translation services, bank charges and miscellaneous office expenditure
24	Telecommunication and postal expenses	67 000	67 000	Data communication such as telephones, video conferences and postal services
25	Expenditure on formal meetings	160 000	160 000	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by GB
26	Running costs in connection with operational activities	500 000	500 000	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects)
27	External communication, information and publicity	650 000	650 000	External communication and events such as Info Days, Stakeholder forums
28	Service contracts	580 000	580 000	Studies, audits
29	Expert contracts and cost of evaluations	620 000	620 000	Costs linked to evaluations, expert contracts
	Title 2 - Total	4 025 000	4 025 000	
	Total Running Costs	8 880 000	8 880 000	
Heading Title 3		Financial year 2014		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementating the research agenda of IMI JU	213 533 700	161 187 993	Grant Agreements - Payments
C2	Carry over from 2013	880 903	733 257	
	Title 3 - Total	214 414 603	161 921 250	
	Total EU (operational and running costs) and EFPIA (running costs) contribution	223 294 603	170 801 250	

Figure 7

Staff establishment plan 2014

Grade	Establishment plan 2013			Year 2014														
				Posts evolution						Organisational evolution			Establishment Plan 2014			Modifications envisaged in application of flexibility rule		
	Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Authorised								
	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	Temp - LT	Temp - ST	Perm	Temp	Total	Perm	Temp	Total
AD16		0	0								0			0	0		0	0
AD15		0	0								0			0	0		0	0
AD14		1	1								0			1	1		1	1
AD13		0	0								0			0	0		0	0
AD12		1	1								0			1	1		1	1
AD11		4	4								0			4	4		4	4
AD10		0	0								0			0	0		0	0
AD9		2	2								0			2	2		2	2
AD8		9	9								0			9	9		9	9
AD7		5	5								0			5	5		7	7
AD6		0	0								0			0	0		0	0
AD5		1	1								10			11	11		3	3
Total AD	x	23	23	0	0	0	0	0	0	x	10	x	x	33	33		27	27
AST11		0	0								0			0	0		0	0
AST10		0	0								0			0	0		0	0
AST9		0	0								0			0	0		0	0
AST8		1	1								1			0	0		1	1
AST7		0	0								0			0	0		0	0
AST6		0	0								0			0	0		0	0
AST5		0	0								0			0	0		0	0
AST4		0	0								0			0	0		0	0
AST3		5	5								5			0	0		5	5
AST2		0	0								0			0	0		0	0
AST1		0	0								0			0	0		0	0
Total AST	x	6	6	0	0	0	0	0	0	x	6	x	x	0	0		6	6
Overall Total		29	29	0	0	0	0	0	0					33	33		33	33

Figure 8

**ANNEX II - PRELIMINARY BUDGET 2015,
INCLUDING PRELIMINARY STAFF ESTABLISHMENT PLAN 2015 (version 26/06/2014)**

STATEMENT OF REVENUE				
Heading Revenue		Financial year 2015		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	EU contribution	222 034 267	190 182 443	Commitment appropriations include EUR 4,440,700 for running costs and EUR 217,593,567 for operational costs. Payment appropriations include running costs of EUR 4,440,700 and operational costs of EUR 185,741,743.
	Title 1 - Total	222 034 267	190 182 443	
20	EFPIA contribution	4 440 700	4 440 700	EFPIA contribution to IMI JU running costs
	Title 2 - Total	4 440 700	4 440 700	
	Total EU (operational and running costs) and EFPIA (running costs) contribution	226 474 967	194 623 143	
STATEMENT OF EXPENDITURE				
Heading Title 1		Financial year 2015		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	4 392 760	4 392 760	Salaries
12	Staff recruitment - miscellaneous expenditure	20 000	20 000	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190 000	190 000	Mission expenses
14	Sociomedical structure	230 000	230 000	Other staff costs: training, language classes, medical service, interim staff
17	Entertainment and representation	20 000	20 000	Representation, receptions and internal meetings (EC/EFPIA)
	Title 1 - Total	4 852 760	4 852 760	
Heading Title 2		Financial year 2015		Comments
Chapter		Commitment Appropriations (CA)	Payment Appropriations (PA)	
20	Office building and associated costs	661 640	661 640	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	561 000	561 000	IT purchases, software licences, software development, IMI website
22	Office equipment (movable property and associated costs)	153 000	153 000	Purchases and rental of office equipment, maintenance and repair
23	Current administrative expenditure	123 000	123 000	Office supply, literature, subscriptions, translation services, bank charges and miscellaneous office expenditure
24	Telecommunication and postal expenses	67 000	67 000	Data communication such as telephones, video conferences and postal services
25	Expenditure on formal meetings	158 000	158 000	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by GB
26	Running costs in connection with operational activities	500 000	500 000	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects)
27	External communication, information and publicity	625 000	625 000	External communication and events such as Info Days, Stakeholder forums
28	Service contracts	580 000	580 000	Studies, audits
29	Expert contracts and cost of evaluations	600 000	600 000	Costs linked to evaluations, expert contracts
	Title 2 - Total	4 028 640	4 028 640	
	Total Running Costs	8 881 400	8 881 400	
Heading Title 3		Financial year 2015		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementating the research agenda of IMI JU	217 593 567	185 741 743	Grant Agreements - Payments
	Title 3 - Total	217 593 567	185 741 743	
	Total EU (operational and running costs) and EFPIA (running costs) contribution	226 474 967	194 623 143	

Figure 9

Staff establishment plan 2015

Grade	Year 2015																		
	Establishment plan 2014				Posts evolution						Organisational evolution			Establishment Plan 2015			Modifications envisaged in application of flexibility rule		
					Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Provisional Draft Budget)					
	Total	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	Temp - LT	Temp - ST	Perm	Temp	Total	Perm	Temp	Total
AD16			0	0											0	0		0	0
AD15			0	0											0	0		0	0
AD14			1	1											1	1		1	1
AD13			0	0											0	0		0	0
AD12			1	1											1	1		1	1
AD11			4	4											4	4		4	4
AD10			0	0											0	0		0	0
AD9			2	2											2	2		2	2
AD8			9	9											9	9		9	9
AD7			7	7											5	5		7	7
AD6			0	0											0	0		0	0
AD5			3	3											1	1		5	5
Total AD	x	x	27	27	0	0	0	0	0	0	x	x	x	x	23	23		29	29
AST11			0	0											0	0		0	0
AST10			0	0											0	0		0	0
AST9			0	0											0	0		0	0
AST8			1	1											1	1		1	1
AST7			0	0											0	0		0	0
AST6			0	0											0	0		0	0
AST5			0	0											0	0		0	0
AST4			0	0											0	0		0	0
AST3			5	5											5	5		5	5
AST2			0	0											0	0		0	0
AST1			0	0											0	0		0	0
Total AST	x	x	6	6	0	0	0	0	0	0	x	x	x	x	6	6		6	6
Overall Total			33	33	0	0	0	0	0	0					29	29		35	35

Figure 10

Annex III – CALLS FOR PROPOSALS TO BE LAUNCHED IN 2014

The first calls for proposals of IMI2 will be launched to implement the 2014 Scientific Priorities. It is expected that at least 2 Calls for proposals will be launched covering at least 4 topics.

1st IMI2 CALL FOR PROPOSALS

The 1st Call of IMI2 shall be launched on 9th July 2014.

INTRODUCTION

The Innovative Medicines Initiative 2 (IMI2) Joint Undertaking has been created³⁰ following the below principles:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps³¹, from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The [IMI2 Strategic Research Agenda](#) (SRA) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include themes on metabolic disorders and neurodegeneration which are addressed in this call.

³⁰ The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

³¹ Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in an EU Member State or an associated country, are eligible for funding.

Applicant consortia are invited to submit short outline proposals to one of the topics. These proposals 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.

While preparing their short outline proposals, applicant consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. 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.

Before submitting a short outline proposal, applicant consortia should familiarize themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria.

1. TRANSLATIONAL APPROACHES TO DISEASE MODIFYING THERAPY OF TYPE 1 DIABETES MELLITUS (T1DM)

BACKGROUND AND PROBLEM STATEMENT

The global prevalence of diabetes has risen dramatically over the past decades. Whilst the connection between change in lifestyle patterns and type 2 diabetes mellitus (T2DM) seems undisputed, the connection between increased urbanization and type 1 diabetes remains a conundrum. Type 1 diabetes mellitus (T1DM) is a chronic disease affecting worldwide around 17 million people (World Health Organization's Priority Medicines for Europe and the World 2013 update, p.88). Type 1 disease has its peak incidence at puberty, but may occur at any age. The incidence rate is highest in Europe affecting altogether 22/100.000 per year, with major regional differences and an overall 25% higher incidence rate than in the United States of America (USA) (www.diapedia.org). The incidence of childhood T1DM is rapidly on the rise worldwide, especially in the under 5 year old age group.

T1DM is characterized by hyperglycemia due to destruction and loss of insulin-producing pancreatic beta cells and function over time. Furthermore, T1DM can be differentiated from the more common T2DM based on one or several autoantibodies directed towards antigens of the endocrine pancreatic islets. The emergence of islet autoantibodies as biomarkers preceding clinical islet beta cell failure has led to the generally held view that T1DM is an autoimmune disease and that immunologic abnormalities occur well ahead of clinical onset. The precise cause of type 1 diabetes is unknown, and believed to be due to one or more of the following: genetic susceptibility, dysfunctional programming of immune tolerance,

diabetogenic trigger(s) and/or exposure to a driving antigen. Recent analyses of pancreatic autopsy specimens from individuals with longstanding T1DM surprisingly demonstrate a heterogeneous but unexpected persistence of residual pancreatic beta cells despite insulin deficiency and active autoimmunity. These unexpected findings highlight the need for additional translational research to enable a deeper understanding of the pathophysiology, heterogeneity, and natural history of T1DM in humans.

The disease is currently not preventable and no cure is available. The only available pharmacotherapy for T1DM patients is the lifelong injection of insulin. Management of T1DM is not trivial as it is associated with multiple daily “finger pricks” to control blood glucose and requires multiple injections of insulin replacement therapy. A significant further burden is the risk of insulin induced hypoglycaemia which is currently considered the most significant barrier for optimization of adherence. An alternative approach to subcutaneous insulin replacement therapy is pancreas or pancreatic islet cell transplantation but existing cell replacement therapies require immunosuppression and are limited to very few recipients.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

For almost a century, pharmacotherapy of T1DM has been synonymous with insulin therapy. Although undisputedly very successful, insulin therapy is associated with recognized limitations, such as adherence and drug induced hypoglycaemia. Stakeholders involved in care of people with T1DM as well as patients themselves agree that truly disease modifying therapy remains the ultimate approach to solve the challenge. Very few experimental alternatives to insulin therapy have been approached and clinical experimentation in the field of T1DM care has been modest at best. Considering the rapid growth of T1DM prevalence and the gravity of the problem, stakeholders in the T1DM community agree that is about time to intensify innovation in the field of T1DM therapy.

The pharmaceutical industry represented through EFPIA is highly motivated to play a leading role in establishing the widest possible cross-functional consortium with representatives from patient advocacy groups, health authorities, diabetes care givers, innovators, and industrialists. The objective is clearly to launch discovery programs in the field of T1DM that could lead to prevention as well as disease modifying and ultimately curative therapy. To achieve this ambitious goal deeper insight into the heterogeneous, phenotypic characteristics of people either at risk of developing T1DM or having manifest disease is required. This goal can only be achieved by pooling the knowledge, expertise and resources of all key stakeholders in the area, both public and private. Using state of the art technologies it is envisioned that this initiative will focus on a complete mapping of interactions between the immune system and pancreatic beta cells in humans and on the environmental changes that has led to increased disease incidence.

Through a thorough mapping of environmental and molecular mechanisms leading to T1DM, it will become possible to draft preventive strategies and to design future disease modifying therapies. The research strategy of the call shall embrace a strong focus on translational medical activities initiated at the bedside, refined at the workbench, and then finally brought back to the bedside for clinical validation of potential therapeutic approaches aiming at fundamentally preventing, halting, and reversing the β -cell destructive course of T1DM.

OVERALL OBJECTIVES

The overall aim of the initiative is to significantly progress the understanding of T1DM disease by bringing together patients, health authorities, leading clinicians, and researchers from the areas of immunology, beta cell biology, and biomarker research from both academia and industry.

Based on the assumption that T1DM is primarily driven by immunological dysfunction leading to beta cell destruction, it is expected that this initiative will significantly progress the understanding of the pathophysiology, heterogeneity, and natural history of T1DM in humans.

Translational medicine efforts mapping all stages of the disease are considered a pre-requisite for the initiation of rational drug discovery programs. As the program progresses, leading to the formulation of hypotheses of central pathophysiological processes in the development of T1DM, it is envisioned that the consortium will initiate clinical experimental studies that focus on validation in clinical studies of the newly acquired insights of dysfunctional molecular pathways leading to manifest T1DM.

POTENTIAL SYNERGIES WITH EXISTING EU SPONSORED CONSORTIA

It is expected that the project generated by this call will synergise and build on the results and assets of previous and ongoing European effort in diabetes including IMI projects in the diabetes area. The IMIDIA project (<http://www.imidia.org/>) has established a unique standardized, continuously growing human biorepository of biofluids (plasma, serum), pancreatic tissue and pancreatic beta cells from mostly adult diabetes and non-diabetic control subjects (predominantly T2DM).

The DIRECT project (<http://www.direct-diabetes.org/index.php>), while focussing on type 2 diabetes also is establishing a comprehensive collection of biosamples and clinical information on non-diabetic control subjects that can be of high value for the T1DM call.

In addition synergies with FP7-supported consortia in the fields of T1DM can be seen, e.g. to BIOSID (http://ec.europa.eu/research/health/medical-research/diabetes-and-obesity/projects/biosid_en.html), DIABIL_2 (<http://www.diabil-2.eu/>), DIABIMMUNE (<http://www.diabimmune.org/>), DIAMAP (<http://www.diamap.eu/>), DIAPREPP (<http://www.diaprepp.eu/>), NAIMIT (<http://naimit.eu/>), PREPOBEDIA (<http://www.prepobedia.org/>).

In addition synergies in the field of type 1 diabetes could be established with BBMRI (<http://bbmri.eu/>).

Another important synergy can be envisaged with the efforts of the global TRIALNET initiative (<https://www.diabetestrialnet.org/about/index.htm>).

The JDRF nPOD resource (<http://www.jdrfnpod.org>) of tissues (pancreas and other organs) from donors with diabetes, at-risk of developing T1DM, as well as non-diabetes controls, will also synergize with the efforts of this program.

EXPECTED KEY DELIVERABLES

Disease Biology and Translational Medicine (Target & Biomarker Identification)

It is envisioned that a pan-European clinical trial and translational research network will be built, including creation of a T1DM patient registry of readily accessible cohorts of T1DM patients willing to participate in future clinical research in the field. The network will facilitate a systematic and comprehensive functional and molecular profiling of disease heterogeneity, and identification of high-risk subjects beyond the use of islet-autoantigens.

The expanding on existing patient registries and prospective cohorts as well as the establishment of new cohorts shall be used to focus on:

- Systematic prospective and retrospective launch of broad “-omics” characterization of human biological samples from new-borns/infants/children/adolescents/adults at risk of developing diabetes as well as from newly diagnosed T1DM patient cohorts undergoing standard glucose control therapy. Such “full -omics” analysis should include both “at risk” subjects (HLA+AA-, HLA+AA+), as well as new onset T1DM patients to identify molecular markers in patient biofluids (blood, plasma, serum, lymph, urine)
 - Transcriptome assessment from enriched cells / particular fluid samples (including short RNAs and microRNA profiling)
 - SNP mapping & eQTL analysis, next generation sequencing of fast progressing, “at risk” subjects
 - Analysis of the gut microbiome
 - Metabolomics assessment (from available biofluids)

- Proteomics and phosphoproteomics assessment (from exosome/biofluids)
- Systematic epigenetic analysis (incl. methyl- & acetylation profiles).
- Phenotypic characterization (in silico based on medical records, as well as through active experimental clinical studies)
 - Identification of the glucose responsiveness as an indicator for patient beta cell status (OGTT, fasting blood sugar, hypoglycaemia propensity)
 - Pilot studies of imaging pancreatic inflammation
 - Behavioural phenotypes (therapeutic adherence, dietary preferences, exercise, cognitive)
- Establishment of systematic large-data and bio-bank repositories enabling extensive cross functional data mining and modelling of disease incidence and progression.
- Long term glucose control (HbA1c) status in recent onset patients as well as in relevant controls
- Exploration of imaging technologies for the use of identification and stratification of high-risk patients and as a surrogate end point in clinical studies.

Further activities could embrace novel methods to measure auto reactive T cell functional responses. Characterization of leukocytes obtained from patient blood, lymph or tissue samples to identify immune cell targets and surrogate end points are desired. A goal will be to define, standardize, and ultimately approve biomarker and immune profiling analysis that could be implemented for staging participants in future T1DM clinical trials in Europe. Prerequisite for successful outcome of such standardization effort is active participation of innovators, regulatory authorities, health care providers, and patient representatives.

In parallel, the project must focus on the metabolic characterisation of T1DM patients, such as the status of β -cell function, or changes and defects in β -cell proliferation mechanisms (glucose, glucokinase, PDGF(R), WNTs), and beta cell stress/death in people with T1DM. Leveraging and enabling access to human pancreatic beta cells, islets, and pancreatic tissue from T1DM patients, through direct or collaborative efforts, should be prioritized by the consortium. In some instances implementation of surrogate assays of immune system interaction with islet function may be required, and it is suggested that the consortium integrate learnings from previous IMI and EU funded projects.

Qualification of identified biomarkers as diagnostics, as well as detailed characterization of the prediabetic period using novel diagnostics such as implantable micro-devices and early detection of autoantibodies (“Lab on a chip”) should be considered. Innovation of technically viable diagnostics solutions may require involvement of specialized entrepreneurs not traditionally represented by EFPIA members.

Identification and validation of biomarkers reflective of the disease progression including β -cell specific “ID tag” to quantify/monitor beta cell mass is also of high interest as it will assist novel disease taxonomy.

Defining and refining disease taxonomy for T1DM may create the foundation for personalized therapy of T1DM by the use of novel biomarker candidates and imaging technologies for the identification and stratification of high-risk patients and as a surrogate end point in clinical studies (consolidate health authority acceptance of T1DM disease classification as basis for medical decision making and approval of novel T1DM therapies).

Furthermore, the initiative will consider the development and characterization of most translatable preclinical T1DM models for discovery of novel clinical therapies to verify the newly acquired molecular knowledge for their human disease translatability.

Translational medicine efforts mapping all stages of the disease are considered a pre-requisite for the initiation of rational drug discovery programs aiming at treating the underlying causes of β -cell failure in people with T1DM.

Innovative clinical trial paradigms

During the past decade, a limited number of clinical trials have tested a variety of therapeutic approaches aimed at modifying immune function in people at risk for developing T1DM or with manifest disease. Therapeutic approaches have included attempts to induce immune tolerance to known islet autoantigens (proinsulin, GAD65), immune suppression through T cell modifying therapies (e.g. anti CD3), and anti-inflammatory antibodies (e.g. anti-IL-1 β and anti-TNF α). These therapeutic approaches have been characterized by highly diverse clinical trials protocols and inconsistent primary end-points, rendering direct comparisons of efficacy and safety difficult. Guided by translational insights to the disease, the program is expected to facilitate the development of standardized clinical trial protocols with clearly defined, clinically meaningful, evidence based end-points providing indisputable medical value for people with T1DM as well as society.

As it is expected that the thorough characterization of “at risk” populations and newly diagnosed T1DM patients will consolidate existing as well as spur novel hypotheses for T1DM aetiology and pathophysiology, a clinical trial network shall also be used as vehicle for clinical research aiming at validating potential novel therapies.

Existing evidence suggest that a highly targeted T-cell mediated immune response is responsible for the islet destruction seen in T1DM. Therefore, modelling sequential T cell activation, T cell mediated cytotoxicity, and dysfunctional T cell regulation has led to a number of possible immunomodulatory approaches that have yet to be tested in people with new onset T1DM. In particular, in silico modelling based on in vitro and on animal data suggest that sequential combination of immunomodulatory agents (T cell specific antibodies, modulators of chemotaxis, inducers of immunological tolerance) may provide rational approaches for clinical trials aimed at halting the progression of the immune based destruction of beta cells and ultimately inducing tolerance to the triggering autoimmune event. It is expected that the established clinical trial network will engage in testing such novel immunomodulatory and tolerance inducing principles. The following deliverables are envisioned:

- Generation of a European comprehensive network of clinical and translational research centres capable of recruiting and conducting clinical trials in people with T1DM (providing a prospective clinical trials database for T1DM).
- Development of standardized entry criteria and endpoints for T1DM trials (both metabolic and immune profiles) preferably in collaboration with clinical centers in the US and with participation of patient advocacy groups, and regulatory authorities.
- Implementing the use of electronic data capture devices to collect an array of “real world data” useful for verification of therapeutic area hypotheses, regulatory rapports, etc.
- Testing and development of novel bio-statistical methodologies applicable to new compositions of relevant end points for T1DM clinical trials.
- Evaluation of novel mono- and combination approaches (i.e. combining multiple immune modulatory approaches, immune cell migration modification, immune tolerance inducers, β -cell enhancing therapeutics) in people with T1DM.
- The pan-European clinical trial and translational research network is expected to make important contributions to the evaluation of new emerging biomarkers and diagnostics indicative of T1DM disease progression or disease modification in clinical settings.

Patient participation

To aid in making the projects generated by this call more patient-centric, the project will be expected to establish a T1DM Patient Advisory Committee to enable input from patients and family members into the research involving subjects with T1DM and their biosamples and research around the development of innovative clinical trial paradigms. The T1DM Advisory Committee should include patients with T1DM of varying age and varying duration of disease, individuals at-risk of developing T1DM, and family members of children and adults with T1DM.

INDUSTRY CONSORTIUM

From the pharmaceutical industry consortium it is expected that specialists from the areas of molecular biology, chemistry, biologics, preclinical & clinical pharmacology, bioinformatics, translational medicine and clinical trials will actively participate in the projects work packages.

EFPIA PARTICIPANTS AND ASSOCIATED PARTNERS

Sanofi (coordinator), Juvenile Diabetes Research Foundation (JDRF) (co-coordinator), Novo Nordisk, Eli Lilly, GSK, Helmsley Charitable Trust. The EFPIA partners have invited the JDRF and Helmsley Charitable Trust to participate as equal partners in the steering group formulating this T1DM focused call. The JDRF (<http://jdrf.org/>) is a not for profit organisation focusing on patient advocacy as well as funding of research in the field of T1DM. The Helmsley Charitable Trust (<http://helmsleytrust.org/>) is a charitable organisation supporting research in health, selected place-based initiatives, education and human services. Both organisations participate in the present topic as Associated Partners to IMI2.

Additional companies are under consideration and the final list is to be confirmed.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 84 month (7 years). This duration allows in depth systematic molecular analysis and immune and metabolic phenotyping of retrospective and prospective collected biological samples from T1DM patient cohorts. Further, the obtained insights will be integrated into novel to be established and existing models. Finally, the comprehensive patient characterization will be thoroughly integrated in to be defined prospective clinical trials.

FUTURE PROJECT EXPANSION

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, if so foreseen in the applicable annual work plan, may publish at a later stage another call for proposals restricted to those projects already selected under this call in order to enhance their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit.

In the context of this topic, the EFPIA companies already envision the possibility to expand the project scope, during its implementation, to support clinical trials with immune-modulatory compounds in development. A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables related to innovative clinical trial paradigms (e.g. clinical trial networks, identification of at risk patient population, definition of standardized entry criteria and endpoints, and novel bio-statistical methodologies for T1DM clinical trial). The detailed scope of the call will be described in the relevant annual work plan.

INDICATIVE BUDGET

The indicative contribution from EFPIA companies and Associated Partners is EUR 17 630 000.

The financial contribution from IMI2 JU will be a maximum of EUR 17 630 000.

Justification for Sanofi and JDRF non-EU in-kind contribution

Sanofi's non-EU in-kind contribution amounts to EUR 3 000 000. Studies in preclinical models for the evaluation of the role of the autoimmune system in the development of T1DM are available at Sanofi sites based in the US (Genzyme). The inclusion of these autoimmune models in the project and the linkage of their results to the outcome from studies on beta-cell function are required to evaluate novel translatable preclinical models mimicking human T1DM. Comparable preclinical autoimmune models are not available at EU-based Sanofi sites. Furthermore, non-EU contribution will be generated by the partial manufacture of the autoimmune antibody that will be investigated in a clinical trial of the "Innovative Clinical Trial Paradigms in T1DM" part of the project.

JDRF non-EU contribution amount to EUR 420 000, to cover costs of their US based personnel.

TYPE OF ACTION

Research and Innovation action

APPLICANT CONSORTIUM

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

To address the complex tasks of the call adequately, the project is expected to build a pan-European clinical trial and translational research network including a clinical registry of eligible people with T1DM. Such network will include:

- Academic endocrine clinics and associated supporting departments
- Basic, translational, and clinical researchers from the fields of T1DM autoimmunity and β -cell biology,
- Drug discovery and medical staff in Pharmaceutical Industry and Small and Medium size Enterprises.
- Hands-on data base specialists and big data managers
- Patient organizations/representatives
- Experts in regulatory science and health technology assessment preferably representing European health authorities.

Cross fertilization in this team of experts is the key for the success of the initiative.

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The above described cross functional and cross sector team members are recommended to work together in dedicated work packages addressing the different aspects of the overall call. Each work package team is recommended to consist of academic and industrial/biotech members with regular interactions to ensure knowledge exchange between the different expertise. Inter-work package knowledge transfer should be ensured at all times via regular management board meetings. The jointly used data documentation tool is considered a key piece for the success of the overall call ensuring maximum information gain by applying systems biology.

In addition a plan for interactions with Regulatory Agencies/Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

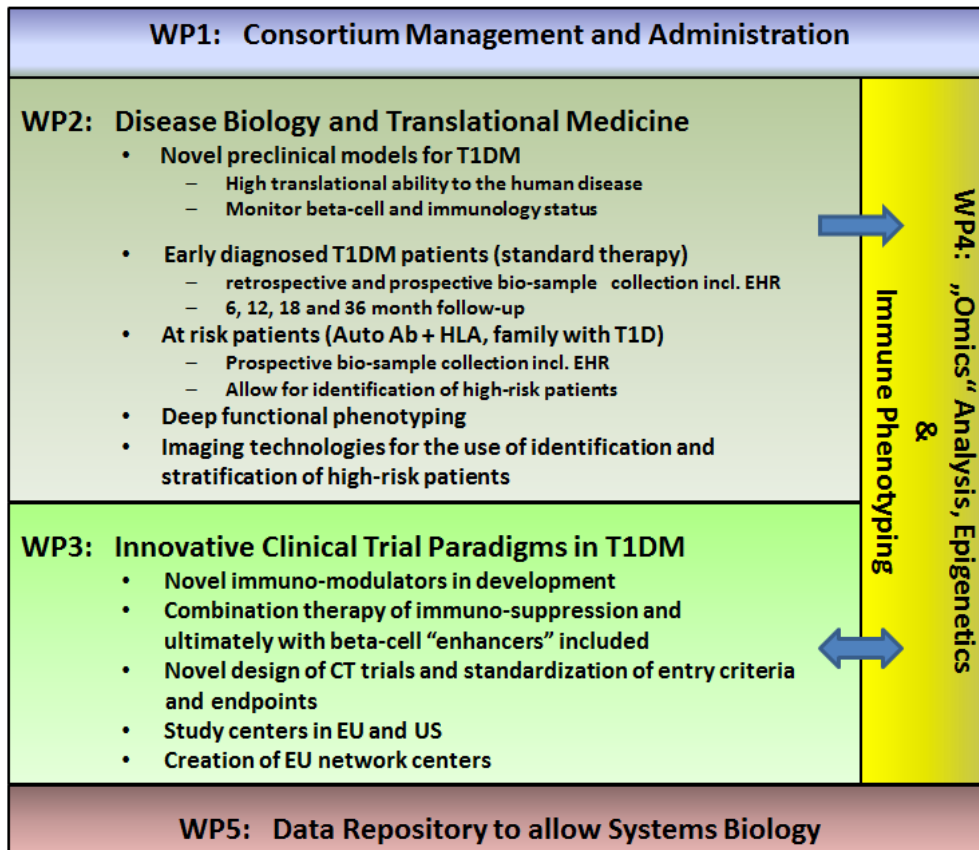
Please also note that the following outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

Suggestion for project structure

This project is suggested to be organized in 4 major work packages:

- WP2: Disease Biology and Translational Medicine
- WP4: “Omics” Analysis, Epigenetics and Immune Phenotyping
- WP3: Innovative Clinical Trial Paradigms in T1DM
- WP5: Data Repository to allow Systems Biology



As a result of this, the project will:

- significantly progress the understanding of the pathophysiology, heterogeneity and natural history of T1DM in humans,
- improve the knowledge on translatable preclinical models for T1DM,
- facilitate the development of standardized clinical trial protocols with defined clinically relevant, evidence based entry- and end-point criteria and the evaluation of novel mono & combination treatment approaches.

2. DISCOVERY AND VALIDATION OF NOVEL ENDPOINTS IN DRY AGE-RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

BACKGROUND AND PROBLEM STATEMENT

Diseases of the retina are among the leading causes of blindness world-wide. Substantial progress has been made in the treatment of neovascular age-related macular degeneration (neovascular AMD) and diabetic macular edema (DME). However, for other common retinal conditions such as the dry form of AMD (dry AMD) or diabetic retinopathy (DR) treatment options remain limited. One major development hurdle is the lack of suitable, patient-relevant study endpoints with clinical relevance both in early exploratory and pivotal trials. Moreover, there are significant gaps in the understanding of how pre-clinical findings translate into outcomes. This results in the following problem statements:

- Best corrected visual acuity (BCVA) and derived variables are the only endpoints that have served as basis for regulatory approval of retinal drugs. However, BCVA captures only a small portion of visual function. Dry AMD or DR patients may have good BCVA, in spite of significant clinical impairment resulting in difficulties with daily activities such as reading or driving. There is a lack of methodology/instrumentation to quantify this type of vision impairment robustly and reliably.
- There is a lack of short-term endpoints predictive for visual acuity outcomes that would qualify as sufficiently predictive proxy in an early proof-of-concept or dose-finding study or even as surrogate endpoints in pivotal trials.
- There is a lack of predictive markers and models (animal models and cellular systems) translating from the preclinical to the clinical setting. It needs to be evaluated to what extent novel visual function measures will translate from pre-clinical to clinical studies as well as to what extent preclinical effect sizes will translate into clinical effects.
- There is a gap in understanding of endophenotypes in diseases like dry AMD or DR that are currently perceived as close disease entities, but in reality may have very different natural courses or response to therapy. This may have significant medical and health-economic implications.

In ophthalmology there are many and very diverse techniques that allow to measure functional and anatomic parameters. Despite this methodological wealth, the relevance of different parameters for the assessment of disease severity remains uncertain, and so does their translation into outcomes relevant for patient daily activities and Quality of Life (QoL). For example, in neovascular AMD and other well-evaluated

indications, it has been shown that many promising imaging parameters are weakly or not-at-all correlated with patient relevant visual function. It is obvious that significant methodological validation work needs to be done. Therefore, an important focus on endpoint research is to validate existing technologies and to leverage the large armamentarium of contemporary ophthalmological examination techniques.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The topic tackles a problem of a scale that cannot be achieved by a single institution and requires combination of expertise and collaboration of stakeholders across different sectors:

- **Pharmaceutical companies** have expertise of drug discovery, drug development as well as regulatory and HTA requirements.
- **Academia** has expertise in methods to assess visual function and structural (bio-) markers that may correlate with visual impairment both pre-clinically and clinically. They have access to databases on the natural history and the course under treatment of the diseases in-scope that would allow a retrospective analysis of potential correlations.
- **Imaging and medical device companies** have expertise in development and application of contemporary examination methods.
- **Hospitals/practicing physicians** have access to dry AMD and/or DR patients. They have a good understanding of epidemiology, pathophysiology, or other evidence to predict clinical benefit.
- **Patients, users and caregivers** can also play an important role in the establishing the value of new endpoints.
- **Regulators, Health Technology Assessment (HTA) bodies and payers** could provide guidance on prerequisites for acceptability of endpoints.
- **Others such as technological centres and Contract Research Organisations** may be able to contribute to the deliverables of the project.

OVERALL OBJECTIVES

The aim of the project is to evaluate novel endpoint candidates for dry AMD and DR for use in clinical trials investigating drug or other therapies. The evaluation should cover the technical, medical and health economic appropriateness of a method and bridge preclinical and clinical studies. The following methods are in scope:

- **Novel approaches to subjective visual function testing beyond BCVA:** Methods falling into this category include methods of visual acuity testing under different conditions such as dim light or low contrast. Additional methods may comprise parameters such as microperimetry, motion or pattern detection, contrast sensitivity, color vision, visio-motor coordination or reading speed. The main research objective on this type of endpoints is the validation of patient relevance and/or predictive strength for each potential endpoint.
- **Electrophysiology:** Electrophysiological methods offer a broad array of largely objective parameters to quantify visual function. They are less dependent on patient co-operation than subjective visual function tests. Electrophysiological methods can be used in animal models and as such they have an inherent potential in translational research settings. The key objective of electrophysiological studies is the translation of pre-clinical results into clinical outcomes as well as correlation with patient-relevant endpoints.
- **Imaging:** Imaging devices that quantify anatomic changes in the retina have evolved tremendously in the last decade and have revolutionized disease diagnosis and monitoring. The further development of the techniques by means of image processing, detectable biomarkers in the retina and potentially photonics will further change the diagnostics and follow-up of retinal diseases. It would be important that such parameters are put into perspective and correlated to patient-relevant outcomes and prognosis of the disease.
- **Patient reported outcome (PRO) tools and QoL-related endpoints:** There are few validated PRO tools and the most prominent example, the NEI-VFQ-25³², is only well-correlated to the BCVA of the better-seeing eye, therefore being of little additional value. Studies in that field should focus on development of better-designed and researched PRO tools capturing the patient-relevant impact of visual impairment, beyond visual acuity.
- **Soluble and genetic biomarkers:** Several soluble and genetic biomarkers correlate with progression of diabetes and its complications as others do with age-related-macular degeneration. Activities in this field should focus on putting these and novel markers like proteomic and metabolomics biomarkers into perspective with outcomes, prognosis and severity of the ocular disease.
- **A combination of the aforementioned methods:** The consensus is that the likelihood of a single method fulfilling all the above criteria is low and therefore research on combinations of the aforementioned approaches will be required.

³² National Eye Institute Visual Functioning Questionnaire 25 (www.nei.nih.gov)

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies and complementarities with existing initiatives, both in Europe and globally should be considered, building on achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Applicants should include considerations in their proposal how the interactions with ongoing consortia, such as the following ones, are envisaged.

The SUMMIT is an ongoing IMI project on diabetes complications (<http://www.imi.europa.eu/content/summit>; www.imi-summit.eu). One of the work packages is dedicated to characterisation of retinal phenotype in diabetic patients and thorough documentation of the eye status along with the status of the systemic condition (including soluble bio-markers). There are clear opportunities for synergies with this project.

In addition, there are potential synergies with on-going FP7 projects within the field of macular degeneration and diabetic retinopathy, for example, HELMHOLTZ³³, ENDHOMRET³⁴ and REDDSTAR³⁵.

The proposal should also build on achievements and learnings from any relevant European and Member state initiatives and aim to create synergies with H2020 generated projects and global initiatives.

EXPECTED KEY DELIVERABLES

The key deliverable will be the generation of adequate data resulting from robust retrospective and/or prospective studies in patients that could serve as basis for initial discussion with regulatory agencies and/or HTA-bodies for acceptance of the resulting outcomes as endpoints for future clinical programmes. Interactions and advice from regulatory authorities will be sought early-on during set-up of the studies.

It is expected that the proposed research programme delivers data for each of the proposed conditions on:

- Technical evaluation of potential methods in regards to validity, repeatability, reliability, interpretability, and translatability from preclinical to clinical. The technical evaluation includes also an assessment whether a method is acceptable for patients with the disease.
- Development of novel methods (e.g. imaging, proteomics, metabolomics, genomics, epigenetics) and models, including animal models, and tools as applicable (e.g. disease/endophenotype specific patient reported outcome tools or novel visual function testing protocols).

³³ <http://www.vision-research.eu/index.php?id=909>

³⁴ <http://erc.europa.eu/erc-funded-projects>

³⁵ <http://www.reddstar.eu>

- Clinical validation of methods/tools in patient studies for dry AMD and DR. Preferentially, the studies should evaluate several candidate methods head-to-head. The collection of biomarkers (e.g. genomic or soluble biomarkers including proteomic and metabolomics markers) during the study will permit to explore the selection of high risk populations.

It is expected that each proposed study focuses either on a translational aspect or on patient-relevance of a given outcome parameter or combines both if applicable. If translational aspects are studied, the investigation should be set-up to show the correlation of data from an experimental model with the clinical outcome parameter. For studies aiming to show patient-relevance, a concept should be provided on how to link the novel parameter to an accepted parameter (e.g. a PRO tool), either previously validated or to be validated within the proposed project.

Wherever there are synergies between dry AMD and DR these should be leveraged, e.g. by combining both conditions within one study. However, it is also important to clearly address how the applicant consortium intends to investigate condition-specific aspects.

INDUSTRY CONSORTIUM

The industry consortium will comprise pharmaceutical and imaging companies. Industry contribution will include study support with central study functions (data management, statistics, project/study management, regulatory etc.).

EFPIA PARTICIPANTS

Bayer HealthCare (coordinator), Sanofi, Novo Nordisk, Zeiss

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years (60 months).

INDICATIVE BUDGET

The indicative EFPIA contribution is EUR 7 000 000.

The financial contribution from IMI2 JU will be a maximum of EUR 7 000 000.

TYPE OF ACTION

Research and Innovation action

APPLICANT CONSORTIUM

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

The applicant consortium is expected to be multidisciplinary and have a proven track record of:

- Strong clinical expertise in ophthalmology (including advanced examination techniques)
- Strong clinical research experience
- Access to patients and databases
- Public health expertise
- Health economic expertise
- Understanding of pre-clinical models in ophthalmology
- Biomarker expertise (biomarkers research and development)
- Data and knowledge management
- Regulatory, ethics, patients and project management.

It is intended that an advisory panel to the consortium, which comprises payers, regulatory agencies and other relevant expert advisors is instituted for this project.

The contribution from the applicant consortium should be the setting-up and running of the studies that are required to meet the call's objectives. These activities will be supported by in-kind and financial contribution from the EFPIA companies.

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The consortium is expected to suggest architecture for the full proposal addressing all objectives and key deliverables.

A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, and appropriate resources allocation, should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

CONDITIONS FOR THIS CALL

Applicants intending to submit a short outline proposal in response to the IMI2 Call 1 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier:	H2020-JTI-IMI2-2014-01
Publication Date:	9 July 2014
Stage 1 Submission start date:	9 July 2014
Stage 1 Submission deadline:	12 November 2014 – 17:00:00 Brussels time
Stage 2 Submission deadline:	21 April 2015 – 17:00:00 Brussels time
Indicative Budget:	From EFPIA and Associated Partners: EUR 24 630 000 From the IMI2 JU: EUR 24 630 000

IMI2-2014-01-01	The indicative contribution from EFPIA companies and Associated Partners EUR 17 630 000. The financial contribution from IMI2 JU is a maximum of EUR 17 630 000	Research and Innovation action Two stage submission and evaluation process Only the applicant consortium whose proposal is ranked first at stage 1 is invited for stage 2
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IMI2-2014-01-02	<p>The indicative EFPIA contribution is EUR 7 000 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 7 000 000</p>	<p>Research and Innovation action</p> <p>Two stage submission and evaluation process</p> <p>Only the applicant consortium whose proposal is ranked first at stage 1 is invited for stage 2</p>
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Eligibility and admissibility conditions

The conditions are described in parts B and C of the General Annexes to the H2020 work programme.

Evaluation criteria, scoring and threshold

The criteria, scoring and threshold are described in the IMI2 Evaluation Criteria, with the following exception:

<p>IMI2-2014-01-01 IMI2-2014-01-02</p>	<p>If a proposal fails to achieve the threshold for a criterion, the evaluation of the proposal will be stopped.</p>
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Evaluation procedure

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award.

The procedure for setting priority order for proposals with the same score is given in the IMI2 Evaluation Criteria.

The applicant consortium of the highest ranked proposal (stage 1) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (stage 2).

The applicant consortia of the second and third-ranked proposal (stage 1) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. Such contacts should be done in priority order, i.e. the second ranked proposal should be contacted only after failure of pre-discussions with the first ranked, and the third after the second ranked.

Indicative timetable for evaluation and grant agreement

	Information on the outcome of the evaluation (first stage)	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
IMI2-2014-01-01 IMI2-2014-01-02	Maximum 5 months from the date of submission to the first stage.	Maximum 5 months from the date of submission to the second stage.	Maximum 3 months from the date of informing the applicants following the second stage evaluation.

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions³⁶ and the IMI2 model grant agreement, participants in Research and Innovation actions are required to conclude a consortium agreement prior to grant agreement.

Submission Tool

Please note: The IMI electronic submission tool **SOFIA** (Submission OF Information Application) is to be used for submitting a short outline proposal in response to a topic of the IMI2 Call 1; no other means of submission will be accepted. SOFIA will be opened for submission of proposals on 9 July 2014. Updates of the proposals may be submitted online until the Call submission deadline. Only the most recent version shall be considered for the evaluation procedure (including eligibility check).

To access the IMI electronic submission tool SOFIA, applicant consortia wishing to submit a short outline proposal will need to complete a request for access to the tool.

³⁶ Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

2nd IMI2 CALL FOR PROPOSALS

INTRODUCTION

The Innovative Medicines Initiative 2 (IMI2) Joint Undertaking has been created³⁷ following the below principles:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps³⁸, from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The [IMI2 Strategic Research Agenda](#) (SRA) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include a theme on infectious diseases which is addressed in this call.

Applicant consortia are invited to submit proposals to one of the topics. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted to the scientific goals and the expected key deliverables.

While preparing their proposals, applicant consortia should consider the participation of any legal entities carrying out activities relevant for the topic objective and ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Synergies and complementarities with other national and international projects and initiatives are expected in order to avoid duplication of efforts and to create synergies on the global level and to maximise European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Before submitting a proposal, applicant consortia should familiarise themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria.

DISSEMINATION AND DATA STANDARDS

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale.

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#)"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.

³⁷ The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

³⁸ Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in a EU Member State or an associated country, are eligible for funding.

- 2) IMI2 projects should use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably, existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organisation (e.g. CDISC).

IMI2 EBOLA AND OTHER FILOVIRAL HAEMORRHAGIC FEVERS PROGRAMME

BACKGROUND AND PROBLEM STATEMENT

Filoviruses is a family of viruses of which the most commonly known members are Ebola virus and Marburg virus. Both viruses cause severe, usually lethal haemorrhagic fever in humans and non-human primates (monkeys, gorillas and chimpanzees). Filoviruses differ from dengue and other haemorrhagic fevers due to the fact that they can spread directly from person to person, where many other haemorrhagic fevers require an intermediate host, like a mosquito, to spread the disease. Ebola virus disease (EVD), previously known as Ebola haemorrhagic fever, is a rare and deadly disease caused by infection with one of the Ebola virus strains. It has an incubation period of 2-21 days, and it usually begins as a sudden influenza-like syndrome, which rapidly progresses to multi-organ failure and coagulation abnormalities which manifest as internal and external haemorrhages.

The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission via bodily fluids. Because Ebola virus is spread through contact with the body fluids of symptomatic patients, transmission can be stopped by a combination of early diagnosis, contact tracing, patient isolation and care, infection control, and safe burial. Before the current epidemic in West Africa, outbreaks of Ebola in central Africa had been limited in size and geographic spread, typically affecting one to a few hundred persons, mostly in remote forested areas.

The current outbreak in West Africa is due to the Zaire Ebola virus, a strain that historically has been the cause behind most EVD-related deaths.

The World Health Organization (WHO) was notified on March 23, 2014, of an outbreak of EVD in Guinea. The disease soon spread to the bordering countries of Liberia and Sierra Leone, which are the most severely affected countries. On August 8, 2014, the epidemic was declared a “public health emergency of international concern” (ref WHO Ebola Response Team, NEJM 2014, 371, 1481). Suspected cases of EVD have since been reported in seven affected countries (Guinea, Liberia, Nigeria, Senegal, Sierra Leone, Spain, and the United States of America).

Unprecedented in scale and geographical distribution since the identification of Ebola in 1976, the current epidemic has an apparent overall case-fatality ratio of about 70%; but it is suspected that many more cases have gone unrecorded. The WHO reported on October 14, 2014 that the number of new Ebola cases could reach 10,000 per week by December 2014. On October 31, more than 4.900 deaths and 13.567 cases had been reported in Sierra Leone, Liberia and Guinea, according to the WHO.

While there is no licensed treatment yet available for EVD, a range of blood, immunological and drug therapies are under development and two potential vaccine candidates are undergoing evaluation, according to the WHO (<http://www.who.int/mediacentre/news/statements/2014/ebola-therapies-consultation/en/>).

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The European Union is currently funding research addressing Ebola under the EU's Seventh Framework Programme (FP7) for Research and Development: on the development of new antiviral drugs and vaccines, on linking up high-security laboratories, on the clinical management of patients particularly in Europe, and on solutions to ethical, administrative, regulatory and logistical bottlenecks that prevent a rapid research response. Due to the emergency situation caused by the current outbreak of EVD, the European Commission has also recently mobilized a total of EUR 24.4 million (EU financial contribution) under Horizon 2020 through a fast-track exceptional procedure. As a result, five projects were selected for funding; these projects include a phase II trial of the GSK vaccine candidate ChAd3-EBOV (EU financial contribution EUR 15.1 million) as well as clinical trials on compounds (Favipiravir) and passive immunotherapy (convalescent plasma and horse serum). Also included is a project conducting translational research to provide answers to relevant clinical questions.

In view of the current epidemic, several other major public and private funders are engaging into funding urgent Ebola research. Main funders include the U.S. National Institutes of Health and the Bill and Melinda Gates Foundation in the US, the Department of International Development (DFID) and The Wellcome Trust in the UK, as well as individual EU member states like France and Belgium.

However, a programmatic approach addressing different challenges across the entire innovation cycle and leveraging input and multidisciplinary expertise across stakeholders is needed. IMI2 offers a unique opportunity to complement the ongoing European and international efforts by offering a multi-company, cross-sector and multi-stakeholder programmatic approach to address the challenges of EVD and other filoviral haemorrhagic fevers.

CALL TOPICS

The topics of the proposed IMI2 Ebola and other filoviral haemorrhagic fevers programme (the Ebola+ programme) cover actions that will address short term challenges of the current epidemic as well as actions needed to address EVD and other filoviral haemorrhagic fevers in a sustainable way for the long-term (see also conclusions from the high level WHO meeting on Ebola Vaccines Access and Financing of 23 October 2014³⁹). To address the present challenges of the ongoing epidemic, the following topics are launched in the current Call for proposals in a fast track single-stage procedure:

IMI2-2014-02-01	Vaccine development Phase I, II, and III
IMI2-2014-02-02	Manufacturing capability
IMI2-2014-02-03	Stability of vaccines during transport and storage
IMI2-2014-02-04	Deployment and compliance of vaccination regimens
IMI2-2014-02-05	Rapid diagnostic tests

Additional topics under the Ebola+ programme may be launched at a later point and may cover the following areas:

- Immunotherapy
- Formulations for cold chain
- Rapid diagnostic tests – long term
- Antivirals development and repurposing
- Multivalent filovirus vaccine development

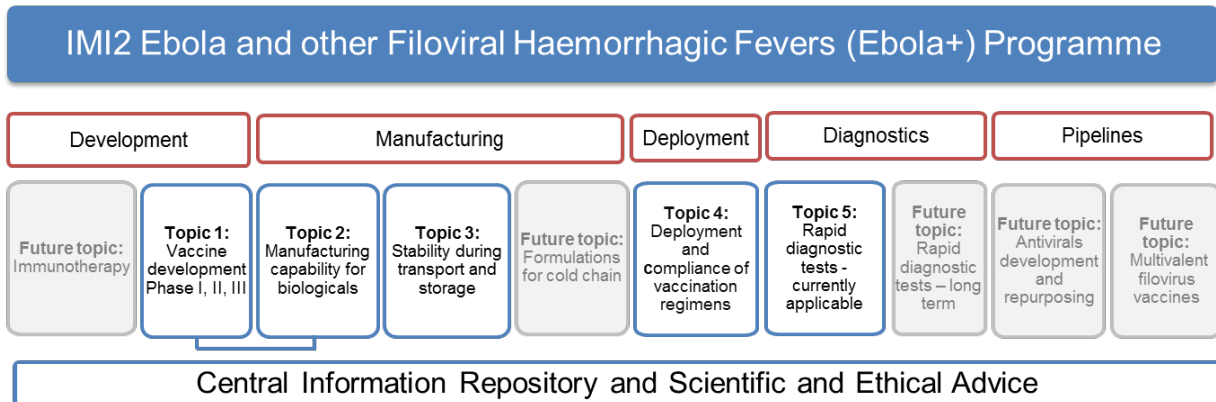


Figure 1: Proposed structure of the IMI2 Ebola and other filoviral haemorrhagic fevers (Ebola+) programme. Topics addressed in the current Call for proposals are highlighted in blue boxes. Potential future topics to be launched at a later point are shaded in grey.

All consortia participating in projects funded under the programme should closely interact and collaborate to ensure that learnings, knowledge and skill sets are maximised across the teams and in collaboration with the five projects selected for funding under the Commissions fast-track exceptional procedure. To facilitate information sharing and collaboration, a Central Information Repository will be established under Topic 1. All projects under the Ebola+ programme are expected to contribute to that repository. Likewise, a

³⁹ <http://www.who.int/mediacentre/news/ebola/23-october-2014/en/>

Scientific Advisory Board as well as an Ethics Board will advise all projects under the programme and will be established under Topic 1.

The establishment of this Ethics Board under Topic 1 notwithstanding, all projects to be funded remain fully responsible for respecting all ethical requirements.

Projects to be funded must comply with all relevant European laws, regulations and rules as well as the laws of the countries in which the studies take place. Particular attention needs to be paid so as to ensure compliance with all ethical rules, notably those related to the conduct of clinical investigations and clinical trials. Consortia are expected to interact with the EMA for advice on the conduct of trials and manufacturing-related questions⁴⁰ and when relevant with African regulatory bodies.

A template⁴¹ is available to help applicants provide all the relevant information for the planned clinical studies. Use of this template is not mandatory and the necessary information for experts to evaluate the projects involving clinical trials can also be provided in the regular proposal template.

JUSTIFICATION FOR NON-EU IN-KIND CONTRIBUTION

In order to meet the objectives of the different topics under the Ebola+ programme, part of the in-kind contribution from EFPIA companies will originate from third countries other than countries associated to H2020:

- A range of expertise and resources of the participating EFPIA companies and of many companies' virology franchises that are necessary to carry out the key activities are placed in third countries other than countries associated to H2020.
- Clinical trials against Ebola and other filoviral haemorrhagic fevers will have to be conducted in endemic countries (typically in West Africa).
- Since activities are meant to progress development and access to products globally, regulatory expertise covering all geographies will be required.

CALL PROCESS

The current Call for proposals includes the first 5 topics under the Ebola+ programme. It is expected that additional Calls will be launched at a later time so as to address additional topics under this programme.

The current Call for proposals will follow a single-stage fast track process. Industry companies that are constituent entities of EFPIA or their affiliated entities and/or IMI2 JU Associated Partners contribute with in-kind and direct financial contributions. Academia, SMEs, hospitals, healthcare professionals, regulators, public health authorities, etc. are eligible to receive IMI2 JU financial contributions. Legal entities from across the world can participate and participants from the majority of potentially participating countries are eligible to receive IMI2 JU financial contribution, in accordance with the applicable rules⁴². Applicant consortia need to fulfil the criteria as outlined in the Rules for participation applicable to IMI2 JU actions. To facilitate setting up consortia, the IMI2 JU provides a partner search tool⁴³.

All proposals evaluated under the 5 different topics will be ranked in one single list. Best-ranked proposals, in the framework of the available budget, will be invited to prepare a Grant Agreement.

INDICATIVE BUDGET

The indicative IMI2 JU financial contribution for the five topics mentioned in this call is up to EUR 140 million. EFPIA companies are expected to provide an in-kind contribution of around EUR 140 million.

⁴⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000624.jsp&mid=WC0b01ac0580841e30

⁴¹ http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2015-two-stage/1620124-essential_information_for_clinical_studies_2015callsv2_18082014_en.pdf

⁴² http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/Summary_of_provisions_for_particip_2014.06.26.pdf

⁴³ <http://www.imi.europa.eu/content/partner-search>

TOPIC 1. VACCINE DEVELOPMENT PHASE I, II, III

TOPIC DETAILS

Topic code	IMI2-2014-02-01
Project type	Research and innovation action (RIA)
Submission & evaluation process	Single stage fast track

SPECIFIC CHALLENGE

In view of the current epidemic, the WHO has identified the progression of vaccine candidates currently in development as an urgent public health need. Several candidate vaccines are available. Prime/boost vaccine approaches are promising, as they may provide protection against Ebola infection that is of longer duration.

SCOPE

Design and implementation of Phase I, II, or III clinical development of vaccine candidates, including prime boost combinations against Ebola virus disease (Zaire), to start in early 2015. The applicants must have vaccine candidates available and demonstrate the ability to roll out clinical trial vaccination programmes in EU / Africa, and to conduct studies in areas where Ebola virus disease is endemic. The clinical development programme(s) need(s) to be aligned with the global effort coordinated by the WHO.

Proposals addressing Topic 1 must include plans to set up a Central Information Repository for the Ebola+ programme for sharing results, learnings and data both amongst Ebola+ partners and with the outside community. The information repository should include (but not exclusively be restricted to): The capability to capture basic experimental data via an electronic lab notebook; A pharmacological screening platform for the capture, analysis and sharing of assay data and a system for capturing, analysing and sharing translational/clinical data. Applicants should in the first instance re-use capabilities that have been developed in other IMI projects and new capabilities should only be developed where no other alternative already exists. Finally any solution should include a strategy that ensures the long term sustainability of the data so that it remains accessible to the scientific community beyond the time-line of the project.

In addition, proposals addressing Topic 1 should include plans to set up a Scientific Advisory Board including proposed membership representing key stakeholders to give scientific and strategic advice to both specific projects and to the overall programme. Likewise, proposals should include plans to set up an Ethics Board whose role would be to ensure that all activities carried out under the programme fully account for any ethical considerations⁴⁴.

It is considered that an IMI2 JU financial contribution of 70-110 million and an EFPIA in-kind contribution of EUR 10-20 million would allow this specific challenge to be addressed appropriately. Nevertheless, this does not preclude submission and selection of proposals requesting other amounts.

Clinical study designs and therefore costs are likely to be influenced by several external factors such as; evolution of the current outbreak in West Africa and the precise requirements of regulatory authorities.

EXPECTED IMPACT

The vaccine development programme(s) are/is expected to provide the data to assess the safety, immunogenicity and efficacy of the candidate vaccine(s) in preventing EVD. The projects are thus expected to have a major impact on global health, both at the individual and the public health level. Learnings from this programme will also have an impact on the worldwide capacity to quickly develop vaccines in situations of global public health emergencies.

⁴⁴ Ethics pre-screening and ethics review - IMI2 Manual For Submission, Evaluation And Grant Award

SPECIAL INFORMATION

Since the implementation of Phase I, II, and III clinical trials is linked to manufacturing capability, projects funded under Topics 1 and 2 of this Call are expected to work in collaboration to ensure maximal impact.

TOPIC 2. MANUFACTURING CAPABILITY

TOPIC DETAILS

Topic code	IMI2-2014-02-02
Project type	Research and innovation action (RIA)
Submission & evaluation process	Single stage fast track

SPECIFIC CHALLENGE

In view of the current epidemic, the WHO has identified the progression of vaccine candidates currently in development as an urgent public health need. Because Ebola vaccines are recombinant adenovirus or other viral-based vaccines and need to be produced in facilities meeting an appropriate biosafety level, manufacturing the quantity of vaccine doses necessary for large-scale clinical testing and that can be thereafter urgently deployed represents a major challenge.

SCOPE

The project(s) will work on scaling up the currently available production techniques to the necessary scale and will be fully compliant with good manufacturing practices (GMP) and biological safety level requirements.

a. Costs and milestones are requested for manufacturing activities at volumes in the range of:

- 100,000 – 250,000 vaccine courses
- 250,000 – 2M vaccine courses
- 2M – 20M vaccine courses

Consideration to Drug Substance manufacture (formulated vaccine bulk) and finished Drug Product (vialled vaccine doses) should be given. Alternative manufacturing platforms to those currently utilised, or process improvement activities to increase vaccine manufacturing yields, may also be proposed.

b. Production and release of finished Drug Product is currently foreseen as a key bottleneck. Based on current regulatory requirements, non-replicating viral vaccine vectors need to be filled in BSL-2 compliant manufacturing facilities. This limits the number of manufacturers (CMOs and pharmaceutical companies) that are able to offer their services for fill and finish of an Ebola vaccine. Proposals are sought to generate additional data to help provide the necessary scientific, technical and regulatory justifications to seek a reclassification of such vectors such that they require BSL-1 containment, thereby opening up the potential for more manufacturers to assist in responding to the current outbreak.

It is considered that an IMI2 JU financial contribution of 10-20 million and an EFPIA in-kind contribution of EUR 70-110 million would allow this specific challenge to be addressed appropriately. Nevertheless, this does not preclude submission and selection of proposals requesting other amounts.

EXPECTED IMPACT

The project will deliver a manufacturing platform to provide the capacity for producing the required number of vaccine doses in GMP quality. Getting this type of production capacity online will have impact more generally for European competitiveness in the area of biological production under appropriate biological safety level conditions.

SPECIAL INFORMATION

Since the implementation of Phase I, II, and III clinical trials is linked to manufacturing capability, projects funded under Topics 1 and 2 of this Call are expected to work in collaboration to ensure maximal impact.

TOPIC 3. STABILITY OF VACCINES DURING TRANSPORT AND STORAGE

TOPIC DETAILS

Topic code	IMI2-2014-02-03
Project type	Research and innovation action (RIA)
Submission & evaluation process	Single stage fast track

SPECIFIC CHALLENGE

Currently available vaccine candidates need to be stored and transported at low temperature to maintain activity. Maintaining these conditions for deploying the vaccine in the areas targeted for vaccination can be challenging.

SCOPE

The project(s) will develop tools and technologies to be able to distribute current Ebola vaccine candidates utilising existing vaccine deployment infrastructure while taking into account current stability features (e.g. the need for low temperature) and also taking into account real-world field conditions and the health systems context.

Proposals that cover stability testing and supporting analytical capabilities to be applied at all stages of the shipping, storage and deployment process are encouraged.

It is considered that an IMI2 JU financial contribution of approximately 2 million and an EFPIA in-kind contribution of approximately EUR 2 million would allow this specific challenge to be addressed appropriately. Nevertheless, this does not preclude submission and selection of proposals requesting other amounts.

EXPECTED IMPACT

Better availability of Ebola vaccines. Novel tools and technologies for distributing current vaccines that require very low temperatures for stability.

TOPIC 4. DEPLOYMENT AND COMPLIANCE OF VACCINATION REGIMENS

TOPIC DETAILS

Topic code	IMI2-2014-02-04
Project type	Research and innovation action (RIA)
Submission & evaluation process	Single stage fast track

SPECIFIC CHALLENGE

To control the epidemic, ensuring vaccination coverage is of critical importance. In addition, to ensure lasting protection, a booster dose with a heterologous vaccine may potentially be required. This creates additional challenges for compliance i.e. guaranteeing that the right vaccine dose is given at the right time. Furthermore, the countries mostly affected by the current epidemic experience a climate of distrust in vaccines. Lack of community acceptance represents a significant challenge that could potentially derail both vaccine trials and vaccine distribution.

SCOPE

The project will develop i) technologies and tools that augment the adherence to the vaccination regimen at individual level. It will also ii) look into environmental factors that impact compliance and look at how to favourably influence these at community level.

The project will be rolled out and operationalised during conduct of the large scale phase II and III vaccination trials conducted under Topic 1 of this Call to assess the safety and efficacy of a candidate vaccine. Those trials offer an opportunity to test and validate any new tools and technologies. One option can be to exploit the high penetration of mobile telecommunication and use of mobile apps in West Africa. Proposals that will use mobile communication strategies to increase awareness, acceptance and subject recruitment in the vaccination campaigns or will create specific apps to remind participants of their appointments and keep track of their response or side effects are encouraged. In this type of project it is essential to guarantee privacy of subjects. To that end the operation as such of the telecommunication infrastructure within the study needs to be clearly separated from the scientific work, for example by having different legal entities responsible for the different aspects.

Ethical considerations must also figure in the assessment, taking into account the health-systems context.

The project will develop specific tailor made communication programmes that should help with the overall acceptance of the vaccination programme, and increase the willingness of the community to fully comply with the vaccination regimen.

The scope of the project includes research on community vaccine acceptance and attitude towards vaccines.

Welcome are also considerations on how monitoring of adverse events could be put in place, and how vaccinees who get a fever should be handled.

It is considered that an IMI2 JU financial contribution of approximately 25 million and an EFPIA in-kind contribution of approximately EUR 25 million would allow this specific challenge to be addressed appropriately. Nevertheless, this does not preclude submission and selection of proposals requesting other amounts.

EXPECTED IMPACT

The proposed project is expected to provide a fully validated tool or system that captures critical information for each vaccinee (date, dose, batch no.), allows for automated recalls to the vaccinee for subsequent doses, central tracking of overall vaccination coverage and compliance, all in a user friendly, cost economic way.

Improved overall acceptance and a positive attitude towards vaccination programmes will facilitate the conduct of clinical trials in endemic regions, and will increase compliance and help to combat both the current epidemic and prevent outbreaks in the future.

TOPIC 5. RAPID DIAGNOSTIC TESTS

TOPIC DETAILS

Topic code	IMI2-2014-02-05
Project type	Research and innovation action (RIA)
Submission & evaluation process	Single stage fast track

SPECIFIC CHALLENGE

Rapid detection of Ebola infections in the field or at decentralised healthcare centers is an urgent need in the current crisis of the outbreak of EVD and will remain important even after the current crisis may have subsided. Additional technologies addressing various healthcare facilities settings will also be important to maintain surveillance in the long term. Current PCR-based tests have a number of limitations related to time and procedures requiring infrastructures and specific training. Tools and technologies are needed to provide quality diagnostics at low cost. Several such tests are already under development but their performance and practicability are unknown.

SCOPE

The project(s) will work on developing rapid diagnostics to detect EVD at acceptable costs and with very high sensitivity and specificity. At a minimum a rapid diagnostic test should be able to be deployed at decentralised health care facilities under conditions with minimum laboratory infrastructures available. Projects can work on validating existing tests or on expanding the use of tools currently being developed, through clinical validation to registration and launch. Projects must in any case include a phase of clinical validation in the field under real-world conditions, address manufacturing and access path to ensure sustainable distribution including taking into account ethical considerations and the health systems context. Any suitable technology can be used but the focus should be on practical solutions that meet the following criteria:

- Very high sensitivity and specificity
- Ability to be deployed in resource-limited settings
- Minimal training required to operate
- Capability of multiplexing in order to include different ebola strains
- Time to result 15-30 minutes (desirable) – 3 hours (acceptable)
- Sample type for intake: blood (capillary fingerstick desirable), other less invasive sample types (urine, etc.)

Additional capabilities to provide epidemiological monitoring (eg. Internet connectivity) would be valuable. It is considered that an IMI2 JU financial contribution of approximately 7.5 million and an EFPIA in-kind contribution of approximately EUR 7.5 million would allow this specific challenge to be addressed appropriately. Nevertheless, this does not preclude submission and selection of proposals requesting other amounts.

EXPECTED IMPACT

Increased availability of rapid diagnostic tests for EVD, providing in a first step immediate impact on public health in regions where the disease is endemic.

Possible impact on business opportunities for European SMEs active in this area.

POTENTIAL FUTURE TOPICS UNDER THE IMI EBOLA AND OTHER FILOVIRAL HAEMORRHAGIC FEVERS PROGRAMME

IMMUNOTHERAPY

Ebola is a highly fatal disease, for which no efficient therapy is available today. There is increasing evidence that transfusion of blood from patients recovered from EVD has therapeutic effect, most likely related to the presence of neutralising antibodies, opening the potential for immune therapy. A potential future topic would be aimed at developing therapeutic products for filovirus infections based on passive immunisation (such as monoclonals, hyperimmune gammaglobulines, etc...), which should result in sufficient treatment regimens available at affordable price.

FORMULATIONS FOR COLD CHAIN

A potential future project will focus on the development of alternative formulations (for clinically active vaccines) that would improve thermo-stability to simplify the vaccine distribution logistics, taking into account real-world field conditions and the health systems context.

RAPID DIAGNOSTIC TESTS – LONG TERM

A potential future project would follow the initial effort (current Topic 5) of developing affordable rapid diagnostics to detect Ebola and other haemorrhagic fevers allowing long term surveillance. The project may address developing new tests through early development, analytical validation, clinical validation, registration and launch.

ANTIVIRALS DEVELOPMENT AND REPURPOSING

Ebola virus is a negative sense ssRNA virus with a 19kb genome encoding just 7 genes. As such there is comparatively limited scope for the development of anti-viral small molecules, with the polymerase and viral entry processes likely to form the most amenable druggable targets. There are also currently a very limited number of facilitates globally with the infrastructure to run CAT4 Ebola virus cell based assays, which is a critical component for progression of any repurposing program. A potential future topic would aim at creating a co-ordinated and collated tool-box of molecules from across the Industry, which are known to have anti-viral efficacy against a range of viral targets and may have been discontinued from development against their primary target. The project would seek to repurpose these molecules by testing in a CAT4 efficacy cell based Ebola virus assay, to determine whether these molecules have any utility in the blockade of Ebola viral entry or replication. If molecule(s) with potential anti-viral activity are identified, then depending upon their readiness for clinical development, a series of pre-clinical and clinical safety studies may be required to underwrite further clinical development.

MULTIVALENT FILOVIRUS VACCINE DEVELOPMENT

Multivalent filovirus vaccine candidates might be better able to protect against a range of current (Zaire) and future filovirus outbreaks. A potential future topic would aim at developing promising multivalent filovirus vaccine candidates. The project would deliver efficacy data in relevant animal models, toxicology data to support entry into clinical studies, and Phase I, II, and III clinical studies.

ACRONYMS

The following list of acronyms is applicable in the current call for proposals document:

IMI2 JU:	Innovative Medicines Initiative 2 Joint Undertaking
EVD:	Ebola Virus Disease
EFPIA	European Federation of Pharmaceutical Industries and Associations
WHO:	World Health Organisation
SAB:	Scientific Advisory Board
EAB:	Ethics Advisory Board
EMA:	European Medicines Agency
PCR:	Polymerase Chain Reaction
GMP:	Good Manufacturing Practice
BSL-2 Laboratory:	Biosafety Level 2 Laboratory
CDISC:	Clinical Data Interchange Standards Consortium
CMO	Contract Manufacturing Organisation
CAT-4:	Category 4
ssRNA	single-stranded RNA

CONDITIONS FOR THIS CALL

Applicants intending to submit a proposal in response to the IMI2 2nd Call should read the topic text, above, the H2020 Rules for Participation⁴⁵, the Commission Delegated Regulation⁴⁶, the IMI2 Manual for submission, evaluation and grant award⁴⁷ and the IMI2 RIA Evaluation Criteria⁴⁸.

Call Identifier:	H2020-JTI-IMI2-2014-02-single-stage
Publication Date:	6 November 2014
Stage 1 Submission start date:	6 November 2014
Stage 1 Submission deadline:	1 December 2014 – 17:00:00 Brussels time
Indicative Budget:	From EFPIA companies: around EUR 140 000 000 From the IMI2 JU: up to EUR 140 000 000

CALL TOPICS

IMI2-2014-02-01	The indicative contribution from EFPIA companies is EUR 10 to 20 million. The financial contribution from IMI2 JU is a maximum of EUR 110 million.	Research and Innovation action. Single stage submission and evaluation process. All proposals evaluated under the five topics will be ranked in one single list. Several proposals may be invited to conclude a grant agreement, depending on budget availability and their ranking.
IMI2-2014-02-02	The indicative contribution from EFPIA companies is EUR 70 to 110 million. The financial contribution from IMI2 JU is a maximum of EUR 20 million.	Research and Innovation action. Single stage submission and evaluation process. All proposals evaluated under the five topics will be ranked in one single list. Several proposals may be invited to conclude a grant agreement, depending on budget availability and their ranking.
IMI2-2014-02-03	The indicative contribution from EFPIA companies is EUR 2 million. The financial contribution from IMI2 JU is a maximum of EUR 2 million.	Research and Innovation action. Single stage submission and evaluation process. All proposals evaluated under the five topics will be ranked in one single list. Several proposals may be invited to conclude a grant agreement, depending on budget availability and their ranking.

45 http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf

46 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:JOL_2014_174_R_0003

47

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/Manual_for_submission_evaluation_grant%20award_2014.06.26.pdf

48 http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/IMI2_C1_S0_Evaluation_form.pdf

IMI2-2014-02-04	The indicative contribution from EFPIA companies is EUR 25 million. The financial contribution from IMI2 JU is a maximum of EUR 25 million.	Research and Innovation action. Single stage submission and evaluation process. All proposals evaluated under the five topics will be ranked in one single list. Several proposals may be invited to conclude a grant agreement, depending on budget availability and their ranking.
IMI2-2014-02-05	The indicative contribution from EFPIA companies is EUR 7.5 million. The financial contribution from IMI2 JU is a maximum of EUR 7.5 million.	Research and Innovation action. Single stage submission and evaluation process. All proposals evaluated under the five topics will be ranked in one single list. Several proposals may be invited to conclude a grant agreement, depending on budget availability and their ranking.

ELIGIBILITY AND ADMISSIBILITY CONDITIONS

The conditions are described in parts B and C of the General Annexes to the H2020 general work programme 2014-2015.⁴⁹

The unprecedented scale and geographical distribution of the current pandemic of Ebola virus disease (EVD) make it a global threat.

Consequently, the IMI2 JU intends to encourage the widest participation possible across the world and ensure the eligibility for funding of the third countries listed in Part A of the General Annexes to the H2020 work programme 2014-2015.

EVALUATION CRITERIA, SCORING AND THRESHOLD

The criteria, scoring and threshold are described in the IMI2 Evaluation Criteria, with the following exception:

IMI2-2014-02-01 IMI2-2014-02-02 IMI2-2014-02-03 IMI2-2014-02-04 IMI2-2014-02-05	If a proposal fails to achieve the threshold for a criterion, the evaluation of the proposal will be stopped.
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⁴⁹ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-ga_en.pdf

EVALUATION PROCEDURE

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award. The procedure for setting priority order for proposals with the same score is given in the IMI2 evaluation criteria.

CALL PROCESS

The current Call for proposals includes the first 5 topics under the IMI2 Ebola+ programme. It is expected that future Calls will be launched so as to address additional topics under this programme.

The current Call for proposals will follow a single-stage fast track process. Industry companies that are constituent entities of EFPIA or their affiliated entities and/or IMI2 JU Associated Partners contribute with in-kind and direct financial contributions. Academia, SMEs, hospitals, healthcare professionals, regulators, public health authorities, etc. are eligible to receive IMI2 JU financial contributions. Legal entities from across the world can participate and participants from the majority of countries are eligible to receive IMI2 JU financial contribution⁵⁰, in accordance with the applicable rules. Applicant consortia need to fulfil the criteria as outlined in the Rules for participation applicable to IMI2 JU actions. To facilitate setting up consortia, IMI2 JU provides a partner search tool⁵¹.

All proposals evaluated under the 5 different topics will be ranked in one single list. Best-ranked proposals, within the framework of the available budget, will be invited to prepare a Grant Agreement.

The IMI2 JU would like to draw the applicants' attention to the fact that due to the fast-track nature of the current Call, the time available for the Grant preparation will be very short. Consequently, all organisations participating in a proposal invited to prepare a Grant Agreement shall be ready to provide in a timely manner the necessary supporting documents for their validation in the Commission system⁵² and to nominate a Legal Entity Authorised Representative (LEAR). Please note that a Grant Agreement cannot be signed until all participants' information has been validated by the competent Commission service.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation	Indicative date for the signing of grant agreements
IMI2-2014-02-01	Maximum 2 months from the date of submission.	Maximum 1 month from the date of informing the applicants following the evaluation.
IMI2-2014-02-02		
IMI2-2014-02-03		
IMI2-2014-02-04		
IMI2-2014-02-05		

⁵⁰ See above

⁵¹ <http://www.imi.europa.eu/content/partner-search>

⁵² http://ec.europa.eu/research/participants/docs/h2020-funding-guide/grants/applying-for-funding/register-an-organisation/validation-of-organisation_en.htm

CONSORTIUM AGREEMENTS

In line with the Rules for Participation and Dissemination applicable to IMI2 actions⁵³ and the IMI2 model grant agreement, participants in Research and Innovation actions are required to conclude a consortium agreement within 6 months of the start date of each action.

SUBMISSION TOOL

Please note: The IMI electronic submission tool **SOFIA** (Submission OF Information Application) is to be used for submitting a proposal in response to a topic of the IMI2 2nd Call; no other means of submission will be accepted. SOFIA will be opened for submission of proposals on **22 November 2014**. Updates of the proposals may be submitted online until the Call submission deadline. Only the most recent version shall be considered for the evaluation procedure (including eligibility check).

To access the IMI electronic submission tool SOFIA, applicant consortia wishing to submit a proposal will need to complete a request for access to the tool.

Organisations willing to participate in a project proposal need to be registered with the Commission service and have obtained a 9-digit Participant Identification Code (PIC) at:

<http://ec.europa.eu/research/participants/portal/desktop/en/organisations/register.html>

For any successful proposal, all participants' information provided at the time of the registration needs to be validated by the Commission service. Please note that a grant agreement cannot be signed until all participants have been validated.

⁵³ Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

3rd IMI2 CALL FOR PROPOSALS

INTRODUCTION

The Innovative Medicines Initiative 2 (IMI2) Joint Undertaking has been created⁵⁴ following the below principles:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps⁵⁵, from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The [IMI2 Strategic Research Agenda](#) (SRA) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include themes on diabetes, psychiatric diseases, vaccines, and enabling technologies which are addressed in this call.

Applicant consortia are invited to submit proposals to one of the topics. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables. While preparing their proposals, applicant consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaborations on the global level and to maximize European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

A template⁵⁶ is available to help applicants provide all the relevant information for the planned clinical studies. Use of this template is not mandatory and the necessary information for experts to evaluate the projects involving clinical trials can also be provided in the regular proposal template.

Before submitting a proposal, applicant consortia should familiarize themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria.

⁵⁴ The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

⁵⁵ Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in a EU Member State or an associated country, are eligible for funding.

⁵⁶ http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2015-two-stage/1620124-essential_information_for_clinical_studies_2015callsv2_18082014_en.pdf

Applicants should refer to the specific templates and evaluation procedures associated with research and innovation actions (RIAs).

1. INTRODUCTION TO THE REMOTE ASSESSMENT OF DISEASE AND RELAPSE (RADAR) PROGRAMME

BACKGROUND AND PROBLEM STATEMENT

With rising health-care costs, all health care stake-holders (payers, physicians, patients) are shifting the onus from a 'pay for intervention' to a 'pay for performance' model. This change in focus towards overall outcomes will drive a paradigm shift towards disease interception, i.e. move from a 'diagnose and treat' to a 'predict and pre-empt' approach. In this model, pre-emption, i.e. intervening early enough in the disease process to prevent serious effects of the disease associated with progression, becomes a critical component of managing chronic disease. Additionally, as the trajectory of chronic diseases is often cyclical, this offers multiple interception opportunities to prevent serious decline — for example, predicting and pre-empting recurrence/suicidality in severe depression, hypoglycaemic event in diabetes , or exacerbations in multiple sclerosis (MS), COPD or asthma.

Measuring physiological and activity-based parameters remotely and continuously via unobtrusive on-body sensors or smartphones has the potential to revolutionise our ability to predict and pre-empt harmful changes in disease trajectory. Developing methods for real-time identification of behavioural and physiological patterns (bio-signatures) that culminate in relapse is of great importance: early detection and communication of "red flags" to both patients, care-givers and providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory.

A platform to acquire data in a real world setting would also enable the development of measures of real world effectiveness of medicines.

RADAR is a multi-topic programme in IMI2 that aims to overcome three key bottlenecks in developing such methods: 1) a lack of fundamental disease understanding into the signals and fluctuations in disease state and 2) the lack of clear policy, guidelines and pathways to develop and license "pre-emptive" therapeutic strategies that use such digital monitoring and remote assessment technology. 3) the maturity of the technology platforms including sensors technology, data exchange standards and the analytical methodology that mean that research is hampered by ad-hoc solutions that are not suitable to develop healthcare product.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The RADAR programme aims to test if new pre-emptive therapeutic strategies based on remote continuous monitoring are both scientifically feasible and also practically feasible as part of a wider healthcare system. Scientific feasibility will be performed via the individual topics of the RADAR programme to focus on the specifics of different disease areas. The first topic, detailed below, will study the fluctuation of the chronic diseases of depression, multiple sclerosis (MS) and epilepsy using remote monitoring technology to provide a foundation for developing a novel paradigm based on prediction and pre-emption. In the future, we intend to add other diseases to the CNS topic, such as pain and schizophrenia, and also add further topics in other disease areas such as airways disease and diabetes. Research in these areas needs to bring together physicians, patient groups, sensor manufactures, ICT providers, data management and analyst specialists with the pharmaceutical industry.

Introducing a therapeutic strategy based on such science and technology requires a second type of public private research to be undertaken to 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention 2) understand and develop a framework to support new digital based interactions

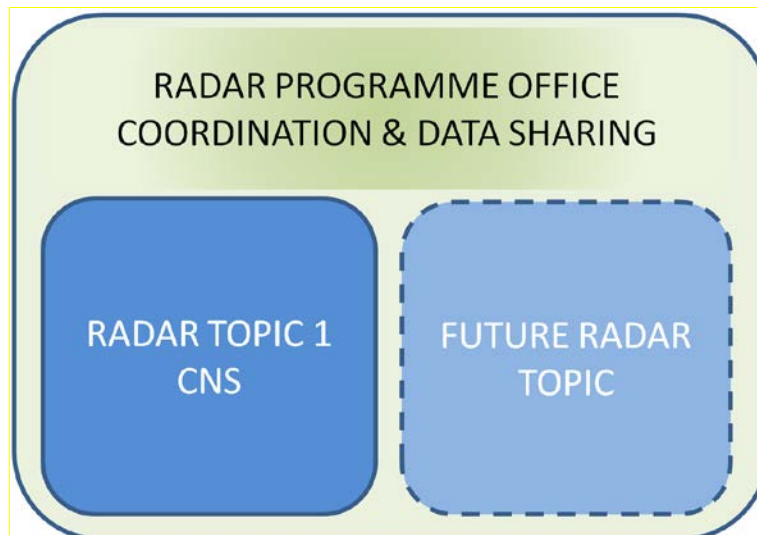
between patients and health care providers. This will require key stakeholders such as patient groups, regulators, healthcare providers, communications organisations, device manufactures and infrastructure providers to understand and develop a roadmap of how such interventions can be deployed effectively and safely.

OVERALL OBJECTIVES OF THE RADAR PROGRAMME

The key objective of the RADAR programme is to develop the foundational components to *“Improve patient outcomes through remote assessment”*. These components will be split into several topics with some cross-cutting themes co-ordinated across all topics. Under IMI2 Call 3, one initial topic will be launched, with more topics added to the programme in the future.

Considering the overall objective of the RADAR programme, the actions stemming from the different topics will be deemed to be complementary⁵⁷ to each other. Consequently, the selected consortia will have to conclude collaboration agreements to coordinate their work under the different Grant Agreements.

RADAR PROGRAMME ARCHITECTURE



The full RADAR programme will consist of several topics that are resourced and managed independently but will share key features such as data, technological approach and overall coordination. Under IMI2 Call 3, one initial topic will be launched in CNS.

RADAR PROGRAMME OFFICE

A key element of the RADAR Programme is coordination across all RADAR topics. This will require applicants to reserve some resource to support the coordination across different topics.

RADAR-CNS

The RADAR-CNS project will use a common set of remote assessment technologies to investigate central nervous system based disorders such as depression, multiple sclerosis and epilepsy. This project will be accountable for delivering focused disease research as outlined in the detailed topic description.

As the RADAR-CNS topic includes multiple indications, a critical part of the project will focus on cross cutting themes such as policy and technology standards that are common to all of the disease areas and will be accountable for advancing these themes in collaboration with investigators from future RADAR

⁵⁷ Complementarity should be intended as having common objectives or activities as being part of a specific programme. As a minimum, the collaboration agreements must establish that complementary consortia:

- enjoy mutual participation in the actions' governance;
- share project reports;
- grant mutual access rights to projects' results.

topics. It is anticipated that elements such as the technology platform or regulatory expertise will be applied in later topics to accelerate and group these reusable experiences.

FUTURE RADAR TOPICS

At a later stage, the IMI2 JU may publish additional topics which will become part of the RADAR programme. In that respect, potential applicants must be aware that all or some of these additional topics, if so foreseen in the applicable annual work plan, and if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, may be restricted to those projects already selected under this call by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit to fill critical skills gaps in the consortia that reflected the extensions in these work plans.

GENERAL PRINCIPLES FOR ALL PROJECTS CONDUCTED UNDER THE RADAR PROGRAMME

DATA SHARING

Data sharing is paramount to the success of the RADAR programme. The framework supporting this data sharing (i.e., the type of data to be shared and the access governing data sharing) will be fully established during the preparation of the full proposals in line with IMI2 IP policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners will be committed to sharing all data (clinical, bio-sensor etc.) available to, or generated by the RADAR program amongst all members of a RADAR topic, and across topics as required. In addition to data, RADAR constituents will also share code, technology, learning and expertise developed in IT architecture, data management, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures.

DISSEMINATION AND DATA STANDARDS

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale.

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#)"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- 2) IMI2 projects should use well-established data formats and content standards in order to ensure interoperability to quality standards. Preferably, existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

RADAR TOPIC 1: CNS

TOPIC DETAILS

Topic code	IMI2-2015-03-01
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

BACKGROUND AND PROBLEM STATEMENT

Severe mood disorders (major depression, bipolar disorder) are highly prevalent, chronic, and disabling diseases, with depression alone affecting an estimated 121 million people worldwide. Ranking first in terms of disease burden, as measured by disability adjusted life years (DALYs) in North America and Europe, mood disorders are far ahead of other serious conditions such as ischemic heart disease, chronic obstructive lung disease, and lung cancer.⁵⁸ The World Economic Forum (2011) has calculated that mental illnesses will represent the costliest diseases globally in the next two decades (2011-2030), exceeding the cost of cancer, diabetes, and chronic obstructive pulmonary diseases combined. Additionally, neurodegenerative diseases that include multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease and associated disability and dementia are fast becoming one of the leading challenges for health-care systems due to rapidly aging demographics. For example, the most recent Dementia 2014 report indicates that currently dementia alone costs EUR 33.5 billion a year, whereas a 2013 RAND report⁵⁹ put the cost of caring for dementia patients as exceeding the treatment costs due to cancer and heart disease. It should be noted that, in addition to direct costs to healthcare systems, CNS diseases inflict an unprecedented cost and burden on care-givers and family members.

The RADAR-CNS proposal seeks to address/utilise two important aspects of CNS diseases. Firstly, most CNS diseases are dynamic in nature with multiple reoccurrences and relapses each of which accelerate the downward spiral of the underlying disease pathology and lead towards chronification, morbidity and mortality. Secondly, the onset of reoccurrences, exacerbations and relapses in CNS disease causes changes in parameters related to sleep, physical activity, speech, cognition, social connectivity, memory etc.; parameters that can increasingly be measured remotely and passively via unobtrusive on-body biosensors and smartphones. The vision of RADAR-CNS is to reduce cost and trauma to the patient and care-givers and reducing hospitalisations by predicting and pre-empting relapses and reoccurrences via the use of remote assessment technologies. RADAR-CNS will focus initially on unipolar depression, multiple sclerosis (MS) and epilepsy with the main goal of using available clinical information and streaming data from on-body sensors to predict relapse, symptom exacerbations and seizures respectively. Initial RADAR diseases were selected on the basis of unmet need in terms of prevalence, disability caused, feasibility of developing a remote bio-signature predictive of a change in disease state, and the therapeutic interests of contributing EFPIA companies. Depression, MS and epilepsy are prevalent, disabling conditions that effect all age-groups, and are characterised by rapid and distinct changes in disease states at varying time-scales that, if predicted and pre-empted, would result in significant improvement in overall patient outcomes. Furthermore, depression and MS are often co-morbid in a patient, thus offering opportunities to study both diseases in a common population. It should be noted that learnings in terms of sensor development, data management, analytics, privacy, regulatory and health-care policy issues etc. will transfer to other disease areas in this topic. Indeed, the long-term goal is to build upon the learning of the first three diseases and in the future include other disease areas such as bipolar disease, Alzheimer's disease, schizophrenia and pain.

⁵⁸ WHO report on Global Burden of Disease

⁵⁹ N Engl J Med 2013; 368:1326-1334 April 4, 2013 DOI: 10.1056/NEJMsa1204629

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

RADAR and RADAR-CNS represent an intersection between diverse areas ranging from telecommunications, bio-sensors, devices, mobile computing, streaming analytics to clinical care, diagnostics and therapeutics development. As such, progress in this area will require cooperation and partnerships between multiple entities from diverse industries and academia. Furthermore, this lies outside the core area of expertise and focus for the pharmaceutical industry, as it does for the telecom/sensor industry and academia. While many projects are already underway in individual disciplines, cross-disciplinary collaborations such as RADAR are not just desirable, but essential, to ensure these rapidly developing technologies can be integrated with clinical and regulatory pathways to make a difference to the day to day lives of patients.

RADAR-CNS OBJECTIVES

The aim of RADAR-CNS is the characterisation and prediction of changes in disease state in central nervous system (CNS) disorders via non-invasive remote sensing.

This topic is planned to be focused on the three diseases of unipolar depression, multiple sclerosis and epilepsy. For each disease it is proposed that a non-interventional/observational study of subjects is undertaken with three objectives:

- Characterisation of changes in disease state.
- Characterisation of changes in disease state due to drug effects.
- Prediction of change in disease state from remote sensing data.

To co-ordinate across all three disease areas a common set of measures and measurements tools will be used to track the sleep architecture, physical activity, speech, cognition, social connectivity, and memory of subjects of all of the target diseases. We also intend to take advantage of the fact that depression has a high rate of co-morbidity with both MS and epilepsy, and intend to recruit a population that has overlapping morbidity between depression, MS and epilepsy such that we have patients representing each disease as a primary indication, as well as patients who are co-morbid with more than one disease. The overall goal would be to design an observational study, in collaboration with our consortia partners that maximises the power to detect bio-signatures of disease state change and relapse, as well as assess other important considerations such as patient acceptance of wearable devices, adherence, usability and data management.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Applicants should take in consideration any initiatives already on-going in this field, both in Europe and globally. Synergies with such consortia should be explored to build on their achievements, and to incorporate, when possible, data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

EXPECTED KEY DELIVERABLES

- 1) Candidate bio-signatures that predict relapse and track disease state changes in MS, depression and epilepsy using at least a common minimal set of metrics: **sleep architecture, physical activity, speech, cognition, social connectivity, and memory.**
- 2) Development of algorithms and an analytic infrastructure suitable for collecting and analysing data from the RADAR-CNS studies.
- 3) Proposal of actionable privacy and usability parameters that would drive eventual uptake of, and adherence to, remote assessment solutions in CNS diseases.

- 4) Delineation of putative regulatory pathways necessary for approval of remote sensing solutions in real-world patients. This deliverable will be developed in consultation with regulators.
- 5) Delineation of putative clinical care pathways and use cases of remote-sensing solutions and how they impact and interface with stake-holders such as patients, care-givers, case-managers, physicians etc. This deliverable will be developed in consultation with relevant external stakeholder groups (see above).

INDUSTRY CONSORTIUM

Industry consortium members will bring the following assets and skills to the project:

- 1) Clinical/ regulatory expertise: Janssen, Lundbeck, BiogenIdec and UCB have years of experience developing therapeutics in CNS disease areas, and will bring expertise related to clinical study design execution and regulatory approval pathways.
- 2) Clinical data: Industry members will be bringing bio-sensor, clinical and patient self-report data collected in observational studies in relevant patient populations.
- 3) Data capture/ data management/ analytics/ data mining: Industry consortia members will bring expertise in data management and data-mining through our internal IT and informatics groups.
- 4) Devices: Industry partners will also bring devices to measure actigraphy, stress (galvanic skin response), cognition and other relevant parameters.

Full details regarding the above contributions will be provided in the full proposal.

EFPIA PARTICIPANTS

Janssen, BiogenIdec, UCB, Lundbeck, Merck.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET

The indicative contribution from EFPIA companies is EUR 11 000 000. Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non EU in kind contribution.

The financial contribution from IMI2 JU will be a maximum of EUR 11 000 000.

FUTURE PROJECT EXPANSION

Potential applicants must be aware that the IMI2 JU may publish at a later stage another call for proposals restricted to those projects already selected under this call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would then be entitled to open to other beneficiaries as they see fit.

In the context of this topic, such a call could allow the incorporation of other CNS disease areas such as bipolar disease, Alzheimer's disease, schizophrenia and pain. The detailed scope of the call would be described in the relevant annual work plan.

APPLICANT CONSORTIUM

Applicant consortium will be multi-disciplinary. We expect device and sensor companies to bring the latest remote assessment technologies that could be further developed or modified for use as intended in CNS diseases. Academic, clinical and disease area experts will help to design the clinical study (end-points, inclusion criteria etc.) and interpret results for clinical significance. IT/ analytics partners will help develop data management architecture, state-of-the-art algorithms to derive bio-signatures of symptoms and relapse from collected streaming data. Regulatory and health-care systems experts will help define regulatory and clinical-care pathways respectively for the remote assessment solutions. All consortia partners are expected to actively participate in publications to raise awareness and gather further input from the larger scientific community.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

We suggest that the RADAR-CNS consortium be organized in the following architecture, though the application consortium is free to propose alternative models, with justification, if they consider them superior.

Work package: CLINICAL STUDIES

This work package will include the design and execution of the clinical programme of the RADAR-CNS project including protocol development, ethics submission, the operations of clinical observational studies that will include diagnosis and symptom data from physician visits, remote continuous data from wearable devices and other self-reported measures. The exact design of the clinical studies will be developed in consultation with the consortium partners, however, as previously noted, depression and MS are often co-morbid and our goal would be to study these diseases independently, as well as in the same patients to optimize overall study size. Epilepsy will likely be studied in a smaller cohort more focussed on validating and improving existing predictors of seizures. The final allocation of resources between disease clinical studies as well as sensor development and other work-packages will be finalized in consultation with the consortium partners and will reasonably reflect the interests and relative contributions of EFPIA partners.

Work package: DATA CAPTURE & REMOTE ASSESSMENT TECHNOLOGIES

This work package will be responsible for the remote assessment technology platform that is to be used to measure the core metrics of **sleep architecture, physical activity, speech, cognition, social connectivity, and memory** of subjects across all disease area. This will include preparing and operating the platform in support of the clinical trial and providing data for the data analysis work package. This work package is also responsible for developing the appropriate privacy policies and collaborating with privacy and technology such groups in future RADAR programme topics.

Work package: DATA ANALYSIS AND BIO SIGNATURES

This work package will be responsible for the analysis of data collected in the clinical trials and identifying candidate bio-signatures of symptoms and relapse. This work package is responsible for the collaborating with the appropriate groups in future RADAR programme topics regarding methodology development.

Work package: HEALTHCARE PATHWAYS

This work package will be responsible understanding both the regulatory and healthcare pathways that would enable the use of bio-signatures of disease and relapse to be used in a real world healthcare setting. This work package is responsible for the collaborating with the appropriate groups in future RADAR programme topics regarding regulatory and health care engagement.

2. ASSESSING RISK AND PROGRESSION OF PREDIABETES AND TYPE 2 DIABETES TO ENABLE DISEASE MODIFICATION

TOPIC DETAILS

Topic code	IMI2-2015-03-02
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stage

BACKGROUND AND PROBLEM STATEMENT

The incidence of type 2 diabetes is increasing at epidemic proportions. The resulting disease burden of diabetes substantially increases morbidity and mortality for citizens in nations within the European Union and worldwide, augments health care expenditures, and reduces economic productivity.

Current therapies for type 2 diabetes largely focus on the control of blood glucose levels rather than the modification of the disease. To attenuate the epidemic rise in the incidence and progression of type 2 diabetes, additional therapeutic approaches will be needed. Multiple gaps exist to enable feasible and successful development of novel therapeutic approaches to either 1) prevent the progression of prediabetes to type 2 diabetes and/or 2) to delay or prevent disease progression in individuals diagnosed with type 2 diabetes. More robust delineation of clinical risk factors, phenotypes, and molecular biomarkers is needed to identify which individuals with prediabetes are at risk for rapid progression to type 2 diabetes for disease prevention therapeutic intervention trials. More intensive phenotyping of individuals with type 2 diabetes is needed to characterize rates of disease progression and to identify and validate biomarkers and/or indicators of “rapid failure” of insulin-producing pancreatic beta cells and of cellular targets of insulin-mediated glucose disposition, including hepatocytes, skeletal muscle, and adipocytes. Validation of robust markers of type 2 diabetes disease progression would facilitate patient segmentation for feasible assessments of new therapeutic options for disease modification. Biomarkers discovered in diabetes-related IMI1-sponsored consortia should be leveraged to support the opportunity within IMI2 for biomarker prioritization, selection, and high throughput assay implementation to enable drug development for diabetes disease modification. Following the future discovery, development, and regulatory approval of effective disease-modifying drugs for diabetes, new patient screening methods will need to be developed and integrated into clinical practice to support appropriate access to therapeutic and public health benefits.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The magnitude of the issue is such that it can only be addressed by a major Public-Private-Partnership involving a variety of stakeholders, including those primarily involved in understanding molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complementary experience and expertise, as well as regulators. This is a program which cannot be successfully administered by an individual research group or company but will require a broad consortium to be successful.

- c. Pharmaceutical companies contribute expertise in diabetes drug discovery and development, including understanding of regulatory, economic, and logistical challenges facing drug development for disease prevention and modification. Companies bring unique expertise in biomarker discovery, data analysis, assay development, and prospective clinical trial design.
- d. Academic investigators contribute expertise in a range of methods to discover and validate molecular phenotypic biomarkers from human tissues and biofluids, to assess clinical phenotypes,

and to analyze the relationship of molecular phenotypic biomarkers with clinical evaluation of disease progression.

- e. Hospitals, clinical research centers, and practicing physicians with access to patients with prediabetes and type 2 diabetes contribute understanding of epidemiology, pathophysiology, clinical and biochemical phenotypes and provide bio banked samples that may be used in combination with novel molecular biomarkers to predict type 2 diabetes disease progression.
- f. Patients donate biofluid or tissue samples and participate in clinical research studies to enable more precise molecular understanding of prediabetes and type 2 diabetes.
- g. Biotechnology and diagnostics companies facilitate development of high throughput biomarker assays and access to unique technologies.
- h. Regulatory authorities contribute expertise in diabetes drug evaluation and approval to enable innovative approaches for developing new therapies for disease prevention or modification in type 2 diabetes.
- i. Health care payers and economists provide important perspectives to evaluate the economic impact and value of preventing the onset or delaying the progression of type 2 diabetes.

OVERALL OBJECTIVES

The overall aim of the project is to discover and validate a molecular taxonomy of type 2 diabetes to enable feasible patient segmentation, clinical trial design, and regulatory paths for diabetes prevention and for modification of diabetes disease progression.

To fulfil this aim, the following project objectives are proposed:

- 1) to prioritize and/or validate a panel of human biomarkers or assays of pancreatic beta cell function, stress, mass, and death to enable prospective selection of *a*) subjects with rapid progression from prediabetes to type 2 diabetes and *b*) type 2 diabetes subjects with accelerating pancreatic beta cell dysfunction.
 - Biomarker validation component should explore and assess available predictive biomarkers identified from existing IMI1 diabetes-related consortia (i.e., IMIDIA, SUMMIT, DIRECT, EMIF, StemBanCC), from other cohorts, from published literature, and from discovery studies within this project
 - Biomarker discovery component should leverage a range of technologies including targeted and non-targeted biochemical biomarker discovery in human tissue and/or fluid samples, genomic biomarkers accessible in clinical trials, imaging biomarkers indicative of changes in cellular functions and/or tissue structure, and biomarker discovery from selected preclinical models
 - Validated biomarker panels should encompass multiple mechanisms of pancreatic beta cell stress that may contribute to disease progression, for example oxidative stress, ER stress,

nutrient stress, impaired adaptation to changing insulin resistance, apoptosis, and autophagy.

- 2) to prioritize and/or validate a panel of human biomarkers or assays of hepatic, skeletal muscle, and/or adipose cellular dysfunction derived from or contributing to progression of insulin resistance that enable prospective selection of *a*) subjects with rapid progression from prediabetes to type 2 diabetes and *b*) type 2 diabetes subjects with accelerating type 2 diabetes disease progression.
 - Biomarker validation component should explore and assess available predictive biomarkers identified from existing IMI1 diabetes-related consortia (i.e., IMIDIA, SUMMIT, DIRECT, EMIF, StemBanCC), from other cohorts, from published literature, and from discovery studies within this project.
 - A range of technologies should be leveraged to assess human samples, ex vivo models, and selected preclinical models to generate a validated biomarker panel reflective of multiple mechanisms of pathophysiology of insulin resistance, including biomarkers reflective of hepatic, skeletal muscle, and adipose cellular dysfunction.
 - Biomarker discovery component should emphasize human tissue and/or body fluid biomarkers predictive of environmental contributions to disease progression, including microbiome, toxin exposure, dietary exposure, exercise, and epigenome.
- 3) to develop innovative potential regulatory approaches in collaboration with regulatory experts, including adaptive clinical trial designs, enabling feasible and robust benefit/risk assessments in clinical trials for *a*) therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes and *b*) therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression
- 4) to model short- and long-term economic and public health morbidity and mortality benefit/risk assessments of *a*) therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes and *b*) therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression.
 - modelling should engage multidisciplinary teams of patient advocates, health care economists, and health care payers.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

When developing their short proposal, applicants should take into consideration that there are already several initiatives on-going in the field, both in Europe and globally.

Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

This project is intended to provide the opportunity within IMI2 to leverage substantial diabetes-related biomarker discovery from multiple IMI1 projects, including IMIDIA, SUMMIT, DIRECT, EMIF, and StemBanCC. Through the data integration work package, this consortium may also enable hosting of secure data repositories of accessible, integrated IMI1 and IMI2 diabetes-related project data. In addition the consortium seeks to leverage research findings, phenotyping, and bio specimens from multiple existing and emerging prediabetes and diabetes longitudinal cohorts, for example, UK Biobank, EU 7th framework supported programs, Interconnect, and EFPIA-sponsored clinical trials.

Collaboration by design should be a cornerstone of the proposed strategy.

EXPECTED KEY DELIVERABLES

- Validation and/or discovery of human phenotypes and biomarker panels predictive of rapid declines in pancreatic beta cell health and function that enable prospective identification of *a)* “rapid progressors” from prediabetes to type 2 diabetes and/or *b)* accelerating type 2 diabetes disease progression for clinical trial recruitment
- Validation and/or discovery of human phenotypes and biomarker panels predictive of rapid declines in insulin action-targeted hepatic, skeletal muscle, and/or adipose cellular functions that enable prospective identification of *a)* “rapid progressors” from prediabetes to type 2 diabetes and *b)* acceleration of type 2 diabetes disease progression for patient identification for clinical trial recruitment or therapeutic intervention
- Prioritization and selection of robust phenotypes and biomarker panels that enable feasible prospective patient segmentation/selection, clinical trial design and regulatory paths to assess new therapeutic options for prevention of *a)* progression from prediabetes to type 2 diabetes and *b)* acceleration of type 2 diabetes disease progression
- Development of new regulatory approaches or standards enabling innovative and feasible clinical trial designs for disease modification in patients with prediabetes or type 2 diabetes
- Models for public health benefit and economic impact of therapeutic intervention to prevent or delay progression from prediabetes to type 2 diabetes

INDUSTRY CONSORTIUM

- Pharmaceutical companies
- Technology and diagnostic providers

EFPIA PARTICIPANTS

Lilly (Project- leader), Servier (Project –Co-leader), Janssen, Novo Nordisk, Sanofi

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 4 years.

INDICATIVE BUDGET

The indicative contribution from the EFPIA companies is estimated at a total of EUR 8 130 000. Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non EU in kind contribution.

The indicative IMI JU contribution will be up to EUR 8 130 000.

FUTURE PROJECT EXPANSION

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would be entitled to open to other beneficiaries as they see fit.

In the context of this topic, a second phase would most likely have a duration of 3 years and would only be initiated after a futility analysis of the progress of phase 1 and if certain milestones have been passed that justify a Phase 2 of the project to expand knowledge by implementing prospective prevention clinical studies to assess the potential for approved medication(s)

- to prevent the progression of prediabetes to type 2 diabetes,
 - including assessment of predictive value of biomarkers and clinical assays used for prospective selection or for surrogate markers of disease progression of subjects with prediabetes most likely to rapidly progress to type 2 diabetes
- to prevent the acceleration of disease progression and worsening of pancreatic beta cell and other cellular function in subjects with type 2 diabetes
 - including assessment of predictive value of biomarkers and clinical assays used for prospective selection or for surrogate markers of disease progression of type 2 diabetes subjects with rapidly accelerating disease progression

A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables. The detailed scope of the call for the second phase of the project would be described in the relevant annual work plan.

APPLICANT CONSORTIUM

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium. This may require to mobilise, as appropriate, expertise in: basic, translational, clinical research; regulatory aspects; economic or public health modelling; as well as project management.

Applicant investigators should include complementary expertise in biomarker discovery and clinical assay implementation across the range of relevant technologies, in human pancreatic beta cell, hepatic, muscle, and adipose biology, in conducting intensive clinical phenotyping of prediabetes and type 2 diabetes patients, and in prospective and retrospective assembly and assessment of large longitudinal cohorts and biobanks from subjects with prediabetes and type 2 diabetes. Applicant investigators should have confirmed access to retrospective cohort collections of biospecimens for use in biomarker discovery and validation.

Investigators should leverage existing retrospective cohorts and collaborations with ongoing studies of individuals with prediabetes and with type 2 diabetes that include clinical phenotype data, biomarker data, longitudinal outcomes data, and available biobank biofluids and/or tissues. These cohorts must be

appropriately consented to enable additional biomarker discovery or validation. Individual investigators within the applicant consortium should have a proven track record of productive and highly collaborative basic, translational, and/or clinical research with enthusiasm for working in interconnected private-public research teams. The consortium should also anticipate that results and resources generated by this project will likely interface with and/or be made available to other type 2 diabetes-related projects within the IMI1 and IMI2 frameworks.

Valuable assets that the applicants could provide include:

- Relevant existing datasets and existing clinical studies
- Relevant longitudinal clinical cohorts and registries
- Relevant biobanks and bio-samples
- Involvement of patient organizations and appropriate ethical considerations

SUGGESTED ARCHITECTURE FOR THE FULL PROJECT PROPOSAL

The following outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.

WP1. ADMINISTRATION, MANAGEMENT, AND COMMUNICATIONS

- Provide professional consortium management support
- Secure and facilitate access to data from previous IMI1 consortia
- Foster collaborations and external communications

WP2. DATA INTEGRATION, ANALYSIS, AND INFORMATICS

- Mine and integrate accessible dynamic databases from IMI1 and other available diabetes-related projects
- Identify external biomarkers from literature and other consortia for validation
- Integrate, maintain, and analyze data generated within the consortium

WP3. PANCREATIC BETA CELL PREDICTIVE BIOMARKER DISCOVERY, PRIORITIZATION, SELECTION, AND VALIDATION IN HUMAN SAMPLES, EX VIVO MODELS, AND PRE-CLINICAL MODELS REFLECTIVE OF DIABETES-RELATED BETA CELL FUNCTIONS AND PHENOTYPES FROM

- the local islet environment and
- beta cell signalling interactions with other organs
- systemic effects detectable in body fluids

WP4. INSULIN ACTION TARGET CELL PREDICTIVE BIOMARKER DISCOVERY, PRIORITIZATION, SELECTION, AND VALIDATION IN HUMAN SAMPLES, EX VIVO MODELS, AND PRE-CLINICAL MODELS REFLECTIVE OF DIABETES-RELATED CELLULAR FUNCTIONS AND PHENOTYPES FROM THE FOLLOWING TISSUES

- liver, including hepatic nutrient handling, NASH, and NAFLD phenotypes
- skeletal muscle
- adipose
- systemic effects detectable in body fluids

WP5. ASSAYS AND TECHNOLOGIES DEVELOPMENT

- High throughput assays established to enable convenient and robust use in clinical trials
- Novel technologies leveraged for cellular phenotyping, i.e., innovative imaging
- Diagnostic test development enabled for patient selection for clinical trials and therapeutic intervention

WP6. REGULATORY CONSENSUS FOR DIABETES DISEASE MODIFICATION

- Implement a dialogue platform with the European Medicines Agency (EMA) and other non EU regulators, industry, and academic partners
- Enable the development of operational definitions, qualification of biomarker panels and innovative regulatory tools for addressing the challenge of prevention of diabetes or to delay the progression of T2DM, which is an unmet medical need in the aging European population
- Utilise retrospective data to refine population definitions and validate relevant study endpoints

WP7. MODELING ECONOMIC AND PUBLIC HEALTH IMPACT OF DISEASE MODIFICATION

- Explore potential cost effectiveness, cost utility, and economic impact of innovative prediabetes or T2DM disease modification interventions
- Engage a European network of health economists to develop consensus on economic needs for innovative clinical interventions for disease modification in diabetes
- Communicate economic consensus results to decision- and policy-makers

The applicant consortium partners that will provide data and samples from existing study cohorts and registries need to demonstrate in their application that those envisaged resources can be shared among all the partners. Thus the applicants have to document in their short proposal that applicable ethical and data privacy laws allow sharing such data and samples within the consortium.

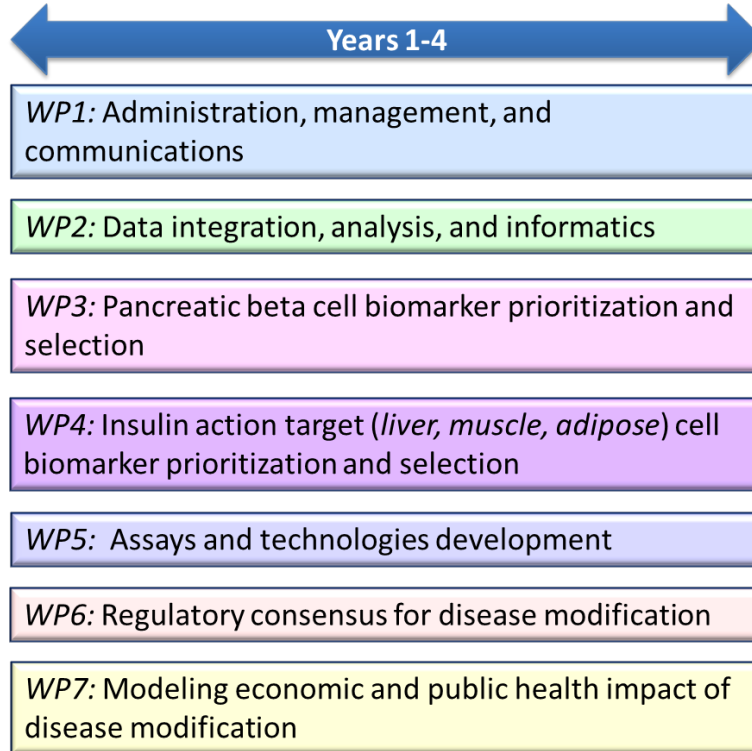
In addition a plan for interactions with Regulatory Agencies/ Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

The applicants are requested in their short proposal to consider:

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#)"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- 2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

PROPOSED ARCHITECTURE OF THE FULL PROJECT PROPOSAL



3. LINKING CLINICAL NEUROPSYCHIATRY AND QUANTITATIVE NEUROBIOLOGY

TOPIC DETAILS

Topic code	IMI2-2015-03-03
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

BACKGROUND AND PROBLEM STATEMENT

The nosology of neuropsychiatric disorders has historically been entirely based upon a clustering of a variety of behavioural symptoms occurring over time using systems such as DSM and ICD. This approach has weaknesses but has allowed a pragmatic approach to treatment choice, regulatory and clinical research processes. However, as a consequence pharmacological research has tended to attempt to identify new drug targets by linking given biological phenomenon to a psychiatric “diagnosis”. The fact that psychiatric diagnoses are only descriptive, without biological rationale, has rarely been properly considered.

Almost as a consequence, the development of novel pharmacological treatments for neuropsychiatric disorders has stagnated over the last two decades. This statement holds true across the whole field; cognitive decline in dementia, the control of psychosis, affect etc. The chronicity of these disorders, which is partly a result of lack of specific neuropsychiatric medications, results in a major burden for patient and society. In addition to the need to treat traditional psychiatric patient groups we have an aging population. This group also presents with more complex pathologies and comorbid conditions thus the need for accurate diagnosis, treatment selection and novel therapeutics will become increasingly important and complex. Indeed, if the current efforts to develop disease modifying approaches are successful then these challenges will be faced by potentially a dramatically larger, longer surviving patient population. To reverse this stagnation a new approach is required.

It is a truism, but one rarely voiced, that drugs affect biological substrates not symptoms. Further, that a specific symptom or cluster of symptoms, in different individuals may stem from different aberrant biologies. For instance both in dementia and schizophrenia aberrant cognition, psychosis and affect are observed. These have different presentations but little has been quantified as to the theoretical biology differences. Improved rational prescription of existing compounds, quantitative diagnosis and measurement of treatment response, identification of novel therapeutic hypotheses and hence the development of improved treatment options would all be facilitated by the development of an aetiological, or quantitative biology-, based taxonomy of these disorders.

The development of a quantitative biological approach to the understanding and hence classification of neuropsychiatric diseases should significantly facilitate more successful drug discovery and development. This approach starting from a defined set of symptoms would drive to a quantitative biologic description. Implicitly this would identify the appropriate tools and lead finally to an enhanced diagnostic framework. By linking behavioural symptoms to a quantitative biology the identification of maladaptive brain circuitries, molecular changes, disease stage and genetic risk regardless of any existing disease classification should all be significantly improved. A developing understanding of the biological substrates is thus expected to lead to translatable, quantifiable biomarkers or endophenotypes that allow us to effectively treat the right patient population.

The aim of this call is to initiate the process that is needed to move towards a quantitative biology based framework for neuropsychiatry disorders. This is timely both to reverse the stagnation in the development of treatments for classical psychiatric disorders, but also to address the challenges offered by the need to treat neuropsychiatric issues associated with the increasing burden of neurodegenerative disease.

To complete a systematic quantitative biological review for the whole spectrum of neuropsychiatry is a vast undertaking. This proposal therefore concentrates on providing a structure and framework for the

approach while encouraging a focus on two or three areas in the first iteration. Purely for example a proposal might be structured to explore two from; agitation, psychosis, cognition or apathy in Alzheimer's and schizophrenia. This will ensure that proposals can be judged to have realistic aspirations and achievable objectives leading to lasting utility within the time and with resources available.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The magnitude of the issue of reclassifying disorders is such that it can only be addressed by a major Public-Private-partnership involving a variety of stakeholders, including those primarily involved in understanding molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complementary experience and expertise, as well as regulators. The potential technical expertise required is likely to involve a broad multidisciplinary consortium bringing together, for example, knowledge and longitudinal samples in "omics", imaging, cognitive and behavioural neuroscience, neuropsychopharmacology, as well as translational, experimental medicine and clinical statistics, bioinformatics and health economics. This is a program which cannot be successfully administered by an individual research group or company but will require a broad consortium to be successful. Paving the way for a new classification by focusing on neuropsychiatric symptom constellations and identifying their biological correlates will lead to an understanding and hence classification of neuropsychiatric diseases which will allow a stratification of patients to enable patient tailored treatment. The project should significantly facilitate more successful drug discovery and development by identification of new hypotheses for therapeutic intervention for specific symptoms.

OVERALL OBJECTIVES

The basic concept of the proposal would be to explore, starting from one or more selected symptom constellations, the same set of quantifiable biological parameters across two or more distinctly classified patient groups. Any resultant framework would have the significant potential to alleviate patient burden by improving understanding of biological aetiology of disease, guiding therapeutic decisions and provide novel entry points for treatment development. These studies would be driven from clinical quantitative biology back through appropriate translation to the measurement of homologous pre-clinical quantitative biological indices.

The aims being to:

- Identify and validate clinically relevant biological substrates of neuropsychiatric symptom constellations through the use of quantitative technologies. These might include but are by no means restricted to: Electroencephalography (EEG) (evoked responses, sleep), functional Magnetic Resonance Imaging (fMRI), quantitative neuropsychological testing, Magnetoencephalography (MEG), peripheral biomarkers. A subset of the all possible domains and clusters will be chosen to focus the project in the first instance.
- Identify the best predictive systems- clinical, non-clinical and pre-clinical - for the exploration of the underlying biological process and the identification and development of novel therapies or targets.
- Generate tools that have a beneficial effect on healthcare costs by, for example, enabling more effective identification of the right patient for a given treatment of a specific symptom constellation.
- Pave the way for a new classification by focusing on neuropsychiatric symptom constellations and identifying their biological correlates.

- Provide sufficient proof-of-principle evidence to begin engagement with the regulatory authorities

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

In the development of their short proposal, Applicants should consider potential synergies and complementarities with other relevant initiatives, both in Europe and globally, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Collaboration by design should be a cornerstone of the proposed strategy. Synergies may be sought among others with other ongoing IMI initiatives, (e.g. AETIONOMY, NEWMEDS, EU-AIMS, StemBanCC and EBISC) with other European research projects investigating neurobiological mechanisms of psychiatric disorders as well as European research infrastructure initiatives and non-European initiatives such as the US-National Institute for Mental Health (NIMH), supported Research Domain Criteria (RDoC) Initiative (<http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml>).

As much of the framework depends upon the emerging technologies there is a key need to explore synergies with technically orientated companies such as those providing imaging. The initiative could well deliver significant advances in our understanding of “best practice” in the use of these technologies.

EXPECTED KEY DELIVERABLES

- Starting from patients selected by symptom identification of a set of quantitative biological parameters/markers, to allow comparison both between symptom domains and across diseases, for each symptom constellation.
- Analysis of the wide range of parameters measured in this experimental context would aim towards selection and validation of a pragmatic subset useful in everyday diagnosis. These new tools/markers would allow stratification of patients to facilitate more effective treatment and design of clinical trials, including the standardisation of measurement across sites.
- Establish a network of clinical research sites able to perform high quality observational studies in neuropsychiatric syndromes beyond the established classification systems.
- Establish a network of pre-clinical research sites able to perform high quality translatable studies to explore the substrates identified as causal in the clinical studies. The tools validated in the study would also then transferable to general use beyond the initial network.
- Identification of new hypotheses for therapeutic intervention for specific symptom constellations.
- Interaction with regulators and to prepare the regulatory path for acceptance of new metrics and approaches

INDUSTRY CONSORTIUM

- Pharmaceuticals
- Medical imaging and electrophysiology
- Experimental medicine providers
- Statistics and data mining

EFPIA PARTICIPANTS

Lilly (Co-coordinator), Boehringer-Ingelheim (Co-coordination), Lundbeck, Pfizer, Novartis, Roche and Takeda.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 3 years.

INDICATIVE BUDGET

The indicative contribution from the EFPIA companies is estimated at a total of EUR 8 080 000. Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non EU in kind contribution.

The indicative IMI JU contribution will be up to EUR 8 080 000.

FUTURE PROJECT EXPANSION

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would then be entitled to open to other beneficiaries as they see fit.

In the context of this topic, a second phase would most likely have a duration of 2 years and would only be initiated after a futility analysis of the progress of collecting data from human subjects but also the progress in the preclinical work package and if certain milestones have been passed that justify a Phase 2 of the project to expand knowledge and to increase statistical power. A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables. The detailed scope of the call would be described in the relevant annual work plan.

APPLICANT CONSORTIUM

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium. This may require to mobilise, as appropriate, expertise in: statistics and study design; clinical study support; IT – Data communication and data basing; quantitative clinical technologies and biomarkers; pre-clinical technologies that are aligned with those identified for use clinically; regulatory expertise translational medicine expertise; and project management. It may also require to mobilise, as appropriate, following resources: existing datasets and existing clinical studies; clinical cohorts and registries; biobanks and bio-samples; engagement of SMEs able to contribute relevant technologies; and involvement of patient organizations and its ethical considerations.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

As currently envisaged it is anticipated that the consortia would select two or three symptom constellations, or domains that should be widely present in most disorders, neuropsychiatric and degenerative, therefore if biological substrates were confirmed these would translate in many areas. The following offer examples that would provide the best chance of recruitment of appropriate subjects and reverse translation to pre-clinical approaches:

- Cognition (Working memory, Episodic, Reasoning and Problem solving, Attention), Reward, Stress, Affect, Agitation, Perception and sensory processing.

Appropriate study cohorts of patients could stem from disease populations, for which selected symptom domains are described, such as:

- Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease or FTL D
- Affective disorders such as Major Depressive Disorder/Treatment Resistant Depression or Schizophrenia.

The applicant consortium partners that will provide data and samples from existing study cohorts and registries need to demonstrate in their application that those envisaged resources can be shared among all the partners. Thus the applicants have to document in their short proposal that applicable ethical and data privacy laws allow sharing such data and samples within the consortium.

In addition a plan for interactions with Regulatory Agencies/Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#) "). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- 2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

The proposal is suggested to be organized in 8 major work packages:

WP1 CONSORTIUM MANAGEMENT AND GOVERNANCE

WP2 SCIENTIFIC CONSENSUS (CLINICAL/PRE-CLINICAL) ON STUDY DESIGNS, INSTRUMENTS AND METHODOLOGY

WP3 DATA MANAGEMENT AND STATISTICS TO ALLOW INTEGRATED ANALYSIS OF DATA SETS

WP4 CLINICAL STUDY IMPLEMENTATION AND OPERATIONS

WP5 CLINICAL HARMONIZATION OF EXPERIMENTAL APPROACHES

In this work-package the applicants should develop and make operational their strategy for selection, validation, standardisation and harmonization of relevant quantitative biology substrates/endpoints. These might include but should not by any means be limited to:

- Imaging
- Electrophysiology
- Bio-samples analysis
- Neuropsychological assessment

WP6 PRE-CLINICAL HARMONIZATION OF EXPERIMENTAL APPROACHES

The activities of this work-package have to be operationally linked to those of the previous one (WP5). In this work-package the Applicants should develop and make operational their strategy for selection, validation, standardisation and harmonization of relevant quantitative biology substrates/endpoints. In analogy to the techniques selected by a consortium above the pre-clinical approaches should all align in a reverse translational manner.

WP7 ENGAGEMENT WITH REGULATORY GROUPS, AGENCIES AND OTHER STAKEHOLDERS

WP8 DISSEMINATION AND COMMUNICATION

4. THE CONSISTENCY APPROACH TO QUALITY CONTROL IN VACCINE MANUFACTURE

TOPIC DETAILS

Topic code	IMI2-2015-03-04
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stage

BACKGROUND AND PROBLEM STATEMENT

In 2010, 79% of the research-based global vaccine companies' production, amounting to 85% of the total market value, took place in Europe. The vaccines sector is therefore a success story for European bioscience, and a key endeavour to ensure public health. But despite its success, it faces a difficult scientific, ethical and economic challenge: the fact that the compulsory testing of vaccines before market release is still relying largely upon traditionally used *in vivo* methods and many of these are now known to be poor in terms of consistency control by current standards. For some vaccines, this rigorous testing is justified: many already established vaccines are complex mixtures of poorly-defined composition, which forces the regulatory authorities to treat each new batch or lot of vaccine individually, meaning that safety and potency must be tested by the manufacturer and by national authorities before release onto the market. However these have been made the same way for many years so a large amount of consistency and process data exists for them. On the other hand, many modern vaccines of well-defined composition or improved quality and process control of older products might allow certification of product quality without the need for animal experimentation.

In vivo final lot testing for safety and potency of vaccines is slow, expensive, relatively imprecise, and not always sensitive enough to demonstrate product consistency. In addition, some of the tests may be painful and distressing to large numbers of animals required. Elimination of these tests would therefore have significant scientific, economic and ethical benefits.

The development of alternatives to many of these tests has been progressing steadily both in the public and in the private sectors for years. While progress has been made in some directions, for example, in applying ELISA methods for quantitation of antigens, or cell-based methods for measuring residual toxicity of toxoids, the main stumbling block has been conceptual: currently in order to supplant *in vivo* assays, *in vitro* tests are generally required to correlate with the *in vivo* counterpart. But unfortunately, such a 1:1 correlation or replacement is mostly impossible to attain, given the large differences in methods, and the inherent imprecision and variability affecting the *in vivo* methods. Therefore a panel of consistency tests needs to be put in place to ensure that each batch is consistent with what has been shown previously as safe and efficacious. We find ourselves thus in a peculiar situation in which a more precise *in vitro* testing cannot be validated because it will not correlate with a more variable *in vivo* assay.

This is why a shift in paradigm has been proposed: moving away from the question that currently decides the issue – “Can *in vitro* assays mimic the *in-vivo* situation?” – to a new formulation that would lead to radical change: “Can *in vitro* testing ensure that each vaccine batch is of the same quality and consistency as those shown to be safe and efficacious? Can an *in vitro* test or tests ensure that sub-standard final lots of vaccines (i.e. inconsistent, unsafe or sub-potent or over-potent) are detected and therefore not released to the market?”.

Such an approach would require a pivotal change in the perspective of the stakeholders involved as it involves not just changing final testing but understanding and controlling the whole production process. This is all about building quality in through the process and not just testing at the end.

Fully *in vitro* release methods are in use by many manufacturers for certain vaccines and the veterinary sector has had success in removing the target animal batch safety tests completely - however, it is far from being a generally accepted paradigm. For established vaccines, a certain level of in-process testing with

non-animal methods is conducted but the collected data is not used for lot releases, but as in-house monitoring and trending of production processes. Such in-process testing is generally based on relatively simple, non-animal methods (e.g. trend analysis monitoring flocculation time (Kf), protein nitrogen levels, optical density or tests for residual formalin), and does not cover all aspects of vaccine quality and consistency. These methods monitor the production process and its consistency but information on the effect of antigen/adjuvant interaction after product blending on potency, on product stability and on product safety still requires extensive animal testing.

And yet, the last decades have seen significant progress in *in vitro* methods, so that it could justify a change in the lot release paradigm. In general, seed lots of established vaccines are better characterised and defined than they were in the past, vaccine production processes are optimised, standardised and carefully monitored, and quality systems such as Good Manufacturing Practice (GMP), Quality Assurance (QA) and pharmacovigilance are now in place to oversee consistency in production.

A push towards change in this field is in line with the IMI2 Strategic Research Agenda, which underlines the importance of the acceptance and qualification of novel tools and technologies for processes controlled by the regulatory system. This is highly relevant for vaccine manufacture processes.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Recent workshops conducted by the European Partnership for Alternative Approaches to Animal Testing (EPAA) have identified large gaps in the armamentarium and regulatory acceptance of *in vitro* tests that would need to be embedded in any new approach to Quality Control (QC) of vaccine lots to ensure potency and safety. Knowledge comes from the vaccine manufacturers who currently use a mixture of *in-vitro* and *in-vivo* methods in their in-process and final lot testing. The manufacturers also have a considerable amount of historical information on the performance of their production methods and their ability to produce material of consistent quality and composition. The information on past QC is vital for defining alert and acceptance criteria for current and future test methods and process control trend analysis that will avoid final lot testing on animals. The technological gaps hitherto identified vary from vaccine to vaccine, and tests and knowledge need to be developed in such a way as to complement existing processes. This is particularly relevant to veterinary vaccines which are produced by a larger number of smaller manufacturers each adhering to their own in-house processes and the broad range of vaccine targets. In such an environment, a public-private partnership approach in which multiple stakeholders each play an important role is required to move forward. The private sector role is clear: to identify gaps, to provide test materials (antigens, vaccines) for assay development, to compare *in vivo* and *in vitro* methods, to establish alert and acceptance criteria for new/current in process controls, to pre-validate new tests (e.g. by showing transferability from one manufacturer to another) and to engage the national authorities in validation and regulatory approval. The public sector and academia's role is to help provide data to support acceptance of new tests and approaches, to participate in the initial proof of concept and to propose innovative approaches to the development of new *in vitro* tests. This includes conducting work to help understand the key parameters for safety and efficacy and therefore consistent quality of an antigen to understand appropriate targets for *in vitro* tests, and identifying key process parameters for product quality and consistency. This work then translates to collaborative (pre)validation data and interaction with regulatory agencies on acceptance of the newly developed methods. The regulator's role in this partnership is key to assure that the right questions are posed such that the right data can be provided to support regulatory acceptance in the EU, and that all approaches are harmonised and globally acceptable.

OVERALL OBJECTIVES

The Consistency Approach (CA) is a new paradigm for improved quality control of established vaccines which moves away from the current focus on testing the final product and high reliance on *in vivo* models, to an integrated in-process and final product quality monitoring programme during vaccine lot production using non-animal methods (in line with 3Rs principle and European Directive 2010/63).

The consistency approach is enabled by the application of a battery of *in vitro* tests and production consistency controls that leads to the characterisation of structural and functional criteria of a batch by generating a “fingerprint” of the physico-chemical and immunochemical properties instead of reading out end points in animals to demonstrate safety and efficacy of each batch release testing.

The main objective of this project proposal is to demonstrate the proof-of-concept of the Consistency Approach (CA), in the global vaccine manufacturing process, focusing both on human and veterinary vaccines and to facilitate its regulatory acceptance, guidance and implementation.

This objective is going to be achieved through a series of innovations, including:

- predictive technology and methodology innovation in the areas of analytical methods
- *in vitro* models demonstrating functionality of immune responses
- bioinformatics
- a final translation of these new technologies into a general approach to consistency testing that will allow improved monitoring of vaccine quality during production and final formulation.

Depending on the current state of the art, some candidate tests will undergo various stages of pre-validation, and their transferability and inter-laboratory reproducibility will be tested through collaborative studies.

In some cases new tests and methods are required, in others simply a framework for consistency requirements to remove existing redundant tests.

Achieving the main objective would lead to an agreed road map for implementing new CA advanced methodologies and approaches into the regulatory guidance involving relevant international bodies (EDQM BSP, WHO ECBS, EMA BWP/VWP and JEG3Rs, OMCL Network, OIE, ICH/VICH⁶⁰, etc...). The project will contribute to overcoming European, but also global regulatory road blocks in harmonisation processes and to improving the problem of structural fragmentation in this area, stepping away from mostly single acting stakeholders and a difficult-to-manage complex framework towards a coordinated, cross-sector, interdisciplinary, long-term, large-scale, trans-national effort.

In addition the project could contribute to the access to medicines, reducing lead time and cost, improving R&D processes beyond vaccine manufacturing, and potentially support any cross-fertilisation opportunity within biologics for convergence of regulations.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

The EPAA working group on the "Application of the 3Rs and the consistency approach for improved vaccine quality control" has been running since 2010 and has conducted a number of workshops and meetings to identify priority vaccines. Members of the working group encompass the main European manufacturers (GSK, MSD, Zoetis, Sanofi-Pasteur, Novartis) and its strength lies in the additional involvement of national and international regulatory bodies (EMA, EDQM, FDA, USDA, Health Canada, Canadian Centre for Veterinary Biologics, WHO), European validation and standard bodies (EDQM, EURL ECVAM) and OMCLs from several European countries, many of which are engaged in research on alternatives. Furthermore, the EPAA working group is closely connected to those involved in validation and regulatory approval of alternatives and is likely to provide a useful platform for further dissemination of project outcomes with regards to tests and guidance.

⁶⁰ EDQM BSP – European Directorate for the Quality of Medicines, Biological Standardisation Programme.

WHO ECBS – World Health Organization, Expert Committee on Biological Standardization.

EMA BWP/VWP – European Medicine Agency, Biological Working Party, Vaccine Working Party.

JEG3Rs – Joint Committee for Medicinal Products for Veterinary Use/Committee for Medicinal Products for Human Use Ad-hoc Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products.

OMCL – Official Medicines Control Laboratories.

OIE - World Organisation for Animal Health.

ICH/VICH - International Conference on Harmonisation / Veterinary International Conference on Harmonization.

There may also be opportunities with other IMI projects such as the project currently under preparation from the IMI 10th Call for Proposals “Immunological assay standardisation and development for use in assessments of correlates of protection for influenza vaccines”, and the FP7 project ADITEC (www.aditecproject.eu).

EXPECTED KEY DELIVERABLES

- 1) Demonstration of **proof-of-concept** for use of non-animal assays and techniques/key process parameters leading to an integrated end to end quality and safety monitoring programme during vaccine lot production for a number of model vaccines.
 - Proof of concept for *in vitro* tests for a range of human and veterinary vaccines, for instance: safety tests for toxoid products (diphtheria and clostridials), potency tests for viral vaccines (rabies) and bacterial vaccines (pertussis and erysipelas), etc.
 - A set of non-animal methods for which proof-of-concept has been demonstrated for model vaccines and that could also be used for other vaccines after optimisation and evaluation. This could include key process parameters to be monitored, antigen assays, adjuvant assays and other consistency measures.
- 2) Development, optimisation and evaluation of techniques to be used in the CA for vaccine lot release testing. Depending on the vaccine to be controlled, one or more of the following:
 - **Physicochemical techniques** to ensure the consistent conformation of the antigen
 - **Immunochemical methods** to analyse epitopes important for the induction of functional/protective cellular or humoral responses as well as to assess antigenicity and adsorption in adjuvanted formulations
 - ***In vitro* functional methods** to demonstrate functional immunological responses
 - **Genomics and proteomics** assays to monitor genetic profiles of specific toxicity.

The assays will be selected to cover the key parameters for demonstrating vaccine consistency and assuring release of potent and safe products.
- 3) Global dissemination of knowledge and training for stakeholders on those new methodologies and approaches.
- 4) Input into improvements of existing or development of new regulatory guidance to facilitate consistency approach to vaccine release testing.

INDUSTRY CONSORTIUM

EFPIA PARTICIPANTS

Boehringer-Ingelheim, GlaxoSmithKline, Merck/MSD Animal Health, Merial, Novartis Vaccines, Sanofi-Pasteur, Zoetis.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is five years.

INDICATIVE BUDGET

The indicative contribution from EFPIA companies is EUR 7 850 000.

The financial contribution from IMI2 JU will be a maximum of EUR 7 850 000.

JUSTIFICATION FOR NON-EU IN-KIND CONTRIBUTION

Whilst vaccine marketing authorization processes are still regulated regionally, vaccines are often designed and developed globally. In addition, animal reduction can only effectively be pursued if regional differences in regulatory requirements and different release testing programs can be gradually reduced. The successful implementation of the objectives will therefore require the participation of non-EU laboratory and manufacturing sites of Boehringer-Ingelheim, Merck, Sanofi Pasteur and Zoetis.

APPLICANT CONSORTIUM

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

The Applicant Consortium is expected to provide both pre-clinical (safety, CMC, assay development) and clinical expertise and ability for interdisciplinary and inter-sectorial work and to cover the following critical fields:

- 1) Physicochemical techniques for conformational fingerprinting of antigens
- 2) Proteolytic susceptibility of antigens to mimic APC action
- 3) Immunochemical assay development
- 4) Manufacturing processes and production consistency
- 5) Antigen-adjuvant interactions
- 6) *In vitro* cell models of immune responses
- 7) Genomic and proteomic profiling
- 8) Regulatory expertise
- 9) Understanding of GLP, QA
- 10) Animal models and laboratory animal science

This may require to mobilise, as appropriate, partners from regulatory authorities (European or national, in line with the objectives), academia, National Control Laboratories, and SMEs.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

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

A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, and appropriate resources allocation, should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organisation (e.g. CDISC), to develop new data standards if no established data standards exist.

Work Package 1: PHYSICOCHEMICAL METHODS FOR CONSISTENCY TESTING

This WP will focus on:

Development of physicochemical methods for conformational fingerprinting.

Development of non-animal proteolytic assays to mimic antigen processing.

EFPIA contribution: Supply of materials e.g. adjuvanted and non-adjuvanted toxoid, technology transfer, inter-laboratory evaluation, comparison of *in vitro* and *in vivo* tests, if relevant.

Expected Applicant consortium contribution: Fluorescence and CD spectroscopy for conformational fingerprinting, electrophoresis and mass spectroscopy for antigen processing.

Deliverables:

- Protocols for the conformational analysis of single antigens in final formulations, regardless of composition to address presence of B-cell epitopes.
- Assays to measure the proteolytic sensitivity of antigen described to address T-cell epitope formation.

Work Package 2: IMMUNOCHEMICAL METHODS FOR CONSISTENCY TESTING

This WP will focus on:

Development and optimisation of immunochemical assays, development of methods for determining antigen content of adjuvanted vaccines.

EFPIA contribution: Supply of materials and reagents including mAbs, standards and vaccines, comparison of *in vitro* and *in vivo* tests.

Expected Applicant consortium contribution: Development of suitable assays e.g. ELISA for intermediate and final lot testing (including adjuvanted vaccines) and stability testing, characterisation of the panel of monoclonal antibodies used, e.g. epitope mapping.

Deliverables:

- A list of suitable methods, together with full SOPs, for subsequent inclusion in inter-laboratory evaluation and transfer studies.
- Full report and analysis describing the extent of concordance between the current *in vivo* methods and the immunochemical methods for selected vaccines.

Work Package 3: IN VITRO FUNCTIONAL MODELS FOR CONSISTENCY TESTING

This WP will focus on:

Development and optimisation of *in vitro* models to monitor parameters that are closely linked to the functionality of vaccines (i.e. capability to induce a protective immune response).

EFPIA contribution: Supply of materials, comparison of *in vitro* and *in vivo* tests.

Expected Applicant consortium contribution: Expertise in cell culture of monocytic cell lines and primary monocytes, dendritic cells and PBMCs; Co-culture of APCs and T cells; Cytokine secretion and cell surface marker expressions assays, FACS.

Deliverables:

- A primary validated cell based and a cell-line based APC assay system that can be used to evaluate vaccine quality for regulatory consistency test(s).
- Validated human and murine T cell activation assays that can be used to evaluate vaccine quality for regulatory consistency test(s).
- Comparison of the *in vivo* and *in vitro* performance of (sub)potent vaccines in murine models.

Work Package 4: BIOINFORMATICS

This WP will focus on:

Development of genomics and bioinformatics techniques to evaluate the safety of toxoid vaccines.

EFPIA contribution: Supply of materials (vaccine production intermediates and final lots). Inter-laboratory evaluation.

Expected Application consortium contribution: Gene expression analysis, QPCR, proteomics (mass spec).

Deliverables:

- Optimise, perform in house-validation and do technology transfer of a genomic derived *in vitro* safety test for selected toxoid vaccines.

Work Package 5: VALIDATION CRITERIA, TRANSFERABILITY AND INTER-LABORATORY REPRODUCIBILITY OF CONSISTENCY APPROACH METHODS

This WP will focus on:

Definition of validation criteria for consistency approach methods, design and coordination of small-scale collaborative studies evaluating the transferability and inter-laboratory reproducibility of the methods identified;

EFPIA contribution: Supply of materials, participation in transferability and inter-laboratory reproducibility studies.

Expected Applicant consortium contribution: Participation in transferability and inter-laboratory reproducibility studies.

Curation of test samples and reagents, coding and shipping.

Deliverables:

- Definition of validation criteria.
- Results of the collaborative studies (including inventory of methods developed and standardised and recommendations for further studies).

Work package 6: PROMOTION OF CONSISTENCY TESTING TO REGULATORY ACCEPTANCE

This WP will focus on:

Definition of a roadmap for regulatory acceptance of the consistency approach with the goal of providing a basis for guidance on regulatory implementation of new tests developed for the CA

EFPIA contribution: Participation in meetings to develop the roadmap.

Expected Applicant consortium contribution: Development of the roadmap and engagement of relevant international regulatory and standards bodies.

Deliverables:

- Roadmap conference.
- General guidance for acceptance and implementation of the CA.
- Publication and communication activities.

Work package 7: CONSORTIUM MANAGEMENT

This work package will focus on:

- consortium and project management, facilitation and streamlining of cooperation between the different partners of the project and between work packages
- communication and dissemination activities

5. PERTUSSIS VACCINATION RESEARCH

TOPIC DETAILS

Topic code	IMI2-2015-03-05
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stage

BACKGROUND & PROBLEM STATEMENT

Globally, CDC estimated that there are 16 million pertussis cases and about 195,000 pertussis deaths in children per year, making it one of the leading causes of vaccine-preventable deaths. While there is a resurgence of the disease in Europe, US and Australia, the heaviest burden is in children in low-income countries.

Since its introduction in the 1940's, vaccination against *Bordetella pertussis* (*B. pertussis*) infection has been demonstrated to be effective in preventing infection and disease. An impressive 99% reduction of whooping cough was observed in infants in European countries during the 1950's and 1960's, as a result of the wide use of whole cell pertussis vaccine, wP (a suspension of formalin inactivated *B. pertussis* with Alum salts). In the 1990's, the advent of biotechnology resulted in the introduction of second generation pertussis vaccines, containing well-defined combinations of highly purified antigens formulated in Alum adjuvant. These vaccines, termed acellular pertussis vaccines, aP, show a much more acceptable local reactogenicity profile than wP vaccines and still offer high levels of protection. Acellular vaccines are primarily used in industrialised countries, while many developing and emergent economies are still using the whole cell vaccines. The WHO recommends vaccination minimally as a primary series of at least three doses of high quality aP or wP pertussis vaccine in infants. Paediatric vaccination schedules in industrialised countries typically include recommendations for additional doses of the aP vaccines to ensure boosting of immunity through schooling years and prevent transmission to younger siblings, who are yet to complete their primary vaccination series. Moreover, some countries offer an additional one-dose aP booster vaccine to adolescents and adults, commonly administered in combination with diphtheria and tetanus toxoids (Tdap vaccines, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine). wP vaccines are not recommended for use as booster vaccines in older children, adolescents or adults because an increase in local reactogenicity has been observed with age and repetitive administration.

Despite the success and relatively large vaccination coverage with pertussis vaccines in industrialised countries, there has been an increase in the incidence of pertussis in certain countries since the early 2000's. USA [CDC], Australia and the UK have declared epidemic outbreaks [Sheridan *et al.* 2014]. In fact, the largest numbers of annual cases of *B. pertussis* in over half a century were reported recently in the USA [Cherry 2012]. In Europe, a resurgence of the disease has been described in the Netherlands, Norway, Germany, the United Kingdom, Spain and Slovenia [ECDC; Sizaire *et al.*, 2014]. Following a resurgence of infant pertussis-related deaths, maternal immunization programs were successfully adopted in the US, UK, and several other countries [Amirthalingam 2014]. WHO has since recommended that countries with a high pertussis burden adopt maternal immunization as the most cost-effective intervention strategy to reduce neonatal pertussis disease [WHO-SAGE 2014]. The pattern of disease resurgence in school-aged children, adolescents and adults is understood to be related to a waning of immunity with age.

Although the effectiveness of current aP vaccines in infants (at risk population) and the benefit of Tdap booster vaccines are not questioned, there is a clear need to investigate the underlying causes of the observed increase in incidence of pertussis disease in certain populations, in particular with regards to the role played by immunological memory and the differences between aP and wP vaccines in generating long-term protection. This will provide the research community, manufacturers and health authorities with valuable information on what is needed to increase the effectiveness of vaccination in the affected population cohorts. It could also pave the way for refining vaccination schedules with currently available vaccines as well as for improving or developing novel formulations.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

While the effectiveness of current aP vaccines in infants (at risk population) and the benefit of Tdap booster vaccines are not questioned, the changing epidemiology of pertussis calls for action. The joint effort of vaccine manufacturers, academic researchers, government, public health bodies and regulatory authorities is needed to increase our scientific understanding of human immunity to pertussis and the role of vaccination in tackling this phenomenon. Ultimately the potential modification of current vaccine formulations and/or immunisation schedules and the development of novel vaccines will be impacted by the outcome of this collaborative research program.

Moreover, this public-private consortium of industrial and academic stakeholders would become a unique platform for interaction and consultation with Regulatory Authorities and Public Health Institutions. Indeed, the validation and acceptance of new biomarkers, new disease models, new vaccines and/or formulations, as well as new vaccination schedules will be a critical step in implementing the results of this project for the benefit of public health.

OVERALL OBJECTIVES

The overall objectives of the project are to pursue the identification and validation of biomarkers of protective immunity to pertussis and the establishment of models of pertussis infection that will enable the refinement of current vaccination schedules and expedite the development and testing of novel or improved vaccine formulations.

In particular, the project aims will be:

- Gaining a more thorough scientific understanding of the pathogenesis of *B. pertussis* and of the underlying molecular mechanisms and biomarkers of protective immunity to pertussis in humans.
- Investigating differences between whole cell and acellular pertussis vaccines, in particular with regards to their ability to generate protection against infection, disease, carriage and transmission, the role of maternal antibody in modulating immune responses to pertussis vaccination in infants, as well as to establish long term immunological memory
- Strengthening our technological means of testing novel vaccine candidates and immunisation regimes in animal and human models of pertussis disease and immunisation
- Interacting closely with Regulatory Authorities and Public Health Institutions including those involved in vaccination and the monitoring and control of infectious diseases to ensure that the results obtained can be translated into relevant regulatory guidance as well as public health and clinical practice.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Applicants should include considerations in their proposal on how interactions with ongoing IMI and other projects are envisaged, if applicable. The following IMI and European Commission funded projects might be considered:

The European research programme for improved pertussis strain characterisation and surveillance (EUPERTSTRAIN), [http://www.2020-horizon.com/EUPERTSTRAIN-European-research-programme-for-improved-pertussis-strain-characterisation-and-surveillance-\(EUPERTSTRAIN\)\(EUPERTSTRAIN\)-s45262.html](http://www.2020-horizon.com/EUPERTSTRAIN-European-research-programme-for-improved-pertussis-strain-characterisation-and-surveillance-(EUPERTSTRAIN)(EUPERTSTRAIN)-s45262.html)

Other IMI projects in the field of infectious diseases and vaccines, such as projects running under the IMI New Drugs for Bad Bugs (ND4BB) programme, the projects BioVacSafe (www.biovacsafe.eu), RAPP-ID (www.rapp-id.eu), ADVANCE (www.advance-vaccines.eu), as well as the project resulting from the topic "The consistency approach to quality control in vaccine manufacture" of the present Call

The FP7 project ADITEC, www.aditecproject.eu

The US National Institutes of Health funded Human Immune Phenotyping Consortium and the Bill and Melinda Gates Foundation funded Systems Biology/Immunology Consortium in the US

In general, the applicant consortium should ensure that all activities that are already ongoing in the field covered by this topic and all expertise that already exists in the EU and elsewhere are leveraged to maximise the potential impact of this action.

EXPECTED KEY DELIVERABLES

The following key deliverables are expected:

- 1) Immunological biomarkers that could reliably be used to streamline vaccine clinical trials:
 - Harmonised classic and novel bioassays to measure immune responses against pertussis, such as In vitro functional killing assays (i.e. bactericidal and opsonophagocytic antibody)
 - Biomarkers that can be used to predict protection against pertussis
 - Biomarkers that can be used to assess long lasting immunological memory to pertussis
 - Biomarkers that can be used to detect early signs of the waning of immunological memory to pertussis
 - Identification of putative correlates of protection that can be studied in future efficacy trials, with an overarching goal to define, in such trials, correlate(s) of protection that are suitable as endpoints for future pertussis vaccine registration
 - Development of a rapid and reliable point of care diagnostic test development may also be considered
- 2) An understanding of the difference in immune response profiles generated by natural pertussis infection and aP and wP vaccines in selected population cohorts (school age children, adolescents, younger adults, older adults) through:
 - A molecular dissection of the immune response to *B. pertussis* including:
 - Dissection of the memory B-cell responses
 - Dissection of the T-cell response, including the validation in humans of differences in T helper cell response profiles observed in animal models with the vaccines.
 - Information on the effect of vaccination on *B. pertussis* colonisation, carriage and transmission
- 3) The laboratory network and technological expertise in Europe to perform preclinical immunisation and *B. pertussis* challenge studies in predictive pre-clinical models, considered relevant models of the disease. This can be used to test experimental vaccines and aid in the identification of biomarkers of vaccine efficacy and immunological memory.
- 4) A molecular understanding of the progression of *B. pertussis* colonisation, infection and disease in the presence or absence of pre-existing immunity, acquired through studies in human cohorts naturally exposed to pertussis and/or via control challenge studies in human adult volunteers (a

human challenge model that would need to be developed). Epidemiological studies that could cast light on the resurgence of pertussis may also be considered (aP and wP vaccines countries)

- 5) A close interaction, collaboration and consultation with Regulatory Authorities and Public Health Institutions to ensure assessment, acceptance and validation of the results of the project so they can be translated into Regulatory Guidance and public health and clinical practice.
- 6) An understanding of the role of maternal antibody in modulating immune responses to pertussis vaccination in infants, so that recommendations could be made for adoption of maternal immunisation programs in low-income countries.

EXPECTED IMPACT

The information and knowledge acquired through this program will be useful in understanding the reasons underlying the resurgence of pertussis disease in school age children, adolescents, and younger adults and ultimately provide clues as to how current vaccines and vaccination schedules can be modified to enhance protection in these populations.

The availability of reliable preclinical models in Europe, in which to test the immunogenicity and efficacy of novel vaccine formulations, will increase the ability of academic researchers, biotechnology and pharmaceutical companies all over the world to screen vaccine candidates and select the most successful for clinical development.

The establishment of a human model of pertussis infection via control challenge studies in volunteers could permit the early evaluation of experimental vaccines for protective efficacy, thus accelerate the development of novel and improved vaccine formulations.

The identification of reliable biomarkers of immunological memory and vaccine efficacy validated by regulatory authorities will facilitate vaccine efficacy trials and streamline clinical development programs.

A concerted effort of the pharmaceutical industry in coming together with academia and public bodies to resolve a pressing public health issue will have an overall positive impact globally. This unique public-private consortium will act as an exceptional interlocutor with Regulatory Authorities and Public Health Institutions allowing a concerted evaluation, validation and acceptance of new biomarkers, new models, new vaccines and/or formulations as well as new vaccination schedules to help combat pertussis disease around the world.

By ultimately understanding and explaining the resurgence in pertussis observed in the face of wide vaccine use, the program is expected to help prevent a further reduction in the public's confidence in vaccination in Europe and increase the coverage of life-saving vaccines around the world.

INDUSTRY CONSORTIUM

The industry consortium will comprise vaccine developers and manufacturers. They will be contributing:

- Licensed pertussis vaccine for prospective clinical studies
- Know-how on clinical development of vaccines
- Expertise in *in vitro*, preclinical and clinical *B. pertussis* research, pertussis vaccination and pertussis epidemiology
- Expertise in the identification of human biomarkers of infectious disease progression, immunological memory and/or vaccine efficacy
- Expertise in molecular epidemiology and use of *in silico* tools to investigate pathogen biodiversity
- Expertise and access to epidemiological data on pertussis disease and effectiveness of pertussis vaccination

EFPIA PARTICIPANTS AND ASSOCIATED PARTNERS

Sanofi Pasteur, GSK, Bill & Melinda Gates Foundation and Novartis.

- The Bill & Melinda Gates Foundation (BMGF) works to help all people lead healthy, productive lives, particularly those in most need. While pertussis is a growing concern in Europe and the US, its heaviest burden is in children in low-income countries. BMGF's aim in this pertussis vaccine research project is to ensure that findings and results from the project can make the biggest public health impact in at risk populations globally.
- The BMGF participates in the present topic as Associated Partner to IMI2.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 5 years.

INDICATIVE BUDGET

The indicative contribution from EFPIA companies and IMI2 JU Associated Partners is EUR 14 000 000. The financial contribution from IMI2 JU will be a maximum of EUR 14 000 000.

APPLICANT CONSORTIUM

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium. The research objectives may require:

- Expertise in *in vitro*, preclinical and clinical *B. pertussis* research or pertussis vaccination
- Expertise in the development of bioassays or immunoassays suitable to assess pertussis infection and functional and memory immune responses to pertussis vaccination.
- Expertise in the identification of human biomarkers of infectious disease progression, immunological memory and/or vaccine efficacy
- Expertise in molecular epidemiology and use on *in silico* tools to investigate pathogen biodiversity and epidemiology of infectious disease
- Expertise and infrastructure needed to set up preclinical disease models, including in non-human primates
- Expertise and infrastructure to perform prospective clinical studies with licensed pertussis vaccines, as well as access to relevant vaccination cohorts
- Institutional expertise /infrastructure to develop and perform control bacterial/respiratory pathogen challenge studies in human volunteers
- Expertise or access to epidemiological data on pertussis disease and effectiveness of pertussis vaccination
- Banking and Documenting clinical isolates of *B. pertussis* or biological samples from infected or vaccinated individuals

This may require to mobilise, as appropriate, stakeholders such as:

- Academic or public research participants with established and well recognised experience in the field of pertussis research, vaccine research and/or human biomarker identification.
- Clinical investigators with the expertise and infrastructure to perform prospective clinical studies with licensed pertussis vaccines in relevant vaccination cohorts
- Clinical investigators with the expertise and infrastructure to conduct controlled challenge studies with respiratory pathogens in human volunteers
- Academic or public research participants with expertise and support infrastructure in the development of preclinical *in vivo* models of pathogens
- SMEs interested in the development of novel pertussis vaccines and/or in developing and validating novel technologies for identification or testing of biomarkers following infection or vaccination (this might also include development of point of care diagnostic tools)
- Regulatory Authorities and Public Health Institutions involved in vaccination and the control of infectious diseases
- Regulatory bodies involved in the regulation of clinical trials and the licensure of new vaccines
- Regulatory bodies involved in the authorisation of clinical trials of new vaccines

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

- Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "[Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020](#)" and "[Guidelines on Data Management in Horizon 2020](#) "). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The work packages that will make up the architecture of this project should be interacting closely with each other to ensure the project achieves all its objectives and has the impact expected. The proposed work package list is the following:

- WP1: Development of a preclinical *in vivo* model of pertussis vaccination and challenge to be used in research of aP and wP vaccines and development of novel pertussis vaccines
- WP2: Immunological studies of pertussis infection in human volunteers naturally exposed to pertussis or via control challenge studies

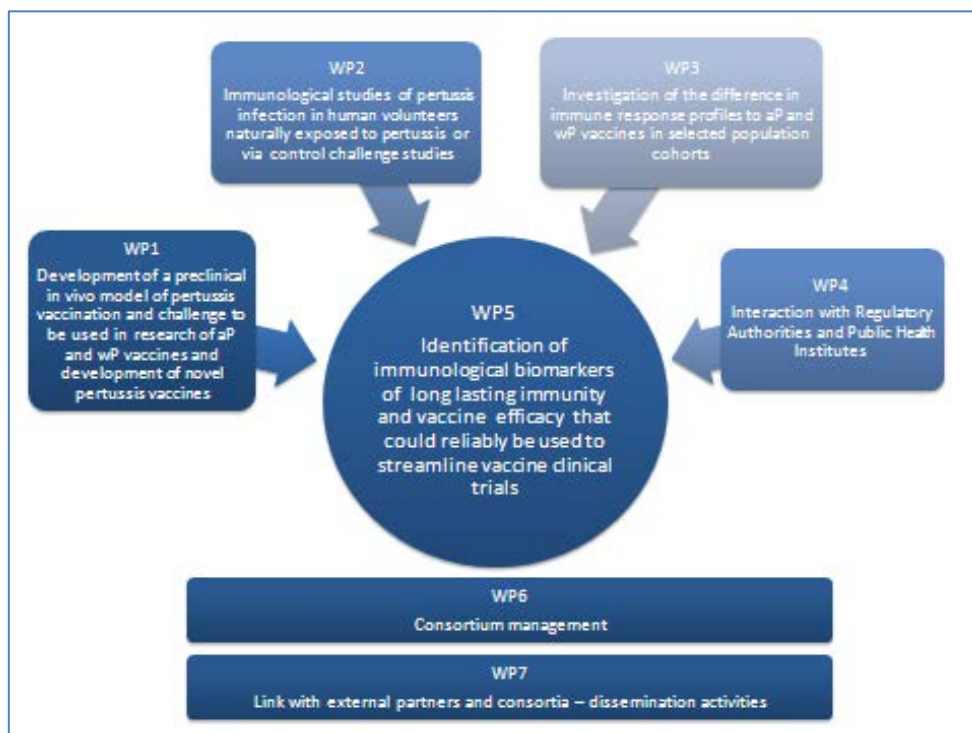
- WP3: Investigation of the difference in immune response profiles to aP and wP vaccines in selected population cohorts
- WP4: Regulatory affairs and Public Health impact of the research, including interfacing with relevant authorities and bodies to ensure the acceptance and validation of biomarkers and their translation into regulatory guidance
- WP5: Identification and assessment of immunological biomarkers of long lasting immunity and vaccine efficacy that could reliably be used to streamline vaccine clinical trials
- WP6: Project coordination and management. To cover all aspects of project governance, management and coordination.
- WP7: Dissemination activities. To cover all aspects of the dissemination of results, and communication strategy

Work packages 1, 2, 3 and 4 should run in parallel as much as possible with the objective to feed results to WP5 that will ultimately lead to the assessment and identification of immunological biomarkers of long lasting immunity and vaccine efficacy . Each work package team, as applicable, is expected to be comprised of academic researchers, industry, and regulatory experts and experts from public health or other institutions to ensure acceptance of results.

A full project plan with suitable milestones resource allocation and timeline shall be included in the proposal. In particular, a plan for interactions with Regulatory Agencies/Public Health bodies should be built into the project architecture of the project. The plan shall also address aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

A suggested architecture is shown in the scheme below. Please note that the suggested outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.



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6. KNOWLEDGE REPOSITORY TO ENABLE PATIENT FOCUSED MEDICINE DEVELOPMENT

TOPIC DETAILS

Topic code	IMI2-2015-03-06
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

BACKGROUND AND PROBLEM STATEMENT

In order to achieve successful patient integration in medicines development, individual players from the pharmaceutical industry must work together and develop an open dialogue on a peer-to-peer basis with patient representatives. To this end a multi-national collaboration with an initial emphasis on the patient-industry relationship was formed: *Patient Focused Medicines Development* (PFMD).

The ultimate goal is to make medicines development faster and more efficient through systematic patient involvement. This can only be accomplished when a rational, structured process for integrated patient involvement is developed and accepted by all stakeholders.

In order to achieve routine patient involvement, all stakeholders need to work together to achieve a meaningful outcome. These include: industry; regulators; patients, patient associations and advocacy groups; purchasers of medicines (including pharmacies and hospitals); healthcare professionals; politicians and legal advisors; HTA agencies; and academia and topic-related think-tanks.

There are a substantial number of organizations and initiatives aiming to improve patient involvement – indicating that this is a common priority. However there is no organized information repository to share best practices, standards and approaches. Real time, searchable information sharing is critical to develop standard approaches and guidance which are shared and embraced by multiple constituents.

A key step is the creation of a knowledge repository and supporting network of stakeholders to capture current approaches, standards, regulatory provisions and best practices to optimize patient engagement information from—and for – stakeholders. A centralized Patient-Inspired Knowledge Hub (PIKH) would capture when patient engagement occurs, and details and standards of how stakeholders are involving patients from early discovery throughout the research and development cycles towards, and following approval. This shared repository will make research leaders more focused on unmet health needs of patients and hence more targeted toward what "end users of healthcare" really want and need.

NEED AND OPPORTUNITY FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

A PIKH will respond to the critical need for more patient involvement in medicines R&D and expand opportunities for supporting such involvement and important role of patients in the industry R&D and regulatory processes.

The development of an open platform like a PIKH requires contributions from multiple stakeholders including patient organizations, companies, regulators and academia.

To ensure neutrality and broad acceptance of the new platform it should be hosted by a public partner / institution in the consortium.

OVERALL OBJECTIVES

The overall objective is to have a Patient Inspired Knowledge Hub (PIKH) that enables sharing non-competitive information with and by users from patient groups, regulators, health authorities, academia and industry. The project is a response to the lack of a uniform process to engage patients in the drug development process. The PIKH will facilitate and enable the incorporation of patient input into the drug development processes, used broadly by stakeholders in a uniform (standardized) way among a range of stakeholder organizations.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

This proposed IMI2 project is expected to develop synergies and avoid duplication of effort with existing consortia (e.g. EUPATI) and other relevant initiatives. The details of these interactions will have to be defined at the full proposal stage and agreed with the EFPIA partners. However, the application should include considerations how the interactions with ongoing consortia and other initiatives, such as the following are envisaged and particularly what / which ones would add most value to the project.

The project may also be aided by:

- The recently developed Chief Medical Officers (CMO)-Roundtable think tank focused on fostering cooperation between Patient Organizations and Industry (PFMD) including MSD, Pfizer, GSK, Novartis, UCB, National Health Council etc.
- Several organizational stakeholders (Patient-Centered Outcomes Research Institute (PCORI), Health Technology Assessment International (HTAi), Brookings Institute, Institute of Medicine) are developing validation methodology and standard approaches for patient input into research.
- The IMI project EUPATI - in parallel to its focus on the development of R&D information programs for patients - has started to identify best practice examples for patient involvement along the whole R&D process and to develop best practice guidance for the interaction / collaboration of stakeholders (Patient Organisations, Ethics Committees, HTA bodies, Academia / Hospitals, Industry, Regulatory Authorities). PIKH would complement these activities and the sustainability plans of the project.
- Another IMI project, EMTRAIN, has developed and enhances a searchable course and information portal (on-course®) for the biomedical sciences, particularly for the pharmaceutical industry, (a section for Patient Organisations via EUPATI is planned) and a collaboration and synergistic use of the database could be explored.

EXPECTED KEY DELIVERABLES

A centralized Patient-Inspired Knowledge Hub (PIKH) that captures when patient engagement occurs, details and standards of how stakeholders are involving patients from early discovery throughout the research and development cycles towards, and following approval.

PIKH will enable and support the following key deliverables according to the three major work streams:

- Identifying the appropriate points in time to interact with patients for development of medicine, including: risks and benefits of interactions, required capabilities, anticipated enabling changes in regulatory affairs and more.
- Standardizing a framework to be used for patient engagement in medicine development
- Providing the ecosystem and mechanisms for stakeholders, for example pharmaceutical companies and patient advocacy groups, regulators, to discuss and share frameworks, methods and knowledge.

A risk assessment and evaluation report of conflict of interest in such a cooperation between industry and patients.

Provide a sustainable service specifically for patient organisations and industry to identify possibilities of interaction/collaboration.

Furthermore by providing data and knowledge management services this consortium will enable:

- Making the framework available for broad use

- Populating the framework
- Improving the framework through group learning

EFPIA PARTICIPANTS

MSD (coordinator), Pfizer, UCB, Bayer

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 3 years

INDICATIVE BUDGET

The indicative contribution from EFPIA companies is EUR 7 370 000.

The indicative financial contribution from IMI2 JU is a maximum of EUR 7 370 000

APPLICANT CONSORTIUM

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see “Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020” and “Guidelines on Data Management in Horizon 2020”). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- 2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

The applicant consortium is expected to consider how the input from special populations such as the paediatric population and older adults etc. can systematically be included in patient informed medicines development.

The applicant consortium is expected to address all the research objectives and contribute on the defined deliverables in synergy with the EFPIA consortium. This may require to mobilise, as appropriate, expertise in:

- Experience with Patient Advocacy
- Regulatory Expertise
- Health Services Research
- Clinical Informatics
- Infrastructure and Software
- Advanced Knowledge Management
- Point of Care Know-how and Integration
- Community Education and Learning

- Education Systems
- Learning and training Management
- Analysis and complex clinical workflow experience
- Drug Development Life Cycle
- Innovation
- Requirements Engineering
- Product Development

Industry profiles assigned to the project will be as follows:

- Clinical
- Business Operations
- Medical Affairs
- Data and Knowledge Management
- Product Development
- Project Execution – Non Technical
- Project Execution – Technical

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The below architecture for the full proposal is a suggestion, different innovative project designs are possible.

WP1 EVALUATE NEEDS & EXISTING LANDSCAPE

- Review existing state of patient engagement in drug development including perspective and needs from: patients, patient advocacy groups, regulatory, pharmaceutical industry, delivery system, and business.
- Review the ethical, legal and regulatory landscape in Europe
- Identify the features and requirements needed for next-generation patient engagement into drug development.

WP2 PLATFORM ROADMAP AND STRATEGIC PLANNING

- Develop a roadmap for the patient engagement platform focusing on the benefit/risk for patients, public-private capability development, and wide-industry dissemination & adoption.
- Develop a sustain business model that would facilitate the platform becoming an industry-standard tool with global sources of revenue.

WP3 PATIENT ADVOCACY ENGAGEMENT

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices, regulatory decision making, and patient participation

WP4 REGULATORY ENGAGEMENT

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices and patient participation

WP5 ACADEMIC ENGAGEMENT

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices and introduce evidence-based science and best-practices.

WP6 ARCHITECTURE AND INTEGRATION

- Define the architecture of platform, implementation and oversee the overall platform integration and operation.

WP7 SEMANTIC INTEROPERABILITY

- Provide tools and services for semantic interoperability between varying data sources, enabling uniform interpretation of data.

WP8 DATA PROTECTION, PRIVACY & SECURITY

- Provide security services for the platform and ensure processes are enhanced for data protection and compliance.

WP9 PLATFORM SERVICES

- Design and implement end-to-end solutions (tools and services) that address the requirements.

WP10 PILOTS

- Demonstrate the functionality of the tools and services provided by Work Packages 3-9 and to evaluate the patient engagement platform in terms of usefulness for facilitating better patient-pharma industry interaction.
- Pilot evaluations will occur for a specific population(s), disease area(s) and pharma company workflow(s)

WP11 DISSEMINATION AND STANDARDIZATION

- Plan dissemination strategy and incorporate it into the design of the platform to ensure high rates of framework adoption.
- Work with pharma companies to integrate platform into their business processes

WP12 COMMERCIALIZATION AND BUSINESS MODEL GENERATION

- Identify problem areas in the healthcare ecosystem that could benefit from application of platform.
- Propose new value propositions for the users and incorporate into product development
- Identify market segments and monetization path for platform to become financially sustainable post-funding.

WP11 PROJECT COMMUNICATION

- Support the communication and training between all Work Package Groups and prepare for platform execution.
- Widely disseminate platform outcomes and communicate with other EC FP or IMI projects in Europe and globally

WP12 PROJECT MANAGEMENT

- Coordinate project work, administer day-to-day operations, manage the collaborative efforts of the Work Packages
- Ensure that the scientific work being conducted is delivered on time and on budgets through optimal project management, including quality monitoring, planning, reporting and financial control

WP13 PRODUCT MANAGEMENT

- Coordinate platform and operations design, and development, ensuring resulting products adhere to best-practice design standards, are well-built and easy to use.

CONDITIONS FOR THIS CALL

Applicants intending to submit a short proposal in response to the IMI2 Call 3 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier: H2020-JTI-IMI2-2015-03-two-stage
Type of action: Research and innovation action
Publication Date: 12 December 2014
Stage 1 Submission start date: 12 December 2014
Stage 1 Submission deadline: 24 March 2015 – 17:00:00 Brussels time

Indicative Budget: From EFPIA companies and IMI2 JU Associated Partners:
 EUR 56 430 000
 From the IMI2 JU: EUR 56 430 000

CALL TOPICS

IMI2-2015-03-01	The indicative contribution from EFPIA companies is EUR 11 000 000. The financial contribution from IMI2 JU is a maximum of EUR 11 000 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-02	The indicative contribution from EFPIA companies is EUR 8 130 000. The financial contribution from IMI2 JU is a maximum of EUR 8 130 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-03	The indicative contribution from EFPIA companies is EUR 8 080 000. The financial contribution from IMI2 JU is a maximum of EUR 8 080 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-04	The indicative contribution from EFPIA companies is EUR 7 850 000. The financial contribution from IMI2 JU is a maximum of EUR 7 850 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2015-03-05	The indicative contribution from EFPIA companies is EUR 7 000 000 The indicative contribution from IMI2 JU Associated Partners is EUR 7 000 000 The financial contribution from IMI2 JU is a maximum of EUR 14 000 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-06	The indicative contribution from EFPIA companies is EUR 7 370 000. The financial contribution from IMI2 JU is a maximum of EUR 7 370 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (first stage)	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
IMI2-2015-03-01 IMI2-2015-03-02 IMI2-2015-03-03 IMI2-2015-03-04 IMI2-2015-03-05 IMI2-2015-03-06	Maximum 5 months from the date of submission to the first stage.	Maximum 5 months from the date of submission to the second stage.	Maximum 3 months from the date of informing the applicants following the second stage evaluation.

CONSORTIUM AGREEMENTS

In line with the Rules for Participation and Dissemination applicable to IMI2 actions⁶¹ and the IMI2 model grant agreement, participants in research and innovation actions are required to conclude a consortium agreement prior to grant agreement.

⁶¹ Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

4th IMI2 CALL FOR PROPOSALS

INTRODUCTION

The Innovative Medicines Initiative 2 (IMI2) Joint Undertaking has been created⁶² following the below principles:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps⁶³, from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The [IMI2 Strategic Research Agenda](#) (SRA) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include themes on regulatory, health technology assessment and healthcare delivery challenges which are addressed in this call.

Applicant consortia are invited to submit proposals on the topic. These proposals should address all aspects of the topic. The size and composition of the consortium should be adapted to the scientific goals and the expected key deliverables.

While preparing their proposals, applicant consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaborations on the global level and to maximize European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Before submitting a proposal, applicant consortia should familiarize themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with coordination and support actions (CSAs).

⁶² The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

⁶³ Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in a EU Member State or an associated country, are eligible for funding.

TOPIC 1. ENABLING PLATFORM ON MEDICINES ADAPTIVE PATHWAYS TO PATIENTS

TOPIC DETAILS

Topic code	IMI2-2015-04-01
Project type	Coordination and support action (CSA)
Submission & evaluation process	2 stages

SPECIFIC CHALLENGE

The pharmaceutical industry is facing considerable challenges as shown by the attrition rates for new medicine developments that have significantly increased across all Research & Development (R&D) phases since the early nineties of the previous century. The regulatory environment is lagging behind rapidly evolving science; conventional R&D models are no longer financially viable and have become a major hurdle to efficient drug development; general response rates to modern medicines are not satisfactory. A more flexible pathway within the current pharmaceutical legislation and reimbursement framework would not only accelerate access of crucial therapies to patients in need but would also increase the probability of success, as therapies would be oriented towards those deemed most likely to respond. Medicinal therapy is rapidly moving towards a personalised medicine paradigm, targeting smaller groups, better defined and better responding groups of patients with the ultimate goal to offer more efficacious and safer treatments. The cost of development for industry and for healthcare providers could be significantly reduced with such an approach. There are already initiatives to explore new regulatory pathways, including the New Drug Development Paradigms (NEWDIGS) initiative at Massachusetts Institute of Technology (MIT)⁶⁴, the FDA's Breakthrough Program⁶⁵, the UK's Early Access to Medicines Scheme (EAMS)⁶⁶ and more recently the EMA Adaptive Licensing Pilot project⁶⁷. These initiatives are encompassed under the concept of Medicines Adaptive Pathways to Patients (MAPPs). MAPPs refers to a flexible development and access pathway within the current regulatory framework that maximizes the positive impact of new medicines on public health by balancing timely access for patients with the need to provide evolving information on benefits and risks. It requires the early marketing authorisation of a product focused on a well-defined and targeted population identified by predictive preclinical and clinical evidence as well as various sources of real world evidence. It implies a clear safety and efficacy profile and may integrate a number of elements such as adaptive clinical trial design, patient centric benefit/risk assessments and the continuous evaluation of a therapy as new evidence (including real world evidence) becomes available. MAPPs, therefore, relate to the entire life cycle of a medicine from development, through licensing to patient access (pricing/reimbursement and healthcare delivery).

Although MAPPs is already discussed in many public forums, a pre-requisite for the success of MAPPs implementation lies in full and common understanding of its value, not just for industry but across the entire innovation life cycle: for regulators, Health Technology Assessment (HTAs) bodies, payers, governments, clinicians and, most importantly, patients.

The EMA's pilot project is testing the concept of adaptive licensing with real assets, in order to gather sufficient knowledge and experience, address a range of technical and scientific questions and refine how the adaptive licensing pathway should be designed for different types of products and indications. At the European Commission, DG Health & Food Safety has started a reflection process with the Member States on legislative and general policy aspects.

⁶⁴ <http://cbi.mit.edu/research-overview/newdigshomepage/>

⁶⁵ <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdact/significantamendmentstothefdcact/fdasia/ucm341027.htm>

⁶⁶ <http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>

⁶⁷ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002046.jsp&mid=WC0b01ac058004d5c1

As compared to adaptive licensing, MAPPs go beyond since encompassing the entire life cycle of a medicine from development, through licensing to patient access (pricing/reimbursement and healthcare delivery). To support MAPPs implementation, new enabling methodologies and tools may need to be developed and tested through research projects. Coordination and pragmatic integration is needed to define a new approach to R&D and patient access, as well as its applicability within the current legislative framework and its viability for all stakeholders.

Support is therefore required to bring together, under a neutral collaborative framework, relevant stakeholders from the public and private sectors to foster discussion and coordinate scientific activities under IMI2 to progress innovative, pragmatic and viable solutions required to implement MAPPs within the current pharmaceutical legislation. Therefore this coordination and support action (CSA) should be operational promptly to coordinate effectively the MAPPs activities within IMI2.

SCOPE

The overall scope of this CSA is to establish an enabling platform with relevant stakeholders for the coordination of MAPPs related activities within IMI2 and engaging a dialogue with relevant stakeholders. More specifically, the CSA will provide a forum that will enable:

- **gap analysis:** identify scientific challenges and opportunities for the application of MAPPs, taking account of tools, methodologies and infrastructures developed in IMI projects and other initiatives including any learnings of the EMA Adaptive Licensing Pilot project;
- **informing research activities:** facilitate the inclusion of MAPPs enablers (tools and methodologies) in new IMI2 research and innovation actions based on the gap analysis;
- **knowledge management:** horizon scanning on non IMI activities relevant to MAPPs to create a comprehensive repository of knowledge and opportunities for coordination.

Activities such as experts meetings, engagement with on-going and future IMI projects and relevant groups involved in IMI projects' definition (e.g. IMI Strategic Governing Groups, EFPIA Research Directors Group, IMI2 bodies) and dissemination/communication of conclusions and recommendations, will contribute to align understanding of impact of MAPPs versus current paradigm and to share learnings between all stakeholders.

EXPECTED IMPACT

The expected impact would be a comprehensive scientific research plan for the development and exploitation of tools, methodologies, infrastructures to help informing the whole product life-cycle and provide the science-based evidence to enable early patient access to innovative prevention and treatment options.

POTENTIAL SYNERGIES

The proposal should build on achievements and learnings from relevant IMI projects and the results from the IMI 'Think Tank' (IMiPACT) initiative. It should aim to create synergies and complementarities with relevant projects, in particular IMI projects such as Get Real and H2020 related projects. The proposal should also consider other initiatives both at EU level (e.g SEED, EMA adaptive licensing pilot) as well as globally (e.g NEWDIGS).

INDUSTRY CONSORTIUM

AstraZeneca (lead), BMS (co-lead), Amgen, Astellas, Bayer, Boehringer-Ingelheim, Eli Lilly, GSK/GSK vaccines, Ipsen, Janssen, Lundbeck, Merck KGaA, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi R&D/Sanofi Pasteur, UCB, Lysogene and EFPIA office.

Industry will provide expertise in regulatory, HTA/pricing and reimbursement, R&D, clinical development, clinical trials, benefit/risk assessment, legal and IP, medical and health affairs and communication. The industry consortium will contribute to:

- perform the analysis of IMI projects outputs, conceptual work around translation of these outputs into regulatory and medical outcomes;
- establish liaison with non IMI initiatives, coordination with various industry fora and across geographic areas, and liaison with other industry sectors;
- interact with on-going and future IMI projects and relevant groups involved in IMI projects' definition (e.g. IMI Strategic Governing Groups, EFPIA Research Directors Group)
- monitor non IMI activities relevant to MAPPs
- prepare materials for internal and external communication and dissemination of recommendations and conclusions of the forum.

The industry consortium will also provide their expertise in the conduct and follow up of management tasks to support to the platform (including any IT system to help the work of the platform and the communication between partners) as well as support to the organisation of meetings/workshops/teleconferences.

APPLICANT CONSORTIUM

The Applicant Consortium is expected to address the objectives and make key contributions in synergy with the industry consortium. This may require to mobilise: Knowledge and expertise in medicinal products' life cycle; Sound understanding of the R&D pathways and their challenges; Ability to develop outreach and communication strategies on the role and challenges of MAPPs to the stakeholders and public at large; Proven expertise for managing and coordinating major projects of this complexity and scale.

The Applicant Consortium is expected to be multidisciplinary and to enable effective collaboration between key stakeholders (e.g regulatory agencies, HTA, payers, academia, hospitals, SMEs, and patient organizations).

The size of the consortia shall be carefully considered by the applicants and limited to secure the operational efficiency of the CSA.

INDICATIVE DURATION

The indicative duration of the coordination and support action is 30 months.

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, if so foreseen in the applicable annual work plan, may publish at a later stage another call for proposals restricted to the action already selected under this call in order to allow continuation of the existing enabling platform and to enhance its results and achievements by extending its duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit. The detailed scope of the call will be described in the relevant annual work plan.

INDICATIVE BUDGET

The indicative EFPIA in-kind contribution will be EUR 1 130 000.

The indicative IMI2 JU contribution will be a maximum of EUR 1 130 000.

SUGGESTED ARCHITECTURE OF THE FULL PROPOSAL

The Applicants are expected to suggest architecture for the full proposal to set up the platform that addresses the scope and the expected impact of this CSA, as well as incorporating and complementing the industry consortium contribution.

The consortium will be expected to keep informed the European Commission of the activities of the CSA, in particular the responsible unit of DG Health & Food Safety.

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

- 1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see [“Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020”](#) and [“Guidelines on Data Management in Horizon 2020 ”](#)). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
- 2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

CONDITIONS FOR THIS CALL

Applicants intending to submit a short proposal in response to the IMI2 Call 4 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier:	H2020-JTI-IMI2-2015-04-two-stage
Type of action:	Coordination and support action
Publication Date:	12 December 2014
Stage 1 Submission start date:	12 December 2014
Stage 1 Submission deadline:	11 February 2015 – 17:00:00 Brussels time
Indicative Budget:	From EFPIA companies: EUR 1 130 000 From the IMI2 JU: EUR 1 130 000.

CALL TOPICS

IMI2-2015-04-01	<p>The indicative contribution from EFPIA companies is EUR 1 130 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 1 130 000</p>	<p>Coordination and support action.</p> <p>Two stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
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INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (first stage)	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
IMI2-2015-04-01	Maximum 3 months from the date of submission to the first stage.	Maximum 2 months from the date of submission to the second stage.	Maximum 2 months from the date of informing the applicants following the second stage evaluation.

CONSORTIUM AGREEMENTS

In line with the Rules for Participation and Dissemination applicable to IMI2 actions⁶⁸ and the IMI2 model grant agreement, participants in Coordination and Support Actions are not required to conclude a consortium agreement.

⁶⁸ Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.