



Innovative Medicines Initiative

9th Call for Proposals 2013

Innovative Medicines Initiative

Version 2

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GENERAL PRINCIPLES

INTRODUCTION

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

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

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

The IMI 9th Call 2013 for proposals includes topics covering the following key research priorities:

- Knowledge Management (correlated to the area of interest: Knowledge, Patient, Development)
- Coping with Regulatory and Legal Hurdles (correlated to the area of interest: Development)
- Beyond Drug Discovery: Drug Development and the Regulatory Framework (correlated to the area of interest: Development)
- Infectious diseases (correlated to the area of interest: Disease Drug Efficacy)

The 9th Call topics are:

- **WEBAE – Leveraging Emerging Technologies for Pharmacovigilance**
- **Developing Innovative Therapeutic Interventions Against Physical Frailty and Sarcopenia (ITI-PF&S) as a Prototype Geriatric Indication**

And, under the theme: *Combating Antimicrobial Resistance: NewDrugs4BadBugs (ND4BB)*

- **ND4BB TOPIC 4: Driving re-investment in R&D and Responsible Use of Antibiotics**
- **ND4BB TOPIC 5: Clinical development of antibacterial agents for Gram-negative antibiotic resistant pathogens**

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

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

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

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

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

Before submitting an expression of interest, the various Call Documents, such as *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals, Rules for Participation, the IMI Intellectual Property Policy, etc.*, shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the 9th Call 2013 launch.

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

DURATION OF THE PROJECTS

The indicative duration of the project is between 3 years and 5 years.

FUNDING OF THE PROJECTS

For this Call, the total available financial contribution from the IMI JU to participants eligible for funding will be maximum EUR 63 120 000.

The indicative EFPIA 'in kind'² contribution will be EUR 72 250 000.

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

SYNOPSIS OF CALL AND EVALUATION PROCESS

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

The Topics included in the 9th Call are associated with a group of pharmaceutical companies that are members of EFPIA (hereafter called the 'EFPIA Consortia') and which are committed to collaborate with public and private organisations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions to support their activities within the research projects.

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

In preparing their EoIs, the Applicant Consortia should carefully read the Guidance Notes for Submission and Preparation of Expression of Interest published on the IMI website www.imi.europa.eu at the time of the 9th Call 2013 launch, in addition to the specific Applicant Consortium expectations/requirements outlined within the description of the individual topic.

The Applicant Consortium shall consider the research contribution that an EFPIA Consortium will make to a given project.

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

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

Each Applicant Consortium with the highest ranked EoI will be invited to develop a full project proposal together with the EFPIA Consortium.

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

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

For full details, applicants should refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest and Full Project Proposals* published on the IMI JU website www.imi.europa.eu at the time of the launch of the 9th Call.

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

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

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

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

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

IMI INTELLECTUAL PROPERTY POLICY

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

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

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

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

Applicant Consortia are invited to read carefully the Guidance Note on the IMI IP Policy (www.imi.europa.eu), whose purpose is to explore ways to handle related issues and pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

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

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

The Full Consortium shall ensure that the negotiation of the Project Agreement is completed no later than the finalisation of the full project Description of Work and prior to signing the Grant Agreement.

1. WEBAE - LEVERAGING EMERGING TECHNOLOGY FOR PHARMACOVIGILANCE

SUMMARY

The last 5 years have seen a number of highly disruptive and interrelated changes in the consumer technology market:

- Digital media and Web 2.0 platforms such as Facebook and Twitter have changed the way people connect and communicate over the Internet.
- Rapid adoption of computing categories such as smartphones & tablets is changing the way that people use the Internet. This has transformed the usage pattern from a static to a highly interactive experience.
- The “appification” of the Internet as people use new software delivery channels for digital media platforms to deliver elements of computing functionality in small packaged chunks or “Apps.”

Application developers have used these technology changes to build highly sophisticated platforms that collect data from across the internet which is then analysed & mined, for example, to build reliable maps without cartographers or to predict winners of reality television shows, and to model and understand their customers better.

The WEBAE project (Web Adverse Events) aims to build on these trends and form a specialist public private consortium that undertakes research into the appropriate policy and technology solutions that enable the leverage of such web based media mining and crowd-sourcing technologies in pharmacovigilance to strengthen the protection of public health.

BACKGROUND

Patient Reporting of Adverse Drug Reactions (ADRs)

The new pharmacovigilance legislation (Regulation (EU) No 1235/2010, Directive 2010/81/EU and Implementing Regulation (EU) No 520/2012) proposes a number of changes to strengthen the way the safety of medicines for human use is monitored in the European Union. The detailed text within the [Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products](#) promotes and facilitates adverse drug reaction (ADR) reporting by patients, consumers and healthcare professionals. An essential part of this will be the enabling of direct reporting to Marketing Authorisation Holders and to the Competent Authorities through development and provision of standard web-based forms. The European Medicines Agency has a responsibility to develop, in cooperation with the Member States, web-based reporting forms for adverse reaction reporting by patients and healthcare professionals. Furthermore, patients and healthcare professionals can choose to report to the marketing authorisation holder, whereby reporting should ideally be facilitated by modern technologies as well.

Patient-based reporting of adverse drug reactions is governed at a European level by Directive 2010/84/EU. Currently this requirement is met through different ways of reporting at national level, from where the adverse reaction reports are forwarded to the European pharmacovigilance database called EudraVigilance (<http://eudravigilance.ema.europa.eu/>). Due to the fact that ADRs do not typically

happen in the presence of an ADR reporting form, and where they do, there is a perceived inconvenience and lack of awareness of the reporting process, many ADRs go unreported. There are many other reasons for under-reporting of ADRs, including misunderstandings, lack of awareness and complexity of paper-based forms.³

The possibility of using an electronic reporting platform was not included in the business requirements when EudraVigilance was first designed, especially since reporting by patients was only recently introduced through the new pharmacovigilance legislation. Hence, the advent of applications that run on smart phones and tablet devices or even within Facebook or other social media opens up the possibility of patient-based reporting directly from simple downloadable applications. ADR reporting by healthcare professionals could also be facilitated using virtually identical applications and software.

European market research indicates that 75 million users accessed the internet for pharmaceutical information in 2010, with Wikipedia being the most visited health resource.⁴ There is an explicit and largely under-met demand for evidence based, balanced (i.e. unbiased), up-to-date information on pharmaceutical medicines. Therefore, in addition to reporting ADRs, the same app could serve as a platform to disseminate accurate and timely information to patients, clinicians, and caregivers, and to provide access to up-to-date information on medicinal products authorised in the EU.

This two-way flow of information creates a conduit for broad engagement in pharmacovigilance and pharmacoepidemiology. Experience has shown that consumers will submit data using medically oriented apps when they derive a tangible benefit to themselves. For example, HealthMap (<http://healthmap.org/about/>), which includes *Outbreaks Near Me* (<http://www.healthmap.org/outbreaksnearme/>) and *Patients Like Me* (<http://www.patientslikeme.com/>).

The time is right to expand the capability beyond classical reporting platforms into mobile platforms. A well-designed system and process may streamline reporting, facilitate data capture and permit acknowledgment directly to the reporter within seconds. A well-designed app will simultaneously serve as an information resource for both healthcare professionals and, especially, patients and carers. By design, the capability could be expanded to include mapping of reporting by country of incidence with the creation of an interface for data display and exploration, as well as more rigorous pharmacoepidemiologic research, and rapid notification on updates to medicinal product information or alerts in case of safety or quality issues.

Adverse Drug Reports from the Internet

In contrast to the structured web-based standardised reporting forms required by the new pharmacovigilance legislation, the recent growth of Social Media platforms such as *Facebook*, *Twitter* and the many specialist sites and blogs such as *Patients Like Me* has given rise to many people sharing their medical experiences publically on the Internet. Such data sharing, if properly harnessed, could provide an extremely valuable source of medical insight especially in the area of post-marketing surveillance for adverse drug reactions and pharmacovigilance. The technical and, more importantly, the policy

³ Inman WH: Attitudes to adverse drug-reaction reporting. *Br J Clin Pharmacol* 1996; 41:433-435; Lopez-Gonzalez E, Herdeiro MT, Figueiras A: Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2009; 32:19-31; Hugman B. The fatal love of forms. *Drug Saf* 2011; 34 (8): 705-707.

⁴ Manhattan Research 2011. *Cybercitizen Health Europe v10.0*. Manhattan Research 2009. *Navigating the European eHealth Landscape*.

challenges social media poses for pharmacovigilance have recently been discussed in an editorial in the journal *Drug Safety*.⁵

Good Vigilance Practice Module VI⁶ which became effective on 2 July 2012 provides detailed guidance in support of the new pharmacovigilance legislation. GVP includes the following recommendations for dealing with information on suspected adverse reactions from the internet or digital media (Section VI.B.1.1.4.):

“Marketing authorisation holders should regularly screen internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorisation holder. The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities within the appropriate reporting timeframe based on the date the information was posted on the internet site/digital medium. Marketing authorisation holders may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions (see VI.C.2.2.1).

If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting. Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied (see VI.B.7).

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country”.

The final guidance still leaves some uncertainty about the scope and scale of monitoring of non-company sponsored digital media. A further complication is that there are two technically challenging requirements, which are amongst the four required elements referenced in the FDA draft guidance for adverse event reporting (and in GVP Module VI) and are the key principles of a valid safety report as defined in the international scientific community (ICH E2B(R2), ISO ICSR, HL7 patient safety):

1. Identifiable Patient
2. Identifiable Reporter
3. Suspect Drug
4. Adverse Event/reaction

⁵ I. R. Edwards and M. Lindquist: Social Media and Networks in Pharmacovigilance. Boon or Bane? *Drug Saf* 2011; 34 (4): 267-271

⁶ Guideline on good pharmacovigilance practices: Module VI - Management and reporting of adverse reactions to medicinal products. Accessed @ http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/06/news_detail_001546.jsp&mid=WC0b01ac058004d5c1#.

In addition GVP module VI (Section VI.B.2, page 12) states:

“When collecting reports of suspected adverse reactions via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient (see VI.B.1.1.4).”

Clearly, this guidance with respect to identifiability of reporter and patient raises many technical challenges which are constantly evolving. Notwithstanding these challenges, the unambiguous identification of medicinal products and adverse reactions is not considered a technically solved problem either at the level of reporting by patients, consumers and healthcare professionals.

There are a number of additional technical challenges to be overcome including:

- Identification of duplicate safety information with respect to data originating from digital media i.e. the same ADR may be reported by the same or a different user on multiple digital media platforms, requiring robust methods for the evaluation of data provenance.⁷
- There is challenge of multiple languages and how data collected in different languages maps to standard ADR.
- Additionally data privacy and personal data protection issues surrounding such mining and discovery also need special attention.
- Data curation and cleaning would also be required to mitigate the risk of spreading rumours or a malicious actor gaming the system with false information.⁸ For example, rather than simply supplying the end-users with reports, many projects in eHealth make use of crowds for evaluating the quality of information as well

PROBLEM STATEMENT

The new GVP module VI re-affirms requirements for pharmaceutical companies to screen digital media under their control and to report as soon as they become aware of potential adverse reactions from non-company sponsored digital media.

There are clear advantages in attempting to better capture spontaneous reports of adverse events and leverage the potential wealth of data emerging technology could provide. However there is still significant uncertainty and challenges in how to best proceed in the rapidly evolving and growing areas of social media and mobile computing such as: 1) understanding how policy can be advanced to include signals from social media, 2) having access to tools and methods that can capture spontaneous reports from social media or mobile apps and by a process of real time data mining provide emerging safety signals or 3) deal with the noisy nature of social media data. Credibility and provenance of self-generated reports are key issues. For example, there is concern that social media with no appropriate checks on provenance can open the avenue to unscrupulous attacks from “pseudo-reporters”.

⁷ Sai Moturu and Huan Liu. "Quantifying the Trustworthiness of Social Media Content", Journal of Distributed and Parallel Databases, Springer, Volume 29, January 4, 2011. DOI: 10.1007/s10619-010-7077-0. Geoffrey Barbier, and Huan Liu. Information Provenance in Social Media. SBP 2011: 276-283. Springer-Verlag Berlin, Heidelberg, ISBN: 978-3-642-19655-3

⁸ Freifeld CC, Chunara R, Mekar SR, Chan EH, Kass-Hout T, et al. (2010) Participatory Epidemiology: Use of Mobile Phones for Community-Based Health Reporting. PLoS Med 7(12): e1000376. doi:10.1371/journal.pmed.1000376

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The challenge of developing a mobile ADR reporting platform, developing pharmacovigilance and pharmacoepidemiology surveillance software, and establishing a technical and policy framework for scanning and mining web and social media sources is great. To ensure success in these objectives, contributions from a large number of partners would be required.

By developing and implementing the applications outlined in this call there would be benefits to patients, healthcare professionals, regulatory agencies and the pharmaceutical industry. It would contribute to strengthen public health by allowing early identification of potential safety or quality issues and provide greater transparency of data at both national and regional level.

Beyond emerging ADRs there could be gained other medical insights from the wealth of user generated health content such as:

- Recognizing/tracking emerging disease/public health threats (epidemiology)
- Emerging unknown side (beneficial/non-beneficial) effect of a drug or emerging off-label/alternative use of a drug (pharmacoepidemiology)
- Lack of effectiveness or comparative efficacy of a drug (benefit assessment)
- Medication errors (risk monitoring)
- Potential interactions (e.g. drug-drug interactions, drug-food interactions)
- Monitoring of abuse and misuse to medicinal products and potential adverse reactions originating from occupational exposure
- Product quality complaints (monitoring of defective medicines)
- Reports of counterfeiting
- Opinion/sentiment trends of a drug/company (market research)
- Inaccurate and inappropriate statements and claims about drugs and devices

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Relevant web3.0 projects: Open PHACTS, DebugIT, Khresmoi, EHR4CR, Wiki/DBPedia WP4 of the PROTECT project is relevant to the proposed Call Topic.

Other projects that are deemed relevant to this call topic are: Signal detection (data mining): EU-ADR, OMOP (US); Signal testing: FP-7/ECDC funded: SOS, ARITMO, VAESCO, SAFEGUARD, GRIP and global systems for collaborative studies (WHO, GRIP, VACCINE.GRID).

OVERALL OBJECTIVES

The primary goal of this partnership is to develop a technical and policy framework for mining publicly available (and licensed) web and social media content outside the control or sponsorship of pharmaceutical and biotechnology companies (i.e. independent web media) for emerging ADRs.

The scientific aim of the consortium is to develop methodologies and adopt data mining algorithms applicable to social media content (forums, blogs, tweets, public posting, etc.) in order to find emerging, self-reported medical insights such as adverse events associated with medicines and medical devices. Special emphasis will be put on the multi-lingual nature of the content.

A further objective would be to provide a working set of applications to enable direct reporting of suspected ADRs to national competent authorities via the established, secure EudraVigilance data-processing network. The applications would be made available free

of charge to all users of tablets, smartphones, and the mobile web, for all major platforms as well as social networking sites like Facebook.

The evolution of the scientific and technical solutions will also inform the necessary evolution of the regulatory guidance and ultimately the practice of the pharmaceutical industry with respect to ADRs discovered in digital media.

EXPECTED KEY DELIVERABLES

- Establishment of regulatory framework for social media mining for ADRs
- Increase public access to enable direct reporting via the secure EudraVigilance data-processing network to the NCA
- Provide direct acknowledgement to the source on receipt of data
- Engage patients in awareness and reporting of safety concerns
- Strengthen the monitoring of potential ADRs in the paediatric as well as the elderly population, the latter specifically affected by poly-pharmacy
- Further engage healthcare professionals (HCPs) in reporting suspected ADRs
- Integration of apps with existing EudraVigilance workflows & tools and the medicinal product identification (Article 57(2), 2 of the new pharmacovigilance legislation) as well as with existing global safety databases used by MAHs
- Develop quality metrics for evaluating ADRs from social or crowd-sourced platforms taking into account the multilingual aspects of reporting.
- Creation of a sense of community around pharmacovigilance
- Improved methods for mining social media for pharmacovigilance and pharmacoepidemiological data
- Enable hypothesis generation for researchers
- Provide a platform for monitoring the effects of risk minimization
 - Provision of safety messages and alerts to patients and health-care professionals (including video and interactive features)
 - Registration/certification for prescribers
 - Enhanced surveillance
 - Potential for enhanced monitoring

EFPIA PARTICIPANTS

Novartis (coordinator), Janssen (deputy-coordinator), AstraZeneca, Sanofi, UCB.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of the project is 3 years. However the aim is also to develop a mobile platform that will endure beyond the life of this particular IMI call.

INDICATIVE BUDGET

Indicative total in kind contribution from the EFPIA companies is EUR 2.29 million and the indicative IMI JU contribution will be up to EUR 2.27 million

APPLICANT CONSORTIUM

The applicant consortium is expected to consist of biotechnology companies, Small & Medium Enterprises (SMEs), regulators {EMA and the national competent authorities (NCAs) in the European Economic Area (EEA)}, policy makers, government agencies, payers, academics, and non-profit organizations (e.g.: patient, disease advocacy and privacy groups).

The proposed public-private partnership model with robust academic and SME involvement would ensure that: (i) a robust mobile reporting platform is developed, (ii) the optimal set of data sources will be discovered and validated (coverage), (iii) data mining will be real-time so that early signs of potential safety signals, risks and unexpected benefits can be efficiently found and reported, and (iv) the credibility and provenance of self-generated reports can be ascertained. The consortium partners should have experience developing commercial-grade software for public health, using principles of agile development (rapid iterations and incremental improvements throughout the product lifecycle) and user-centred design (formally soliciting feedback from end users at each stage of the design process). Special emphasis should be put on the multi-lingual nature of the content.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

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

The suggested architecture below for the full project is one proposed approach; different innovative project designs are welcome, if properly justified.

Work Package 1: Policy Advancement

Further change/development of the regulatory framework is unlikely in the coming years however new technologies for pharmacovigilance can be used within the existing regulatory framework.

One of the critical deliverables to this project is to provide practical guidelines for market authorisation holders of how such social media surveillance can be used to supplement traditional methods of reporting.

Development of guidance with respect to identification of reliable signals from social media mining to ensure a balance between the numbers of signals and the follow-up activities. Definition of the follow-up activities with respect to reporting into Eudravigilance and assessment of the signals in the Electronic Health Record systems filtering out 'confirmed'.

Another policy deliverable will be based on the need to be able to track the provenance of the data with respect to identifiability of reporter and patient (which are key principles of a valid safety report as defined in the international scientific community (ICH E2B(R2), ISO ICSR, HL7 patient safety: Identifiable Patient, Identifiable Reporter, Suspect Drug, Adverse Event/reaction).

Work Package 2: Technical Advancement

The technical work packages of this project are required to provide several deliverables that together provide a reference platform for social media surveillance. These deliverables include

1. An open platform for gathering content from different web sources in real time and organizing such content in a format suitable to analysis
2. A series of algorithms that are coupled to the data gathering platform and enable the extraction and identification of ADRs

3. A series of algorithms and tools that are coupled to the data gathering platform and enable the provenance of data to be established across multiple social media source.

Work Package 3: Mobile platform development

The mobile workpackage of this project is to complement the social media based platform and provide a mobile application for patients that offers the following features:

1. Free to use EudraVigilance Patient Reporting app across multiple platforms
2. Free to use EudraVigilance Healthcare Professional Reporting app.
 - o Both apps (or versions of one app) would be based on the XEVMPD in the context of the implementation of Article 57(2), 2 of the new pharmacovigilance legislation
 - o Both apps would allow storage of reports
 - o The patient app would enable storage of personal list of meds
 - o The HCP app would enable storage of patient specific data with main focus on ADRs
3. Geographic interactive display illustrating patterns of ADR reporting in real time.
4. Interface to the EudraVigilance system enabling creation of ICSRs directly from electronic health records.
5. Potential for two-way communication (data interchange) with reporters, including:
 - a. Direct follow-up, using targeted follow-up questions;
 - b. Targeted transmission of important safety messages and urgent safety restrictions from EMA and NCAs to HCPs and non-HCPs alike.
6. Protection of personal data in mobile devices using open platforms.
7. Provision of reliable information to patients / end users about medicinal products, e.g. a link to European public assessment reports (EPAR) and the public summary of the EMA risk management plan (RMP)⁹
8. Online social marketing campaign for publicizing and adopting the apps.

The mobile platform development is expected to be done in multiple stages:

Year One of the platform development project will include two or three pilot countries, and be devoted to:

1. Understanding the needs of end users (including HCPs and non-HCPs)
2. Technical development of the apps, databases and data visualization interface
3. Formalization of data transfer to EudraVigilance, NCAs and to MAH systems
4. Establish data quality management and security processes.

Year Two will include:

1. Expansion to other countries including language support,
2. Social marketing efforts,
3. Development of new features and bug fixes based on user reports, and
4. Collaboration with researchers to analyse and validate the data.

Year Three will include

1. Further expansion across the EEA and
2. Continued iterative developments of the apps.

⁹http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134650.pdf

Work package 4: Research Study

This work package should provide a motivating research project to evaluate the value of the new technologies to national competent authorities in terms of detection of new safety issues with regards to the type of adverse reactions that would be reported through such systems and the characteristics of reporters (e.g. age); the impact of new technology on resources of regulatory authorities (e.g. need for coding analysis and reporting adverse events) should also be assessed.

Work Package 5: Project Management

It also recommended that a work-package for Project Management and dissemination be included. This work package should address:

- the implementation of the management of the project, encouraging regular meetings and interaction between sub-groups and teams, to coordinate the work effort;
- manage collaboration with external stakeholders and synergies with other related projects
- the communication and dissemination strategy of the project.
- Sustainability. It is also important to recognise that some project deliverables are expected to endure beyond the timescale of the project, and particular emphasis should be put on ensuring the sustainability of these deliverables.

GLOSSARY

ADR	Adverse Drug Reaction
AE	Adverse Event
eHealth (EHRs)	Electronic Health (Records)
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
FDA	Food and Drug Administration
GVP	Good Vigilance Practice
HCP(s)	Health Care Professional(s)
HL7	Health Level 7 Standards
ICSRs	Individual Case Safety Reports
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E2B (R2)	Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of individual case safety reports
IMI	Innovative Medicines Initiative
ISO	International Organization for Standardization
MAH	Marketing Authorisation Holder
NCA	National Competent Authority(ies)
RMP	Risk Management Plan
WHO	World Health Organisation
XEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

2. DEVELOPING INNOVATIVE THERAPEUTIC INTERVENTIONS AGAINST PHYSICAL FRAILITY AND SARCOPENIA (ITI-PF&S) AS A PROTOTYPE GERIATRIC INDICATION

OUTLINES AND KEY OBJECTIVES

Qualification of biomarkers and adapted clinical methodologies for the regulatory development of innovative interventions against Physical Frailty and Sarcopenia (PF&S) in at-risk Older Persons, to prevent or delay mobility disability and its consequences, is the overarching objective of this IMI project, including:

1. Development of an operational definition of **at-risk subpopulations** with undisputable therapeutic need;
2. **Qualification of biomarkers** of muscle **anabolism and catabolism** and indicators of **muscle function** in at-risk sub-populations and their correlation with major outcomes;
3. Development of advanced therapeutic approaches in preclinical settings
4. **Implementation of innovative clinical development methodologies** for testing integrated interventions for the prevention of PF&S and consequent mobility disability;
5. **Scientific and Regulatory Consensus** of these three elements.

BACKGROUND

The number of Europeans aged 65+ will almost double over the next 50 years, from 85 million in 2008 to 151 million in 2060. The increased demand for healthcare products and services resulting from this demographic transition represents a challenge for public authorities, policy makers, healthcare providers and payers. The current healthcare systems and traditional medical paradigms have been built around the treatment of acute disorders in a young population, and are not efficient for the management of chronic conditions and the effects of senescence associated with aging. Optimal use of resources and rising costs will remain an issue, without the development of new models of care for this growing segment of the general population.

The existence of **regulatory gaps** hampering innovative development of geriatric medicines has been acknowledged in the frame of the Active & Healthy Aging pilot project launched by the European Commission in 2011.

In 2011 The European Medicines Agency published its geriatric medicines strategy, which states that the Agency will endeavour to ensure that the needs of the ageing population in the EU are taken into account in the development and evaluation of new medicines. In 2012, the EMA held its first large workshop with stakeholders, to further refine its current appraisal of existing gaps regarding general clinical development and post surveillance objectives.

This project will offer the opportunity to open a platform of discussion focused on the important issue of specific geriatric indications and the development of innovative strategies to fulfil the unmet therapeutic needs in this growing segment of the general population.

Physical frailty is a geriatric physiopathologic condition of decreased reserve resulting from cumulative declines across multiple physiologic systems. Sarcopenia (the loss of muscular mass and muscular strength) observed in older persons is believed to be

central to the development of frailty. Physical Frailty and sarcopenia (PF&S) represent an unmet therapeutic need.

PF&S, with its frequent complications, represents as well a powerful model of a geriatric condition with measurable impact on healthcare expenses PF&S often progresses to mobility disability, a common cause of increased morbidity (including falls and fractures, often complicated by delayed healing and pseudoarthrosis), loss of autonomy, frequent/inappropriate healthcare use, nursing home admission and reduced quality of life. The condition, although increasingly recognized, remains under-diagnosed or neglected in standard general practice, due to the therapeutic nihilism resulting from the absence of proven therapeutic options for the clinician.

Interestingly some key components of physical frailty like the loss of muscular mass and function can be reversed or substantially slowed via integrated multi-disciplinary interventions including physical activity, improved nutrition and advanced therapies with new technologies.

Reversing or slowing sarcopenia in the course of physical frailty could decrease the risk of mobility disability and other complications and thereby generate important cost savings by preventing outcomes such as injurious falls, hip fractures, and prolonged hospitalization.

Interestingly, the prospect of treating physical frailty and its key component (sarcopenia) offers the pharmaceutical industry and all stakeholders a great opportunity to develop innovative clinical methodologies.

Investigational products currently under development (e.g. to counteract muscle mass loss) are facing numerous regulatory obstacles and bottlenecks, due to an unprecedented and uncertain regulatory frame in terms of indications, clinical data requirements and adapted methodology (e.g. regulatory acceptance of functional endpoints vs. outcomes).

Moreover, EFPIA member companies are currently developing a number of biomarkers to estimate muscle mass, as well as to examine the response of muscle proteins to anabolic stimuli or damage.

Currently there are no direct and clinically facile methods for the quantification of muscle mass. Existing methods are indirect, lack precision, and often rely on expensive equipment (DEXA, MRI, CT) that only provides limited (indirect) data on whole body muscle mass. Dual energy X-ray absorptiometry (DEXA) has emerged as a potential precise measure of lean mass, however, it also serves as only an indirect measurement of total-body skeletal muscle mass and its clinical use for determination of changes in muscle mass may be very limited due to instrumentation availability, particularly in field studies, and cost.

As an example, one EFPIA member company is developing non-invasive, and accurate methods for determination of skeletal muscle mass in humans enabling physicians to measure muscle mass in their patients as well as the rate of change in muscle mass over time in response to disease or therapeutic interventions.

This method takes advantage of a number of unique aspects of creatine and creatinine biology. While muscle contains about 98% of the body creatine pool, it has no capacity to synthesize creatine. Oral creatine is digested, absorbed, and transported against a concentration gradient into muscle. We have labelled creatine with a stable, non-radioactive label – deuterium (2H); because creatine is converted to creatinine excreted in urine, enrichment of urine creatinine with 2H provides a measure of creatine pool size and, thus, skeletal muscle mass. In growing rats, we demonstrated that an oral dose of D3-creatine is 100% bio-available and the enrichment of 2H in urine creatinine provided an estimate of muscle mass that was strongly correlated with independent estimates of lean mass.

Data from the first time in human studies have demonstrated that results using this measure correlate well with the muscle mass estimates by MRI, and provided a better estimate than that achieved by DEXA. Clinically, this method involves having a study participant or a patient take a 30mg capsule of deuterium-labelled creatine, followed in 3 to 5 days by a single, spot urine collection. This simple method will allow investigators and clinicians to measure muscle mass directly, with minimal participant burden and without exposure to radiation. Validation studies in several populations of older adults, including at risk, community-dwelling frail older person are planned.

In this regard, EFPIA member companies will make available their data, expertise and functional capacity with the objective to integrate the use of muscular metabolism biomarkers in the context of physical frailty and sarcopenia.

For all these reasons, rather than conducting many dispersed clinical initiatives, it is paramount to generate good quality longitudinal data in this population. In this context it is important for Academia and Regulators to reach agreement regarding a reference clinical trial methodology, including acceptable standard measurements and cut-points, applicable to the European population but comparable to similar undertakings in other regions, specifically in the US.

The potential benefits of establishing a reference regulatory frame for PF&S are several, including:

1. Avoidance of duplication of efforts in early phases and the acceleration of late phases of clinical development of innovative medicines/integrated solutions;
2. Speeding-up access of older patients to innovative treatments that postpone physical disability and related morbidity and that ameliorate the recovery from complications
3. Reduction of societal health care costs through the resulting improved patient outcomes in this growing demographic segment of the general population.

PROBLEM STATEMENT

The innovative pharmaceutical industry is aware of the demographic challenges and of the specific unmet therapeutic needs of older patients. The current gaps and challenges that have been identified as potential obstacles in terms of adequate clinical development require a multi-stakeholder approach for adequate resolution.

There is **no current consensus regarding the operational definition of physical frailty and sarcopenia in older persons.**

There is also **insufficient definition of the target population(s)** for clinical development especially with respect to the identification of subgroups most likely to benefit from intervention.

A further regulatory obstacle is the unclear acceptance of **functional end-points**, hampering the design of confirmatory clinical trials. Furthermore, it will be essential to promote the **availability of validated biomarkers to advance a sound regulatory qualification pathway. Therefore the evaluation of the predictive value of functional endpoints and biomarkers** versus standard long-term outcomes will be a key deliverable of the project.

Finally, a **Health Technology Assessment and the construction of a pharmacoeconomic model** comparing standard practice options versus integrated interventions in order to demonstrate their cost-effectiveness and overall public health impact, will also be considered.

NEED FOR PUBLIC-PRIVATE PARTNERSHIP

In order to address these key objectives it is necessary to establish a multi-stakeholder platform of discussion and to create the framework for generating good quality longitudinal data in the correct population(s). Before launching clinical initiatives in the field it is important to reach agreement with the stakeholders regarding an efficient reference methodology for confirmatory clinical trials, including standards of measurements and cut-point values.

This requires a platform that will enable Academia, regulators, pharmaceutical industry, and industry developing new medical devices, health technology assessors and patients' representatives to discuss, document and agree to the methodological and regulatory tools for moving forward.

This also requires the use of modern technologies to ease data collection, clinical data monitoring, and safety surveillance operations by integrating sensing devices and capture predefined signals, e.g. fall detection. The participation in the Applicant Consortium of an Information and Communication Technologies (ICT) established SME with proven expertise in the field of geriatric applications and large database management seems appropriately required.

SPECIFIC APPROACH FOR ACCEPTING NON-EU CONTRIBUTION EFPIA IN-KIND CONTRIBUTION (SPECIAL CLAUSE 13B)

Partnerships were proposed in the Europe 2020 strategy with the aim of tackling global innovation barriers for major societal challenges. The pilot European Innovation Partnership on active and healthy ageing is the first of its kind and was initiated in recognition of the growing burden that the aging population is now placing on European Healthcare systems. Two priority action areas defined in the Healthy Aging Strategic Implementation plan are

- 1) "Personal health management, starting with a falls prevention initiative" Calling for a private-public action on the implementation of a fall prevention initiative combining innovative tools for screening (e.g. sarcopenia), monitoring, exercising, and maintaining balance functionality.
- 2) "Action for prevention and innovative therapeutic intervention of functional decline and frailty"

Although PF&S are clearly a major global societal challenge, and the strong research base exists in Europe, efforts to develop new medicines and advanced therapies with new technologies addressing this major societal challenge are currently extremely limited. Furthermore, the limited drug development efforts that do exist today largely reside in the US. This lack of investment in Physical PF&S by the private sector is largely driven by the lack of definition of the target population, lack of consensus with respect to clinical trial design and outcome measures together with the subsequent need of the regulatory and health technology assessment frameworks required to support the translation of innovative science to innovative and effective medicines. In order to encourage much needed engagement from the private sector, these current barriers to investment need to be addressed from a global perspective which can require close cooperation of leading scientists, drug and new device developers, the FDA and EMA. Europe is ideally positioned to create a leadership position building on expertise available in Europe but also taken into account US specific perspectives.

The current proposal provides the opportunity to remove these bottlenecks, enable solutions and therefore foster the appropriate significant investment to address this major societal need. Non-EU EFPIA in-kind contribution will provide an excellent vehicle

for collaboration with the US and fully support the ambition of Europe to become a global leader in this area and therefore non-EU EFPIA in-kind contributions have been accepted as eligible contributions (see "Rules for Participation in the IMI JU research projects" published on the IMI website www.imi.europa.eu).

The benefit to Europe of implementing Special Clause 13b

For the patient and society as a whole: The rapidly aging population is placing an unsustainable burden on healthcare systems in Europe indeed across the globe and requires joint and urgent action to be taken if sustainable healthcare solutions are to be secured. Removing the bottlenecks both in Europe as well as in the US currently preventing private investment in the field of PF&S will lead to increased recognition of PF&S, to better diagnosis, improved treatment options and management of the aging population. This will result in individuals having treatment options available to them to increase quality of life through improved physical activity as well as improved overall mental and social wellbeing. This will directly support the long-term sustainability and efficiency of health and social care systems in Europe as well as enhance the competitiveness of EU industry through an improved business environment providing the foundations for growth and expansion of new markets.

For public investigators and SMEs: Research into the Physical Frailty and Sarcopenia is strong within the European Research community, however investment from the Pharmaceutical industry is currently low primarily to lack of consensus regarding clinical definition of the condition and meaningful clinical outcome measures in Europe as well as in the US. The ability to utilise the non-EU in kind contribution in the current project will allow EU investigators to foster international partnerships with drug developers currently operating in the US. This will lead to the combination of expertise in the diagnosis and management of PF&S present in the public sector with the drug discovery and development expertise present in the private sector. This combined approach is required to remove the barriers to private investment much needed to develop preventative medicines in this field in Europe as well as in the US. It is also worth noting that all IMI JU funding will be directed to investigators and SMEs located in the EU, thus this PPP will bring significant funding to European investigators to support employment and growth.

For pharmaceutical and biotechnology companies developing new medicines: The opportunity to work with leading experts in the field, regulators, health technology agencies and healthcare providers to gain consensus both in Europe and the US on the definition of the target population, agreement on clinical trial design and functional endpoints and assessment of value to the healthcare system. This infrastructure will provide the necessary framework to drive new investment in medicines development.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

Synergies may be sought from other IMI initiatives; in particular those already focusing on the relevant methodologies, such as PROactive - project which develops patient reported outcome tools for COPD, as well as those on knowledge management, in particular ETRIKS.

Furthermore synergies will be sought with other European and non-European Initiatives in order to ensure complementarity and alignment of efforts. In particular the Foundation for the National Institutes of Health (FNIH, USA) Sarcopenia Working Group who has analysed existing data sets to assess behaviour of multiple potential definitions of sarcopenia. This information, based on both US and EU data sets, could provide a rich source of starting material for the proposed objectives of the current proposal.

OVERALL OBJECTIVES

Generate real life data in older persons in order to determine/qualify:

- Specific at-risk population(s), specific therapeutic/preventative targets and related regulatory appraisal;
- Economic savings in terms of public health costs;
- Adapted study methodologies, including biomarkers, functional endpoints, ICT based data capture paradigms and applied biostatistics;
- Adapted sustainable clinical development methodologies ;
- Pharmaco-economic modelling of the indication.

EXPECTED DELIVERABLES

- 1) Validate regulatory acceptance for a specific indication in a defined at-risk population;
- 2) Validate regulatory requirements for confirmatory clinical trials;
- 3) Regulatory views over measures of Physical Frailty:
 - Muscle Mass & body composition endpoints;
 - Functional Endpoints:
 - Physical Activity vs. Muscle Strength;
 - Fatigue.
- 4) Qualify biomarkers for muscle mass, simple, easy to implement in the Community (taking note of gender-related differences);
 - Muscle Proteins Anabolism;
 - Muscle Proteins Catabolism.
- 5) Validate patients path through the medico-social pathway in order to define best population to include in clinical studies;
- 6) Establish the HTA criteria and test the pharmaco-economic model of intervention against Physical frailty and Sarcopenia.

EFPIA PARTICIPANTS

Sanofi (lead), GSK (co-lead), Novartis, Eli Lilly

INDICATIVE DURATION

The indicative duration of the project is 5 years.

INDICATIVE BUDGET

The indicative in kind contribution from the EFPIA companies is estimated at EUR 25.31 million. Indicative requested IMI JU contribution is EUR 24 million.

The additional commitment to match the IMI JU funding will be confirmed before the launch of the topic.

APPLICANT CONSORTIUM

(To be selected on the basis of the submitted EoI)

The applicant consortium is expected to contribute *via*:

- State-of-the-art expertise in the field of geriatrics, physical frailty and sarcopenia' capacity to provide specific expertise and supporting objective elements to the clinical, regulatory and HTA table of discussions;
- Geographic capacity to implement the project and specifically the Clinical Trial in at least 5 EU Member States;
- Capacity to establish for all the investigational centres an efficient, representative territorial network to reach older patients living in the community and eligible to the clinical trial, also in collaboration with General Practitioners, Orthopaedists, other Health Care Professionals as appropriate, and informal carers/family;
- Capacity and availability of clinical and care facilities, adequate trained physicians and specialised personnel to implement the clinical trial protocol;
- Functional capacity for effective interfacing with ICT specialists in order to speed all enabling operations;
- Provide the contribution of an Information and Communication Technologies (ICT) established SME with proven expertise in the field of geriatric applications and large database management;
- Provide and effectively inject scientific and medical knowledge throughout the project, including health literacy content;
- Provide novel therapeutic strategies with new technologies to treat PF&S musculoskeletal complications;
- For the Consortium Experts to adequately populate in person and via validated content and regular reporting the tracking of project implementation and the progress of the randomized clinical trial and of its confluent work streams;
- Provide a risk management plan for the RCT and its results;
- Populate in person and via validated content the dissemination work stream as appropriate.

PROPOSED PROJECT ARCHITECTURE

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

The below Work Packages are quite broad in outline and different specific project proposals, along with proper justifications, within each Work Package are expected to be developed by the Applicant Consortium.

Work Package 1: Project Management and Oversight

This Work Package will address the strategy and implementation of the project management. This will encourage regular meetings and interaction between sub-groups and teams, to coordinate and follow up on the work effort.

EFPIA contribution: Project Management including planning, budgeting, follow up and tracking, and consolidation of Work Package reports. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution.

Expected Applicant consortium contribution: providing detailed follow up and tracking, via regular Work Package reports, early report of any unexpected organisational or structural issue or delay with respect to the project deployment and intermediate objectives.

Work Package 2: Clinical Consensus over Indication, Target Population and Clinical Trial Design for Data Generation

Academia, EFPIA, Patients & Carers Representatives and Health Care Professionals will jointly contribute to the overall evaluation of currently available evidence in order to set up the scientific consensus necessary to support sound operational definitions in term of sought indication, population and clinical trial designing for longitudinal data generation.

EFPIA contribution: providing a reliable and feasible operational setting for implementation, in keeping with member companies consolidated expertise and preliminary data made available in the specific field of physical frailty and sarcopenia.

Expected Applicant consortium contribution: build up and consolidation of the scientific consensus necessary to support sound operational definitions in term of sought indication, population and clinical trial designing for longitudinal data generation, on the basis of available scientific evidence at the time of discussions, of their own expertise and their consolidated experience in geriatric care.

Work Package 3: Regulatory Consensus over operational definitions

Regulators, EFPIA, Academia, and Patients Representatives will jointly contribute to the overall evaluation of evidence and results from WP 2.

EFPIA contribution: planning, hosting and organizing workshop(s) with regulators, contributing to discussion of available evidence (including unpublished data), literature analysis, publication support, (co-)authoring of reviews and white paper(s).

Expected Applicant consortium contribution: participate, actively contribute to constructive discussion with regulators to promote and achieve regulatory consensus over operational definitions. (Co-)authoring of reviews and white paper(s).

Work Package 4: Biomarkers qualification

Regulators and Academia will be invited to jointly contribute to the qualification pathway definition and requirements during the initial consultation phase of the project, in order to allow preliminary agreement on the protocol design.

EFPIA: biomarkers operational deployment; member companies will provide specific expertise, investigational/diagnostic products, related centralised bioanalytical facilities, will set up operations, deliver results and reports.

Expected Applicant consortium contribution: scientific clinical expertise and biomarkers pathway per protocol implementation in the predefined population.

Work Package 5: Health Technology Assessment

HTA Representatives will jointly contribute to the definition of relevant outcomes during the methodology consolidation phase, and to the overall evaluation of collected evidence and results at the end of the study.

EFPIA contribution: Literature analysis, publication support, (co-)authoring of review and white paper(s), hosting and organizing workshop(s).

Expected Applicant consortium contribution: participate, actively contribute to constructive discussion with HTA representatives to achieve consensus over operational definitions. (Co-)authoring of reviews and white paper(s).

Work Package 6: ICT enabling infrastructure and operations

In this work package the deliverables are expected to provide the operational definition and implementation of a state-of-the-art ICT platform, enabling optimal data capture in conditions that are adapted and customized to older persons living in the community. This should include integrated sensing/telemonitoring systems complementing standard clinical data collection and data management.

The participation in the Applicant Consortium of an Information and Communication Technologies (ICT) established SME with proven expertise in the field of geriatric applications and large database management seems appropriately required.

- Academia and SME for ITC/devices implementation;
- EFPIA: definition of ICT, data capture and data warehouse requirements adapted to the clinical trial final design;
- SMEs involvement: ICT model testing and up-scaling; interoperability standards set-up; ICT infrastructure deployment and management; project up-scaling and deployment; certification procedures as applicable.

EFPIA contribution: involvement of experts in the field, oversight and quality requirements definition.

Expected Applicant consortium contribution: the Consortium will provide oversight and quality requirements implementation; ICT infrastructure design and planning; implementation and tracking.

Work Package 7: Clinical Study implementation and operations

EFPIA and Academia Experts have identified during an *ad hoc* preparatory workshop a set of operational objectives to be met by a randomized controlled clinical trial. The rationale for the clinical trial is aligned with the scientific community, state of the art knowledge of frailty in older persons and takes also into consideration elements that emerged from the public debate currently underway in the frame of Active and Healthy Aging, European Commission initiative. Outlines are presented below and should be considered as indicative.

The final design of the randomized Clinical Trial will be agreed with EFPIA partners at the Full Project Proposal stage.

Innovative Therapeutic Intervention against physical Frailty and Sarcopenia, a European Study in Older Persons living in the Community as a Prototype Geriatric Indication (ITI-PF&S).

INVESTIGATOR/ TRIAL LOCATION

Multicentre, (final number t.b.c.) each centre corresponds to a catchment area in the community (a geriatric reference centre and its related territorial healthcare network). In order to generate data that reflect EU demographics and different regional situations, the RCT is meant to take place in 5-6 participating EU Member States and in one US comparative catching area.

STUDY OBJECTIVE(S)

Overall Objective

To validate **an interventional paradigm** for identifying at-risk individuals living in the community and **evaluate innovative therapeutic interventions** against physical frailty and sarcopenia in order to prevent/delay mobility disability, through:

1. Creating an operational definition of at-risk (sub-)populations with undisputable unmet therapeutic need;
2. Qualification of muscular anabolism and catabolism biomarkers in at-risk (sub-)populations;
3. Validation and implementation of practical clinical methodologies for testing clinically meaningful interventions for the prevention of Physical Frailty and Sarcopenia and its complications (falls, mobility disability, hospitalisation/institutionalisation);
4. Developing scientific and regulatory Consensus on these three strategic objectives (indication, state and efficacy biomarkers, development methodology);
5. Developing a health-economic model of physical Frailty and its components in a real life setting.

Under this Initiative, clinical longitudinal data will be generated by comparing two groups of older persons who will be randomized to a state-of-the-art integrated intervention against muscular function loss, centered on the administration of a standardized physical activity program, versus an integrated healthy aging counselling program without regular physical activity.

The Consortium will consider opportunities for an add-on design with an investigational drug, within the same investigational setting.

Operational (primary) objectives

To evaluate and compare health changes in the study groups over 2- year intervention in order to correlate chosen biomarkers with physical frailty and sarcopenia major related outcomes: falls, injurious falls, mobility disability, days of hospitalization/year, institutionalization, and other (t.b.d.).

- The incidence of Physical Frailty status defined according to Fried phenotype criteria (*or a predefined Short Physical Performance Battery cut-off*);
- Qualification of novel biomarkers for changes in skeletal muscle mass and functional capacity in older men and women.

Secondary objectives (these are indicative and will be refined by the scientific committee)

- The incidence of major mobility disability (defined as inability to walk 400m or usual gait speed < 0.8 m/s);
- Changes of physical performance (measured by the Short Physical Performance Battery score, gait speed and the handgrip test);
- Ability of biomarkers to predict rate of change in muscle mass and functional capacity;
- Modifications of sarcopenia (defined according to the European criteria);
- The incidence of falls, "near falls", and injurious falls;
- The incidence of death;
- Changes in nutritional status (measured by Body Mass Index, anthropometric measures, and body composition parameters (estimated by dual energy X-ray absorptiometry));
- Changes in physical function (measured using the Pepper questionnaire, including Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) and mobility tasks);
- Changes in cognitive function (measured by the Mini Mental State Examination score) and mood (measured by means of the Geriatric Depression Scale);
- Health care utilization (emergency room admissions, hospitalizations, institutionalizations);
- Changes of quality of life, Patient Reported Outcomes (PRO) specific for sarcopenia.

STUDY DESIGN

Randomized controlled clinical trial based on a two-arm comparative intervention

Duration of the study: **4 years** (1 year of recruitment).

Follow-up of participants: **2-year integrated intervention (t.b.c)**; follow-up until operations are closed.

Closing operations and analysis of results 1 year.

Inclusion Criteria:

- Age ≥ 70 years;
- Summary score < 8 on the Short Physical Performance Battery;
- Sedentary lifestyle, defined by ≤ 125 min/week of activity on the CHAMPS-18 questionnaire;
- Able to complete the 400-m walk test within 15 minutes at baseline without sitting, leaning, using a walker, or the help of another person;
- Willingness to be randomized to either intervention group;
- Living in the community with no project to relocate or moving to a nursing home.

Exclusion Criteria:

- Unable or unwilling to give informed consent;
- Acute or rapidly evolving conditions implying a life expectancy less than 6 months or necessitating heavy chronic treatment(e.g. dialysis, COPD, others).

Temporary exclusion criteria:

Planned surgical intervention or acute benign condition.

NB: Diabetes, hypertension, common cardiovascular conditions (except valvulopathies), cancer in clinical remission, etc. are not exclusion criteria.

STUDY INTERVENTIONS**Physical activity (PA) program:**

The PA intervention includes structured exercise and PA, includes aerobic, strength, flexibility, and balance training.

Health Literacy (HL):

Addressed mainly to the older person but involves the General Practitioner and carers/family.

Nutritional Intervention (NI):

Includes anthropometric measurements, nutritional risk assessment, body composition, and dietary assessment.

ICT intervention:

Includes data capture and sensing devices based at patient's home, integrated with more traditional data collection by the study personnel.

PRIMARY AND SECONDARY ENDPOINT(S)

These will be agreed by the scientific steering committee on the basis of outputs from WP 1, 2 and 3.

STATISTICAL CONSIDERATIONS

Total expected number of patients: will be calculated according to the final agreed primary endpoint; expected between 600-900 participants per group.

The scientific committee will discuss final enrichment inclusion criteria e.g. SPBB<8, previous fall, reported fatigue, etc.

The final overall sample size: to be calculated based on the estimated incidence of the finally selected major events in the chosen at-risk population based on the agreed primary objective.

DURATION OF STUDY (per patient)

Two-years plus follow-up as long the study is on-going

STUDY COMMITTEES:

1. Steering and scientific Committee
2. Safety Data Monitoring Committee
3. Adjudication Committee

Applicant Consortium is expected to contribute mainly by providing:

- state-of-the-art expertise in the field of geriatrics, physical frailty and sarcopenia;
- capacity to establish an efficient, representative territorial network to reach older patients living in the community and eligible to the clinical trial, also in collaboration with General Practitioners, Orthopaedists, other Health Care Professionals as appropriate, and informal carers/family;
- clinical and care facilities and adequate trained physicians and specialised personnel to implement the clinical trial protocol;
- effective interfacing with ICT specialists in order to speed enabling operations.

EFPIA will contribute by making fully available the member companies expertise in randomized clinical trial initiation and conduct, providing oversight over the study management, the accomplishment of overall objectives, providing, hosting and provide technical and logistic assistance for the meetings of the study committees, etc.

Work Package 8: Evaluation of results (includes Data Analyses and Hypothesis generation)

Academia, Regulatory Authorities and specifically the European Medicines Agency and its Experts, EFPIA via the member companies Experts **will collaboratively review the clinical trial results in order to draw the necessary clinical and regulatory conclusions.**

EFPIA contribution: planning, hosting and organizing workshop(s) with regulators; contributing to results discussion via its Experts (including biostatisticians); providing technical support (translations, etc.); (co-)authoring of reviews and white paper(s).

Expected Applicant consortium contribution: participate, actively contribute to constructive discussion with regulators to achieve scientific and regulatory agreement us over the interpretation of study results. (Co-)authoring of reviews and white paper(s). Overall build up and consolidation of the scientific consensus is necessary to support sound operational definitions in term of sought indication, population and clinical trial design for longitudinal data generation, on the basis of available scientific evidence at the time of discussions, of their own expertise and their consolidated experience in geriatric care.

Work Package 9: Stakeholder information and results dissemination

Academia, Regulatory Authorities, EFPIA, Healthcare professionals, Patients representatives will contribute over the 5 years project duration to health literacy planned actions, project awareness, project milestones presentation to stakeholders and media as appropriate.

EFPIA contribution: logistics and organisational support, contribution of EFPIA experts as appropriate; providing technical support (translations, etc.); this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate).

Expected Applicant consortium contribution: provide the scientific and medical content for health literacy elements building, consolidation and update over the project duration; provide personal and collegial contribution to the dissemination program implementation; authoring main papers in peer reviewed scientific journals.

THEME: COMBATTING ANTIBIOTIC RESISTANCE: NEWDRUGS4BADBUGS (ND4BB)

BACKGROUND

Antimicrobial resistance (AMR) is a major global public health threat. Infections caused by resistant bacteria are increasing and are associated with increases in mortality, morbidity, and length of hospitalization.¹⁰ In Europe 25,000 deaths were reported in 2007 as a result of AMR, with two-thirds of these deaths being due to Gram-negative bacteria. This clinical burden is associated with soaring treatment and societal costs, with the cost of AMR being estimated at around € 1.5 billion per year in Europe (see ECDC/EMA joint technical report "The bacterial challenge: time to react," 2009).

The European Commission (EC) is committed to combating AMR, as outlined in its recent communication to the European Parliament and Council, entitled 'Action plan against the rising threats from antimicrobial resistance' (COM (2011) 48) (http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf).

The European Federation of Pharmaceutical Industries and Associations (EFPIA) shares the views of the EC and recognizes that, although a number of activities have already been undertaken at the European Union (EU) (including FP7 funded activities) and international levels, including the Trans-Atlantic Task Force on Antimicrobial Resistance, more concrete actions need to materialize to make a meaningful change.

The ND4BB programme represents a core element of the "Action plan against the rising threats from Antimicrobial Resistance" adopted by the European Commission in answer to the Council Conclusions and European Parliament resolution to "establish an EU-wide plan to combat AMR". Action 6 of this action plan reads:

To promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antibiotics to patients by:

– *Launching rapidly with EFPIA, within the IMI-Joint Undertaking, a program for research on new antibiotics aimed at improving the efficiency of research and development of new antibiotics through unprecedented open sharing of knowledge.*

PROBLEM STATEMENT & OVERALL OBJECTIVES FOR ND4BB

Despite the recognized need for new antimicrobials for clinical use, only two new classes of antibiotics have been brought to market in the last 30 years, and many drug developers have left the field.

There are key barriers to the development and delivery of effective antibiotics:

- Discovery and development of novel antibacterial agents is scientifically challenging. For example, many traditional screening approaches have failed to unearth novel chemical starting points, and Gram-negative pathogens have many inherent barriers and mechanisms preventing penetration of antibiotic agents.
- Substantial regulatory challenges to the introduction of novel antibacterial agents remain, although many are currently being addressed by cross regulatory agency-discussion leading to limited population and pathogen directed development approaches in both the US and the EU.
- Antibiotics have a low return on investment relative to other medicines, making it an unattractive area for drug developers, therefore limiting the future antibiotic pipeline.

¹⁰ Cosgrove, SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006; Jan 15;42 Suppl 2:S82-9.

The goal of the ND4BB research programme is to create an innovative and collaborative public-private partnership (PPP)-based approach that will positively impact all aspects of AMR, from basic scientific challenges and the discovery of novel Leads and Development Candidates to Phase 1, Phase 2, and Phase 3 clinical studies, and from the value demonstration of antibiotics to education around responsible use of antibiotics. These activities will increase the probability of success in the development of new and effective antibiotics and biologics for the treatment or prevention of infections caused by resistant pathogens as well as the consequences of those infections, and it will inform priorities to combat the occurrence of resistance.

One focus of the ND4BB programme is the discovery and development of new agents targeting the treatment, prevention, or management of the sequelae of infections due to resistant priority bacterial pathogens (eg, one or more of the following: Enterobacteriaceae [specifically *E coli*, *K pneumoniae* and *Enterobacter* species], *Acinetobacter*, *Pseudomonas aeruginosa*, *Clostridium difficile*, or methicillin-resistant *Staphylococcus aureus* [MRSA]). In addition, ND4BB focuses on research to better understand the penetration barriers and efflux mechanisms that render infections by Gram-negative bacteria particularly difficult to treat.

Another important goal of ND4BB is to develop a data repository that is sustainable beyond the life of the current programme, providing a key information base for research projects focused on antibiotic resistance. All consortia participating in studies conducted under the ND4BB research programme will be expected to contribute data to the ND4BB data hub and collaborate to share data and experience as widely as possible amongst all programme members and the antibiotic research community as a whole. Furthermore, ND4BB is establishing a clinical development infrastructure, including a network of investigators that will exist beyond the life of the current and future IMI Calls.

Many of the complex scientific challenges in the discovery and development of new antibacterial agents are being addressed under Topics 1-3 of the ND4BB programme. Separate work to review the current regulatory guidance will also provide insights and will be reflected in the clinical programmes presented in Topic 5 in this Call. However, the ability of investors to generate predictable commercial returns on R&D in this arena is crucial to incentivise them to invest going forward. Adding further complexity are the sometimes divergent interests of patients, doctors, public health bodies and innovative companies towards using new products while limiting increased resistance, correlated with amount of use.

The ND4BB Topic 4 aims to develop options for a new sustainable commercial model that will ensure future R&D investment in antibacterial agents leading to new products to combat emerging resistance. In addition, the topic aims to support the appropriate use of all antibacterial agents, both old and new. Both goals will require a trusting and collaborative approach across several stakeholder groups. Industry is committed to engaging to solve these pressing problems, but the project can only succeed by generating deep engagement from the other relevant groups to create a new paradigm for public and private sector collaboration.

ND4BB PROGRAMME ARCHITECTURE

The current Call Topics are the fourth and fifth Topics being launched under the ND4BB research programme (Topics 1a/1b and Topic 2 were launched in 6th Call for Proposals in May 2012 and Topic 1c and Topic 3 in the 8th Call for Proposals in December 2012).

The first two projects, COMBACTE¹¹ and Translocation¹², of the ND4BB programme started in January 2013. The COMBACTE consortium is focused on the clinical development of antibiotics and is building the COMBACTE clinical investigator network (CLIN-net), laboratory network (LAB-net) and statistic-network (STAT-net). It is anticipated that the Topic 5 consortium will directly connect with CLIN-net and LAB-net to build on the ND4BB deliverable of a self-sustaining clinical and laboratory investigator capability within Europe.

Translocation is focusing on research to better understand the preparation barriers and efflux mechanisms that render infections by Gram-negative bacteria particularly difficult to treat.

The upcoming Topic 3 project will be building an antibiotic drug discovery platform and will be focusing on progressing promising Hit molecules up to Clinical Candidate Status.

In the current 9th Call for proposals, the ND4BB programme is expanded with the addition of the following:

- **Topic 4: Driving re-investment in R&D and Responsible Use of Antibiotics**

Total Indicative budget for ND4BB Topic 4: €3.1M EFPIA/ €6.3M IMI JU

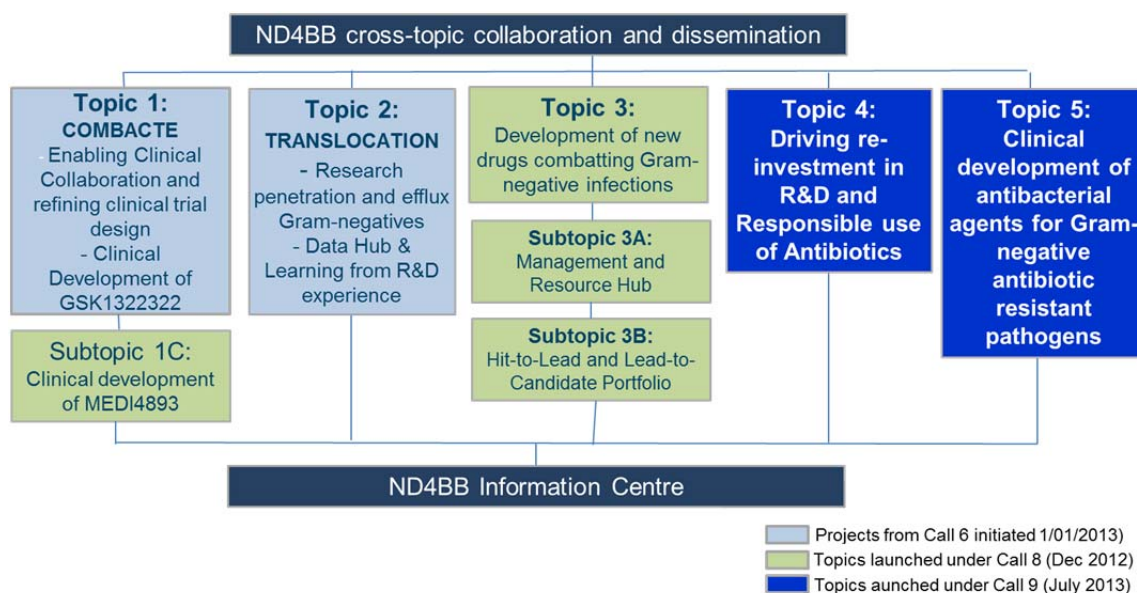
- WP1 (A, B, C, D), WP2, WP3

- **Topic 5: Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens**

Total Indicative budget for ND4BB Topic 5: €41.55 EFPIA/ €30.55M IMI JU

- PART A: WP 1, WP 2 and WP3
- PART B: WP4, WP5 and WP6

A summary diagram of the ND4BB programme is presented below.



All Applicant Consortia are expected to provide plans and resources to support collaboration among projects funded under ND4BB. It is envisaged that this will be a

¹¹ <http://www.imi.europa.eu/content/combacte>

¹² <http://www.imi.europa.eu/content/translocation>

shared activity across the projects generated by the current Call and existing ND4BB projects.

All Consortia participating in topics conducted under the ND4BB research programme will be expected to contribute data to the ND4BB Information Centre, as developed in the ND4BB project Translocation, and to participate in cross-project team meetings as appropriate to ensure learnings, knowledge, and skill sets are maximized across the ND4BB teams.

SPECIFIC APPROACH FOR ACCEPTING NON-EU EFPIA IN KIND CONTRIBUTION (SPECIAL CLAUSE 13B)

Given the current low level of drug development activity to combat antibiotic resistance, the fact that the majority of drug development activities are being conducted outside of the EU and the gravity of the health threat that antibiotic resistance offers, acceptance of non-EU EFPIA in-kind contributions as part of the EFPIA in-kind contribution has been agreed by the Founding Members under the following conditions:

For topics of interest for EU citizens that will benefit European academics and SMEs, where there are few EFPIA research capacities in Europe while academic research is strong or substantially developed in Europe and, in particular research into rare diseases or disease areas of high public interest where creation of a critical mass of research is needed: For these projects a global cap of 30% at programme level of the actual committed EFPIA in-kind contribution to research activities, with no limit per IMI collaborative research project, may apply when agreed at the time of the Call definition and confirmed at the time of the selection decision of full project proposals.

The benefit to Europe of implementing this Special Clause

For the patient and society as a whole: Antibiotic resistance is an increasing threat to health across Europe and action is urgently required to support the development of new antibiotic agents. Without a joint and urgent action from public and private sectors, society will no longer have access to effective antibiotic agents to combat these resistant infections.

For public investigators and SMEs: All IMI funding will be directed to investigators and SMEs located within the EU.

Investigators will have a unique opportunity to gain funding to support the development of new and innovative approaches, while at the same time gaining invaluable insight into the complexities of drug development as well as access to learnings and experience from all partners involved in ND4BB. It gives partners the opportunity to build relationships with EFPIA companies participating (and also those outside of ND4BB) to strengthen their ability to identify partnering opportunities for further development of promising new drugs. It is anticipated that the opportunity to build a network of investigators through which academics, pharmaceutical and biotechnology companies can advance the pre-clinical and clinical development of new assets will attract future drug discovery efforts and future clinical trials to Europe. Investigators will also become part of the broader ND4BB research community through regular joint symposia and sharing of experiences through the ND4BB Information Centre.

Having the opportunity for collaboration has already actively encouraged companies developing new antibiotic agents to focus on running clinical trials within the EU rather than outside of the EU where typically it is easier to recruit subjects with the appropriate resistant infections. This will bring revenue directly to hospitals, universities and SMEs through the ongoing studies as well as establishing a network of European investigators with the expertise and resources required to participate in global trials.

For pharmaceutical and biotechnology companies developing antibiotic agents : The opportunity to work with leading experts in all fields required for successful drug discovery in order to tackle major challenges in drug discovery and development.

3. ND4BB TOPIC 4: DRIVING RE-INVESTMENT IN R&D AND RESPONSIBLE USE OF ANTIBIOTICS

PROBLEM STATEMENT

As the level of resistant bacterial infections grows, there is an urgent need to develop a new generation of antibacterial agents to treat patients with life-threatening or potentially life-threatening infections for which there are few other treatment options. Despite this recognized need, many drug developers have left the field because the development of products for the treatment of resistant bacterial infections does not provide an attractive return on investment.

Future levels of resistance are hard to predict but have the potential to decimate the utility of currently available antibacterials. Consequently, society is rightly calling for investment in antibacterial R&D. However, antibacterial R&D is facing serious challenges. The pharma industry is faced with increasing R&D costs and timelines, and tightening control on access, price and use of new antibacterials. The challenges faced by small and medium-sized companies may be even more complex and include difficulty in finding suitable partners for late-stage development and globalisation of new products. As a result, instead of a much needed investment, the reverse situation is occurring: antibacterial R&D is decreasing. Insufficient new products are in development. If products are to be available to address the crisis of antibacterial resistance, it is not only necessary to address the scientific and regulatory challenges of R&D, but also the commercial challenge of generating financial returns after regulatory approval while maintaining the utility of new antibacterials.

As well as conventional measures such as increasing direct investment to the R&D process (as evident in ND4BB Topics 1-3) and reviewing regulatory guidance, systemic changes should be specified to create new commercial models designed to generate new investment and an attractive return on investment while preserving the utility of these new antibiotics.

This change is needed because there is a misalignment between the current sales-based reward model for the investment required to create new products vs. the clear stewardship-based need for society to achieve responsible use, appropriate valuation of new agents as well as alignment with developing public health priorities. This challenge is exacerbated by a misalignment in the contribution that therapies to treat infection make to public health and the value attributed to antibiotics by the public and payers. The misalignment is most marked in relation to new antibiotics: their incremental contribution to infection management may be masked by the continuing utility of existing medicines to treat the cases of infection caused by susceptible bacteria.

At present, there are embryonic ideas for alternative commercial & stewardship models. However few have addressed the complexity of innovation, international public-health decision-making or the organisational dynamics of a completely new model of collaboration between public and private sector. Without these inputs, it seems unlikely that meaningful progress will be made. Past experience is not encouraging in this area, and it is likely that patterns of disinvestment will continue. A mix of research and new thinking involving multiple stakeholders is needed to build a new business model. The proposed project could provide a critical input to the policy debate through exploring significantly different options to address the issues.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

This project will address the need for a new way for the public and private sectors to collaborate to ensure future generations are not faced with untreatable infections in seriously ill patients. The key will be to develop meaningful, long term public health policies which encourage stewardship for antibiotics while maintaining meaningful levels of research and development.

The present state of antibiotic R&D is in part due to the **misalignment of economic incentives**: a pharmaceutical company aims to generate returns through sales volumes contrasted with the public health goals of minimising resistance by limiting use through antimicrobial stewardship initiatives. The project represents an attempt to achieve a better balance between the two, leading to the development of new forms of collaboration between the public and private sector and shared knowledge resources capable of supporting the need to address any new antibiotic in a responsible and sustainable way.

Any new business model for antibiotic commercialization will be complex. It will involve multiple stakeholders and needs to be viewed from a health systems perspective. All health systems' key components and their interfaces need to be considered. Many stakeholders, including senior government administrators and lawmakers need to recognize the need to change and be involved in developing and endorsing the components of a new model. One obvious solution to private sector incentivisation is establishment of higher prices, but even if feasible this would provide only a partial solution as it would not address the misalignment. Continued education around responsible use of new and old antibiotics will also require coordinated activity.

An integrated solution is needed and we lack a stable, long-term platform to develop one. An IMI-based approach could ensure that all of the different inputs are gathered and synthesised. The project should demonstrate the feasibility of any new approach with an impact assessment and an implementation plan to its adoption by policy-makers. As described in the table below, different stakeholders need to be involved in this public-private partnership in order to secure its successful development and implementation:

Function	Contribution
Public Health	Define the infectious disease priorities (including epidemiology and cost/disease burden) for antibacterials and initiatives to combat the development of resistance
Industry – Big pharma and SMEs, including external investors such as venture capital funds	Define the hurdles to current investment and identifies inputs to economic models. It also provides specific data to support development of case studies
Academia	Provides expertise in economic modelling, and development of commercial model case studies and analytics
Clinical societies	Provides the clinical description of the need for new antibiotics as well as defining guideline and antibacterial stewardship initiatives
Government, payers, & EU member states	Examines respective political, legislative, access and commercial systems in order to enable the delivery of a new commercial model
Patients / Society	Defines infectious disease priorities from the perspective of the patient and overall benefit to public health and society.

As well as an integrated view, the platform provided by IMI can break new ground in enabling future political action to be based on **high-quality analyses developed via multistakeholder collaboration**. It needs to focus on organisational behaviour, political economy, health economics and business economics aligned to a strong guiding frame provided by the realities of innovation in this area. As a result of past work sponsored by EU Presidencies¹³ and EU institutions¹⁴, as well as the ECDC, Europe has built a leadership position in this area. Topic 4 should build on this success, to encourage involvement of global partners and move towards a recommended global solution as well as steps for implementation. As such, this project represents an essential adjunct to the other components of the IMI programme on AMR.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

The focus of Topic 4 has been the subject of repeated discussions over many years. There have been and currently are efforts underway (e.g., the Pew Trust in the United States has recently sponsored a symposium on this topic), but to date no coordinated multinational effort focused on the intertwined problems of novel commercial models and stewardship is in place.

Complementarities and potential synergies with other initiatives on AMR should be taken into account, in particular

- ReAct, Action on Antibiotic Resistance (<http://www.reactgroup.org/>)
- the Joint Programming Initiative on AMR (<http://www.jpamr.eu/>)
- EARS-Net (http://www.ecdc.europa.eu/en/activities/surveillance/ears-net/about_ears-net/pages/about_network.aspx)
- ESAC-Net (<http://www.ecdc.europa.eu/en/activities/surveillance/esac-net/pages/index.aspx>)

The expressions of interest should clearly outline the unique properties of the proposed plan of work and how potential interactions with these initiatives would be managed, avoiding potential duplication and overlap of activities.

OBJECTIVES

Analysis and understanding: This project should develop a vision for a new way for the public and private sectors to collaborate to ensure future generations are not faced with untreatable infections in seriously ill patients. The project needs to develop new insights and collate data to inform the vision. Required outputs need to deliver clarity and agreed approaches to address the following challenges:

- Our lack of implementable commercial models that will incentivize work in this arena by providing rewards to innovators while addressing simultaneously the need for antibiotic stewardship
- Our lack of a shared understanding of the responsible use of antibiotics and how this can be delivered for seriously ill patients
- Our differences in perspectives on ways to set, communicate, and act on Public Health priorities
- Our lack of a broad understanding of the value of antibiotics to society

¹³ Policies and incentives for promoting innovation in antibiotic research, London School of Economics, report commissioned by Swedish presidency, 2009

¹⁴ Communication from the Commission to the European Parliament and the Council : Action plan against the rising threats from antimicrobial resistance COM (2011) 748

Output → Outcome → Impact: Producing a vision is not sufficient: it needs to be turned into policy recommendations and implemented. This will require a significant effort from the Project. The policy recommendations need to cover both current eventualities as well as likely future trends.

DELIVERABLES

General

- Create a multi-disciplinary, multi-stakeholder community with an in-depth comprehension of the complexities of antibacterial R&D and the challenges of the current commercial model
- Generate an analysis of the societal impact of antibiotic resistance. In particular, the analysis should predict the cost to society in 5, 10 and 20 years
- Create consensus on the meaning and use of key concepts underpinning any new model
- Improve linkage between public health perspectives on management of resistance, challenges faced by small- and medium-sized enterprises, and industry R&D programmes

Models for commercialisation and stewardship

- Develop creative, concrete, implementable options for new commercial models that address the needs of multiple stakeholders, incentivize investment from the private sector, Venture Capitalists and small and medium enterprises, and provide a clear basis for action by policymakers.
 - These should be validated through modelling the effect on selected antibiotic case studies.
- Develop the insights (and perhaps also terminology) required to define *Responsible Use* of antibiotics.
 - The insights should have appropriate and sustainable use of antibiotics as their primary goal.
 - The insights should consider multiple viewpoints and be translated into metrics that can be created to assess progress towards widespread implementation of good stewardship as defined by these principles of responsible use.
 - The definitions and metrics should also address the needs of developing countries.

Implementation

- Provide implementation plans for the proposed new model, both in terms of the areas to be prioritised and ensuring the understanding of stakeholders. These plans should be tested with and then communicated to key leaders within Member States.

EFPIA PARTICIPANTS

AstraZeneca (lead), GlaxoSmithKline R&D, Cubist, Astellas, Sanofi, Pfizer and Merck (MSD).¹⁵

¹⁵ Rempex, a pharmaceutical company currently not member of EFPIA, is also participating and contributing resources in this project.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of this Topic will be 3 years.

INDICATIVE BUDGET

The in-kind contribution from the EFPIA participants is estimated at approximately EUR 3.1 million and the IMI JU contribution will be up to EUR 6.3 million.

This budget should be viewed across all work packages as many elements (e.g., meeting costs) will simultaneously support all three WPs.

PROPOSED PROJECT ARCHITECTURE

WP1: Creating the building blocks for a new economic model for antibiotic development and responsible use

In order to develop a new model, build a framework for access and support appropriate use of antibiotics, the project should produce new insights regarding the following key issues:

Commercial models

- Identification of concepts that provide an **alternative to a conventional sales volume-based return** and, for at least some products, provide a return based on criteria that reflect the unique public health needs for antibiotics. Such criteria may be neither normally used today, nor easy to quantify and reward appropriately. For example:
 - Rewarding the risk taken by antibacterial investors in developing agents for emerging resistant infections, when the level of the future resistance is unknown and difficult to predict
 - Rewarding the public health value created by holding a therapy in reserve against the emergence of future resistance
 - Reward value in terms of preservation of antibiotic effectiveness, or
 - Rewarding the value of substituting one therapeutically-comparable product for another in order to slow development of resistance.
- Creating a **more predictable Return on Investment**. Acknowledging that uncertainty as well as absolute returns influence investment, consider how both the reward to an innovator company and the means of managing use can be made more predictable in the context of long-term investment decisions. It is important that the risks of both investment and reward are reduced for both innovators and payers and shared between them. This will require a robust analysis of the available policy levers and institutions.
- **Adaptable to different commercialisation models and geographies**. Any model should encompass both restricted use as described above (usually in hospitals) and broader use in community settings. It needs also to be adaptive to changes in the pattern of use (reserve therapies can become mainstream and vice-versa) and anticipate geographic differences in political realities.

Responsible use of antibiotics

- To be successful, a new model will need to develop an approach to responsible use. The project will need to define good stewardship in this context for both new and existing molecules by creating suitable terminology and suggesting possible approaches to measuring good stewardship.

- As with the commercial models, new approaches to stewardship will need to be adaptable to different use settings (hospital vs. community) and different geographies. Approaches to stewardship may require the project to explore ideas not currently in use. Possible concepts to explore could include:
 - In what ways would use of a diagnostic improve stewardship? Could use of a diagnostic be a measure of stewardship?
 - Use of combination therapies is standard in some disease areas (e.g., tuberculosis) due to the rapid and predictable emergence of resistance. Might we be approaching an era when responsible use of antibacterial agents also requires combination use? How should use of combinations be balanced against the possible increase in toxicity from a combination?
 - Controlled use of antibiotics could, in some settings, reduce access to life-saving drugs. Does responsible use always entail an interaction with a physician? Can trained care providers (e.g., pharmacists) manage such interactions by following an algorithm?
 - The use of therapeutic drug monitoring of plasma concentrations of antibiotics may soon help physicians to optimise treatment.
- While a primary focus of new models will be development of novel compounds, incentives for both exploring new indications and good stewardship of old compounds would be an additional option to consider. It is recognised that there will be further complexity in rewarding investment in existing molecules that no longer have IP protection.

General

- Any model should, to the extent possible, anticipate or be adaptable to potential technological and regulatory changes that could impact commercial viability, such as effective and rapid point-of-care diagnostics.
- The outputs of this EU-based project will be most directly relevant in the EU. In order to achieve global investment and conservation goals, alternative frameworks need to be found for other regions. The project could usefully explore the extent to which a collaborative European effort can generate insights that contribute to improved global investment and conservation measures.
- Reward to innovators should be in response to public health priorities. As these priorities may change over time, there must be mechanisms to identify and signal new priorities
 - In particular, the proposal should define ways to improve quantification of the current global burden of resistant bacterial pathogens (mortality and cost) and development of new HTA/valuation mechanisms that reflect the unique value of antibiotics.
- The Applicant Consortium must provide plans to the budget and infrastructure required to implement these new models and stewardship approaches

Taken together, this work package seeks to build a path to agreement from key stakeholders including industry, senior policy makers, public health, payers and patients of the need for a new model, the willingness to balance the risk of development of new antimicrobials and the long term commitment to delivering new antibacterials to address emerging resistance.

WP 1A: Responsible use of antibiotics, both new and old

Any new economic model must take into account how antibiotics should be used in clinical practice. There are many different views held by the different stakeholders involved and their respective priorities. Public conversation has stalled due to the lack of a common language or consensus on roles and responsibilities. To address this issue, this WP should:

- Define Responsible Use both for existing and future antibiotics.

- This should include analysis of the perspectives of different stakeholder groups
- This should also include possible measures and approaches to compliance
- Create concepts and terminology that would inform and enable the other workstreams
- Present analysis of the challenges in different healthcare settings and countries to delivering responsible use. This work should include an analysis of how current antibiotic use differs across healthcare settings.
- Create case studies to anchor these concepts in concrete examples
- Include behavioural and social science aspects of responsible use of antibiotics

Deliverables for WP1A are a framework for agreeing responsible use parameters built from common terminology and definitions. It should also deliver a set of metrics to support and document progress towards the appropriate and sustainable use of all antibiotics, incorporating the specific needs of developing countries.

WP 1B: Setting, communicating and revising Public Health Priorities

Economic incentives should encourage investment in infections considered to be a priority, from a Public Health point of view. It is essential to also define the characteristics of a novel antibiotic that would address the greatest unmet need. Determining these areas of medical need and developing an optimal target profile is not simple: resistance is largely unpredictable; priorities will differ geographically; and a balance between short and long-term perspectives must be taken, given the timescales of drug development. This WP needs to address the following questions:

- What mechanisms are needed to detect future needs?
- What mechanisms are needed to agree and communicate those signals?
- Who needs to respond to those signals?
- Will these signals evolve over time? If so, how should a need to change the signalling mechanism be addressed?
- Given the long cycle time of discovery and development, quick changes in the range and variety of pipeline products are not possible. How often should public health priorities change? How should products that are not well synchronized with current demands (but that might have value in the future) be treated in the context of setting public health priorities?

Deliverables for WP1B are a strategy (or set of strategies) that could be implemented by public health authorities to detect and communicate future needs.

WP 1C: Antibiotic valuation

Many stakeholders believe that antibiotics are generally under-valued by healthcare systems. Antibiotics have unique properties (e.g., their ability to be lifesaving based on a brief course of therapy) that may mean that standard approaches to valuation (e.g., comparative health technology assessment) do not reflect the value provided to society. In addition, the value will differ for treating resistant and susceptible infections and yet this is often unknown at the time of use. This WP should address the following topics:

- What are the sources of value of an antibiotic? This workstream should distinguish value of immediate use from overall societal value:
 - Value of holding antibiotics in reserve
 - Value of the access to antibiotics as insurance at the societal level
 - Value of years of life restored
 - Value of proactively addressing future resistance (that is, having the antibiotic already developed means that society need not wait if an epidemic emerges; conversely, if we wait until the epidemic emerges then it is too late)

- Values from different perspectives: Patient, Physician, Payer, Health-Care System
- Value of diversity of mechanism across the range of (new) antibiotics — this protects vs. emergence of novel forms of resistance.
- Value from extended periods of exclusivity: Progressive registration might permit an innovator to receive earlier access to return from a product — what is the impact of this? Are prolonged periods of market exclusivity practical and what are the challenges to their implementation?
- Value in the context of large vs. small company developers: Existing models typically presume that the final development and commercialisation will be delivered by larger companies, but what conditions would need to exist for small-to-medium enterprises to be able to support products globally? Would this approach offer greater value to innovators?
- What alternative valuation paradigms are possible?
- Vaccines offer a model of industry-government collaboration and procurement of health care products as a public health commodity. Does this paradigm offer a relevant approach to valuation of antibacterial agents? If not, why not? If so, what lessons can be transferred?
- What are the implications of evolving regulatory paradigms in which initial approval may be based on smaller amounts of data (with post-approval accrual of supplemental data)?
- What are the implications for HTA processes, considering also other ongoing national/EU/IMI funded projects and initiatives?

The key deliverables for WP1C are economic models of the current and future costs to society of resistance, the value new antibiotics would generate in managing this, and options for how this value should be assessed for any new product.

WP 1D: Developing novel reward models

Currently, antibiotics are rewarded in the same way as all other medicines (volume and price), which contributes to the misalignment of interests discussed earlier. Other reward models have been tried or discussed to improve the alignment. This WP should propose and review alternative models that would be consistent with the needs and characteristics of antibiotics. In doing so, the WP should consider the following aspects of any reward model:

- Greater predictability of return on investment
- How to separate financial reward from usage (volume)
- At what step(s) during the R&D cycle should the innovator be rewarded?
 - Incentives early in the process (push-type incentives) and late in the lifecycle (pull-type incentives) have different impacts and different levels of feasibility and both should be explored
 - This question also links to the possible views of value from WP1C. For example, if novel mechanisms of action are thought of high value, then push incentives designed to encourage this higher risk R&D should be designed.
- Who should pay? Are there novel funding sources?
- How can the community ensure appropriate access to new antibiotics, including in the developing world?
- As a secondary priority, the work should also cover mechanism for addressing reward for researching new indications for products that no longer have intellectual property protection. The additional complexity to this is recognized and it may prove to require a separate process.

WP1D should deliver a set of options for new models for paying innovative companies for developing new antibiotics that treat emerging resistant infections.

EFPIA Partner Contribution: The industry has direct experience of the distribution of medicines and the practical challenges involved in achieving antibiotic conservation goals. Pharmaceutical companies also have expertise to offer in analysing data relevant to infectious disease. In addition, both the pharmaceutical and other private sector partners will provide input on the costs and attrition of antibacterial R&D and the effects of different financing proposals on commercial behaviour and R&D decision-making.

WP2: Creation and testing of new economic models

WP1 develops a set of concepts and ideas that cover the main areas of any new economic model individually. WP2 must assemble these concepts into a set of coherent policy options, which tie together to address the full set of issues.

WP2 must also test these options against several requirements for success:

- Legal, political and regulatory feasibility
- Geographical reach and differences (EU vs. US vs. rest of world)
- Impact of evolving medical practice (e.g., use of diagnostics, novel forms of administration, etc) and other macro trends (e.g., the steady change distribution of ages across the population)
- Impact on real-life antibiotics in development by innovator companies

Depending on the level of direct involvement of key policy-makers in this project, it is likely that an iterative approach will be required. New proposals are developed and then tested with the relevant stakeholders. Deliverables from WP2 would be a concrete, implementable set of policy recommendations that would define the new economic model, including measures to support appropriate use, which have been validated against the above criteria. It should also include an implementation plan for these recommendations including sequencing or priority elements, if relevant. Consensus of all relevant stakeholders is needed on the meaning and use of key concepts underpinning any new model.

EFPIA Partner Contribution: The industry has related experience in the distribution of medicines not only for antibiotics but for other therapeutic areas as well. This knowledge would be applied to the areas challenging infection to determine their relevance as alternative models as well as examining models used in other industries. Pharmaceutical companies also have expertise to offer in analysing data relevant to potential options and developing economic models to test their feasibility.

WP3: Project coordination and management

Overall coordination of the project is key, given the inter-connectedness of all work packages. A multi-disciplinary, multi-stakeholder community with an in depth comprehension of the complexities of AMR and antibacterial R&D and the challenges of the current commercial model will be the key mechanism to achieve this coordination. This community should meet regularly throughout the project. WP 3 encompasses this element of the work, together with the administrative tasks involved with managing the project.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise

INDICATIVE EXPECTATIONS FROM THE APPLICANTS

The applicant consortium should address all WPs. Specifically the applicant consortium applying for this project should offer at the minimum the following, originating in academic institutions, SMEs, public health bodies, public health budget holders, HTA assessors:

WP1: Creating the building blocks for a new economic model for antibiotic development and responsible use

- *Ability to assemble and coordinate multi-stakeholder discussions*
- *Experience with economic modelling and assessment of economic consequences*
- *Experience with public health issue management and disease modelling in diverse settings (developed world vs. developing world; managed health care vs. fee-for-service systems)*
- *Experience with the problematic of AMR*
- *Behavioural and social science expertise*
- *Experience with pharmaceutical development*

WP2: Creation and testing of new economic models

- *Multinational experience with government policy and regulation*
- *Ability to assemble and coordinate multi-stakeholder discussions*

WP3: Project management

- *Proven project management skills*
- *Ability to manage stakeholders and resolve blockers*
- *Proven ability to support and manage communications*

4. ND4BB TOPIC 5: CLINICAL DEVELOPMENT OF ANTIBACTERIAL AGENTS FOR GRAM-NEGATIVE ANTIBIOTIC RESISTANT PATHOGENS

PROBLEM STATEMENT

The incidence of serious infections due to multi-drug resistant (MDR) Gram-negative infections continues to rise. The profile of MDR bacteria is changing with Gram-negative Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*, showing resistance to cephalosporins due to extended-spectrum β -lactamases (ESBLs) or plasmid-mediated AmpC enzymes. Many of these isolates are also resistant to other first-line agents such as fluoroquinolones or aminoglycosides, leaving few available options for therapy. In addition we have the increasing challenge of opportunistic pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter* species, with a combination of innate and acquired multidrug resistance. Carbapenems are the preferred treatment option for severe infections due to MDR Gram-negative bacteria but carbapenemases have steadily accumulated in the Enterobacteriaceae with the expression of OXA (class D) and metallo-carbapenemases such as VIM and NDM-1 in isolates from specific geographical regions such as southern and eastern Europe and the Indian sub-continent being of increasing concern. For infections with such isolates treatment options are now limited to poorly understood and relatively poorly tolerated options such as colistin, fosfomycin and tigecycline. New antibiotics or combinations of existing antibiotics with resistance enzyme inhibitors are urgently needed to provide treatment options for patients with infections known or suspected to be caused by MDR Gram-negative pathogens.

Development of new antibiotics to combat serious infections by emergent MDR Gram-negative pathogen, such as those expressing carbapenemases is not feasible via the classical two phase 3 studies per indication approach (Tier A, Rex et al, Lancet Infectious Diseases, Volume 13, Issue 3, Pages 269 - 275, March 2013; doi:10.1016/S1473-3099(12)70293-1. . Current regulatory frameworks recognize the extent of unmet medical need and that the feasibility of the study of the intended population control the amount of clinical data needed for drug registration. This framework enables pathogen-directed development programmes to be suggested for the development of antibiotics for infection due to MDR Gram-negative infections. Pathogen-directed programmes will deliver a combination of therapeutic efficacy with robust pharmacokinetic-pharmacodynamic data sets to provide extrapolation of efficacy across body sites. Such limited population approaches may require external controls to provide valuable support for data interpretation in active treatment studies at a range of body sites. Controlled observational research will provide much needed information on the clinical management and outcomes of serious infections due to MDR Gram-negative pathogens. This will include contemporaneous control data on best-available therapy that will aid the design of interventional studies for targeted antibiotics.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

The effort required to significantly impact the challenges facing the development of novel antibacterial agents targeted for emerging MDR pathogens is too great for any single entity; collaboration is essential. Furthermore the diversity of skill sets required to tackle the challenges faced requires contribution from a number of key stakeholders. For example, the lack of a robust pipeline illustrates the scientific challenges that the industry faces; consequently, a framework for sharing knowledge and resources across distinct companies, small and medium sized enterprises (SMEs), and academia is needed

to increase the success of antibiotic research and development (R&D). It is essential that the antibiotic research community works together to ensure that societal needs for novel and effective antibiotics are fulfilled for the foreseeable future.

POTENTIAL SYNERGIES WITH EXISTING CONSORTIA

The proposed Topic 5 addresses areas for which there are complementarities/synergies with other initiatives on AMR in particular:

- Joint Programming Initiative AMR <http://www.jpiamr.eu/>
- EARS-net:http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/about_EARS-Net/Pages/about_network.aspx
- ESAC-NET:<http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx>
- NIH initiative to set up a clinical research network on antimicrobial resistance: <http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-019.html>
- In addition to collaboration with the IMI project COMBACTE, potential synergies may be developed with other existing IMI projects such as RAPP-ID. This project deals with the development of rapid point-of-care test platforms for infectious diseases and will tackle the problem of early diagnosis of microbial resistance. The work of RAPP-ID will bring important contributions to the testing of new antibiotics in clinical trials.
- Portfolio of FP7-funded projects in the area (see http://ec.europa.eu/research/health/infectious-diseases/antimicrobial-drug-resistance/index_en.html)
- Complicated Intra-Abdominal Infections Observational European study (CIAO Study).

The expressions of interest should clearly outline the unique properties of the proposed plan of work and also how potential interaction with these initiatives would be managed, avoiding at the same time potential duplications and overlaps of activities.

COLLABORATION WITH ND4BB CONSORTIUM COMBACTE

The successful applicant consortium will be expected to collaborate with COMBACTE via a memorandum of understanding to build on an objective of ND4BB to develop a self-sustaining clinical and laboratory investigator network (CLIN-net, LAB-net) and study design capability (STAT-net) within Europe.

THE OPEN CALL PROCESS FOR ADDITIONAL BENEFICIARIES TO PERFORM TASKS

When open Calls from within the existing consortium are required to engage additional beneficiaries, these will be handled by the consortium with guidance from the IMI JU. The consortium will propose procedures for implementing an open and competitive Call(s) in order to recruit investigators for the conduct of clinical trials as required in response to protocol requirements. The procedures will comply with the conditions established in the IMI model grant agreement¹⁶ and will be based on the guiding principles provided below:

- The selection shall be based on openness, transparency, efficiency and equal treatment.

¹⁶ Article II.43 of the IMI model grant agreement (IMI-GB-DEC-2013-3).

- Each open and competitive Call shall explicitly describe:
 - the activities to be carried out, the required capacities and the related dedicated budget;
 - the rules for participation (eligible entities);
 - the applicable evaluation, submission and selection procedures.

Based on evaluation outcome the consortium will submit a report to IMI providing evidence that the principles of openness, transparency, efficiency, and equal treatment have been fulfilled. The costs incurred by the consortium in relation to each open and competitive Call may be reimbursed or considered as in-kind contribution provided that the eligibility criteria laid down in the IMI grant agreement are fulfilled special clause for non-EU contribution (special clause 13b).

OVERALL OBJECTIVES

- Increase the efficiency of antibiotic R&D through analysing observational clinical and microbiological data sets and making recommendations for the development of novel antibiotic agents for MDR Gram-negative pathogens
- Understand the clinical management and outcomes of patients with serious hospitalised infections to validate our understanding of the clinical outcomes for patients in areas of emerging and endemic antibiotic resistance.
- Support the sustainability of ND4BB supported investigator and laboratory networks.
- Conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for novel agents directed towards treatment, prevention or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics or clinical endpoints with the aim of reducing the size and cost of clinical trials.

OVERALL EXPECTED DELIVERABLES

- Successful Phase 1, Phase 2, and/or Phase 3 clinical trials demonstrating the pharmacology, safety, and efficacy of new antibiotics against priority pathogens.
- Observational clinical and microbiological data relevant to the future use and development of novel products.
- Working with ND4BB to support for the build of a functioning investigator network(s) for the conduct of antibacterial clinical trials and non-interventional trials in European geographic regions with high levels of resistance.

Activities to be undertaken in Topic 5 will be staged according to pre-defined milestones and regulatory approval. Applicants should propose innovative research approaches to WPs 1-3 (Part A) and WPs 4-6 (Part B).

PART A – Conduct of observational clinical research to inform the design, conduct and interpretation of development programmes for antibacterial agents targeted MDR gram-negative bacteria.

- WP1: Retrospective observational study to assess the clinical management and outcomes of patients with hospitalized complicated intra-abdominal infection or nosocomial pneumonia in areas of endemic and emerging Gram-negative multi-antibiotic resistance.

- WP2: Prospective observational study to assess the clinical management and outcomes of patients with serious hospitalized infections known or suspected to be caused by MDR Gram-negative bacteria.
- WP3: Programme management, collaboration with the other ND4BB projects and dissemination.

PART B - Conduct of Clinical therapeutic studies to support the development of Aztreonam-Avibactam (ATM-AVI)

- WP4 : Phase IIa pharmacokinetic/pharmacodynamic analysis of ATM-AVI in patients with serious infections caused by Gram-negative pathogens.
- WP5 : Phase III randomised, multicentre, clinical study to evaluate the efficacy and safety of ATM-AVI in the treatment of serious infections caused by Gram-negative pathogens proven or strongly suspected to be caused by multi-drug resistant pathogens including metallo- β -lactamase producers.
- WP6 : Management of ATM-AVI Clinical programme, and integration with Topic 5 and ND4BB.

EFPIA PARTICIPANTS

AstraZeneca, Basilea, Cubist, GlaxoSmithKline.

INDICATIVE DURATION OF THE PROJECT

The indicative duration of Topic 5 is 5 years; however, the project duration may be shortened depending on the study designs implemented. Estimated start dates and WP durations are provided within the description for each WP.

INDICATIVE BUDGET

The indicative in-kind contribution from EFPIA is EUR 41.55 million, and from IMI JU is EUR 30.55 million.

The total budget is to be divided among the 6 WPs, along the following indications:

Part A:

- WP 1: The indicative budget is €0.34M EFPIA; €0.96M IMI JU
- WP 2: The indicative budget is €0.61M EFPIA; €3.99M IMI JU
- WP 3: The indicative budget is €1.05M EFPIA; €1.05M IMI JU

Part B:

- WP 4: The indicative budget is €6.5M EFPIA; €6.5M IMI JU
- WP 5: The indicative budget is €32.0M EFPIA; €17.0M IMI JU
- WP 6: The indicative budget is €1.05M EFPIA; €1.05M IMI JU

Allocation of funding, milestone progression decisions and the conduct of Part B (WPs 4 and 5) clinical programme.

The Applicant Consortium should apply with EOIs that address all WPs and include suggestions for biomarkers relevant to study endpoints. Approximately €1.5M is available for biomarker and diagnostic research for WP 2, and WP 5 and is included in the indicative budget figures provided above. Applications for biomarker research must align with the proposed endpoints for the studies, must not deter from the successful conduct of the programme, and should aim to inform the clinical development pathway for ATM-AVI and future compounds where appropriate. AstraZeneca, as EFPIA sponsor company for drug candidate ATM-AVI, is currently assessing the most appropriate and feasible development programme during a dynamic period of change for both regulatory requirements and business models for pathogen-targeted antibiotics. AZ will balance the final regulatory advice, scientific requirements and the overall feasibility of the

development plan when deciding on the appropriate studies to undertake. The requirement to undertake the in-patient PK/PD analysis as described in WP 4 or to include it as part of the WP 5 clinical study will be determined as soon as all the external regulatory and expert opinion has been assimilated and reviewed by the EFPIA company internal governance and discussed within the Consortium. Final decision rests with the EFPIA partner as the investigational medicinal product (IMP) owner and sponsor.

Furthermore the success of drug development is uncertain; only a small percentage of those drug candidates entering clinical trials enter the marketplace. Funding for the clinical studies described in WP 4 and WP 5 will therefore be allocated in a stepwise manner based on milestones review, with the inclusion of the EMA regulatory review and EFPIA sponsor company governance process.

The study results from WP1 and WP2 and other EFPIA partner sponsored research, as well as guidance of regulatory agencies, are expected to impact plans for the conduct of WP 5. The decision to carry out and fund WP5 will depend on the outcomes of WP2 and subsequent regulatory interactions.

The successful conduct of the global phase III programme for ATM-AVI will depend of the involvement of other investigators to conduct non-EU components of the trial. The applicant consortia may need to enter into a collaboration with such investigators if required.

If required, open Calls as described above may be launched within the Consortium to identify additional beneficiaries to ensure the successful delivery of WP2 and WP5. The budget for the additional partners to be recruited through an open Call will have to be already agreed by the Consortium at the time of the Grant Agreement signature.

PROPOSED PROJECT ARCHITECTURE

The Applicant Consortium is expected to address all the research objectives in this Topic 5 and make key contribution to the defined deliverables in synergy with the EFPIA consortium.

PART A: Conduct of observational clinical research to inform the design, conduct and interpretation of development programmes for antibacterial agents targeting MDR gram-negative bacteria.

Key Objectives

- Increase the efficiency of antibiotic R&D through analysing observational clinical and microbiological data sets and making recommendations for the development of novel antibiotic agents for MDR Gram-negative pathogens
- Understand the clinical management and outcomes of patients with serious hospitalised infections to validate our understanding of the clinical outcomes for patients in areas of emerging and endemic antibiotic resistance.
- Support the sustainability of ND4BB supported investigator and laboratory networks.

The following workpackages outline proposals for non-interventional clinical research that is intended as a first-step to provide contemporary data on the clinical management patterns and outcomes of hospitalized patients with serious infections caused by MDR organisms.

There is limited information on the clinical management, antibiotic treatment and clinical outcomes of patients with infections suspected to be caused by these pathogens. This is particularly highlighted in regions of high prevalence of antibiotic resistance eg. South East Asia, Southern and Eastern Europe. The aim of this research is to understand the management of two disease settings initially:

1. Complicated intra-abdominal infection (cIAI)
2. Nosocomial pneumonia (including ventilator-associated pneumonia) (NP)

in countries in Europe (eg. Greece, Turkey, Italy, Spain, Balkan nations) where high MDR prevalence is known to exist. This initial retrospective non-selective approach where all patients with cIAI or NP are included will constitute the first phase of the work. A subsequent prospective phase will include patients with cIAI / NP only where infections are suspected or known to be caused by MDR Gram-negative bacteria. There is an expectation to combine the data sets generated from these studies with country-specific epidemiological data, and data from any similar study programmes outside Europe, e.g. Asia, Latin America and USA.

A key outcome of this research will be to understand the clinical and microbiological outcomes for patients treated with best available therapy (BAT) in these regions. This will inform the rational design of future studies of antibacterial agents targeted against specific antibiotic resistant mechanisms and possibly serve as acceptable historical comparator control data set for regulatory agencies in the context of limited-use antibacterial registration packages.

Applicant Consortia are expected to be aware of complementary and potentially duplicative planned/ongoing research, and to identify how the potentially varied projects may be most usefully integrated from an operational, data management, scientific and clinical perspective. There is an understanding that the call text highlights the key data elements that are to be captured, but is providing limited specific design information to enable the applicants to have the opportunity to design a programme within a framework and budget figure provided.

WP1: Retrospective observational study to assess the clinical management and outcomes of patients with hospitalized complicated intra-abdominal infection or nosocomial pneumonia in areas of endemic and emerging Gram-negative multi-antibiotic resistance.

Applicant consortia are invited to outline an approach to conduct this retrospective observational study based on the framework provided in this text and within the indicative budget.

Estimated Study Start: End of Q1 2014

Estimated Study Duration: 6 to 12 months

Study Rationale:

The aim of the initial retrospective study is to provide recent (within a maximum of 2 years preceding study start) information on the clinical management, microbiological characteristics, antibiotic treatment, clinical outcomes for patients with cIAI and/or NP. This study will identify patients with associated risk factors for treatment failure and investigate the relationship between treatment failure and both prevalence of resistant organisms and specific clinical outcomes. Specific knowledge of the management of both cIAI and NP across the selected geographies is important to inform design of prospective observational research focusing on the those infections with a known or suspected MDR pathogen and facilitate the rational design and interpretation of interventional studies for

antibacterial therapies targeted to limited populations with infections due to bacteria with specific antibiotic resistance mechanisms.

Study design and population

Multinational, multicentre, observational, retrospective cohort study of hospitalized patients with NP and cIAI diagnosed within 2-years prior to study start. The study will be performed over an estimated 6 to 12 month period in approximately 1000 patients (700 cIAI; 300 NP) from at least 6 countries (Greece, Turkey, Italy, Spain, Selected Balkan nations eg., Bulgaria Croatia, Serbia and Romania). The number of sites per country will depend on the existence of hospital networks in the states to conduct the work but is expected to range from 5-10 per country. Diagnosis of NP and cIAI will be determined by chart review and electronic records where appropriate by the investigator based on pre-agreed ICD-9 codes or similar methodologies.

Study Objectives

To provide accurate clinical and microbiological data in patients with NP and cIAI in the selected countries and to evaluate and quantify patient and disease characteristics, treatment options and clinical outcomes. Selected objectives may include the following:

- describe the hospitalized patient population with NP and cIAI demographically, and in relation to pre-existing co-morbidities and MDR-related risk factors
- clinical management including time to initiation of antimicrobial therapy, time to culture result, and the specifics of the antimicrobial and other therapeutic interventions utilized in patient management
- clinical outcomes (morbidity, mortality, hospital stay, time in ICU, ventilator use)
- treatment failures (tolerability-related, breakthrough infections including blood stream infections , secondary infections, emergent morbidity)
- specific treatment failures related to documented antibiotic resistance
- assessment of clinical prediction for carbapenem resistant Enterobacteriaceae infections
- population prevalence of antibiotic-resistant infections

Indicative budget: The cost for the proposed study is estimated to be €1.3M (€0.34M EFPIA; €0.96M IMI JU).

EFPIA contribution: Infectious disease clinical development expertise (infectious disease epidemiology, microbiology and surveillance, clinical, project management, data management, and biostatistics) and oversight where required. Complimentary research conducted outside Europe. Direct financial contribution by the sponsoring EFPIA company, if required, to supplement the study costs (up to 25%) incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.

WP 2: Prospective observational study to assess the clinical management and outcomes of patients with serious hospitalized infections known or suspected to be caused by MDR Gram-negative bacteria

Applicant consortia are invited to outline an approach to conduct this prospective observational study based on the framework provided in this text and within the indicative budget

Estimated Study Start: after WP 1 is complete (End of Q1 2015)

Estimated Study Duration: 2 years

Study Rationale

The aim of this prospective study is to build on the baseline information provided by WP1 and examine the clinical management, microbiological and treatment profiles of hospitalized patients known or suspected to be caused by the following MDR Gram-negative bacteria ;

- a) Carbapenem resistant *Enterobacteriaceae*
- b) Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

This study will identify patients with associated risk factors for both clinical and microbiological treatment failure and link treatment failure to both prevalence of these specific resistance mechanisms and specific clinical outcomes. An assessment of the current best available therapy (BAT) for infections due to these pathogens is required to understand the clinical and microbiological efficacy and tolerability of the preferred options and regimens. This will provide baseline data on "comparator" BAT to inform the rational design and interpretation of interventional studies for antibacterial therapies targeted against limited populations with infections due to bacteria with these specific antibiotic resistance mechanisms.

Study design and population

Multinational, multicentre, observational, prospective cohort study of hospitalized patients presenting with either;

- 1) cIAI
- 2) Nosocomial Pneumonia (NP)
- 3) Nosocomial Bloodstream Infections (BSI)

Known or suspected to be caused by either

- a) Carbapenem resistant *Enterobacteriaceae* and/or
- b) Carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

Patients with infections with suspected but not confirmed carbapenem resistant bacteria will be followed and included in all subsequent analyses as a separate cohort. Causative organisms demonstrated to be carbapenem susceptible will be categorized for absence or presence of an ESBL phenotype.

The study will be performed over an estimated 2-year period with a target enrolment of 1000 patients from at least 6 countries (Greece, Turkey, Italy, Spain, selected Balkan nations eg., Bulgaria, Croatia, Serbia, and Romania). The number of sites per country will depend on the existence of hospital networks in the identified states with the ability to conduct the work but would range from 5-10 per country. Diagnosis of NP, cIAI and nosocomial BSI will be based on pre-agreed ICD-9 codes or similar methodologies.

Study Objectives

To provide accurate clinical and microbiological data for hospitalized patients with infections known or suspected to be caused by selected antibiotic resistant Gram-negative pathogens with the aim of

- a) understanding clinical outcomes in relation to underlying resistance mechanisms across cIAI, NP and nosocomial BSI
- b) Evaluating the efficacy and tolerability of BAT for cIAI, NP and nosocomial BSI due to selected antibiotic resistant bacteria.

Selected objectives may include the following;

- describe the hospitalized patient characteristics demographically, and in relation to pre-existing co-morbidities and MDR-related risk factors (clinical presentation
- clinical treatment including empiric and definitive therapy, time to initiation of antimicrobial therapy, time to culture result, and the specifics of the antimicrobial and other therapeutic interventions utilized in patient management

- clinical outcomes (including morbidity, mortality, hospital stay, time in ICU, ventilator uses)
- treatment failures (tolerability related, worsening infection, breakthrough infections including BSI, secondary infections, emergent morbidity)
- specific treatment failures related to documented antibiotic resistance
- identification of appropriate host specific biomarkers to aid prediction of serious clinical outcomes

Indicative Budget: The cost for the proposed study is estimated to be €4.6M (€0.61M EFPIA; €3.99M IMI JU).

EFPIA contribution: Infectious disease clinical development expertise (infectious disease epidemiology, microbiology and surveillance, clinical, project management, data management, and biostatistics) and oversight where required. Direct financial contribution by the sponsoring EFPIA company, if required, to supplement the study costs (up to 25%) incurred by public partners eligible for IMI funding ensuring that 100% of these costs will be reimbursed.

WP3: Programme management, ND4BB Collaboration and Dissemination

Estimated Start: 2Q 2014

The main purpose of this WP will be to ensure effective programme management, collaboration with COMBACTE, ensure collaboration between Topic 5 investigators, additional ND4BB projects and those in other related consortia, AMR research collaborations and ensure coherent dissemination of ND4BB results to the broader scientific community.

In order to ensure effective communication and collaboration between projects funded under the ND4BB programme, a dedicated team will work with members of the other ongoing projects /future topics to:

- Develop standard communication tools for all the projects funded under the AMR research area/ND4BB programme, e.g. standard templates, externally facing website etc.
- Ensure ND4BB dissemination to the external community is coherent and aligned across all projects /website strategy etc
- Ensuring data from all projects is deposited in the ND4BB data hub in accordance to the ND4BB framework
- Arrange bi-annual meetings between all ND4BB investigators
- Establish a ND4BB Scientific Advisory Board consisting of leading academics and key stakeholders
- Development of processes for the effective alignment of the Topic 5 consortium investigators with the COMBACTE Clin-Net investigator network

Indicative Budget: €2.10M

EFPIA Partner Contribution: Project/Alliance Management personnel if required, meeting facilities, communication expertise. Provision of workshops/seminars/Q&As. Providing training and oversight for ensuring GLP standards for Consortium laboratories, Providing training and oversight to ensure clinical and laboratory sites remain "audit ready." Sharing of learning from clinical networks and the conduct of clinical trials in emerging economies. Information/expertise in clinical trial design, epidemiologic methods, infectious disease surveillance, regulatory requirements, quality assurance monitoring, clinical microbiology requirements and data quality standards.

PART B: Conduct of Clinical therapeutic studies to support the development of Aztreonam-Avibactam (ATM-AVI)

Key objective

- Conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for a novel β -lactam/ β -lactamase inhibitor combination directed towards treatment, prevention or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics, or clinical endpoints with the aim of reducing the size and cost of clinical trials.

Metallo- β -lactamases (MBL) producing Gram-negative pathogens usually have complex patterns of multidrug-resistance. They pose a particular health threat because of their potential for rapid global spread both in community and hospital settings and because there are limited treatment options. Although aztreonam is one of the few established antibiotics that is not hydrolysed by metallo- β -lactamases, its clinical utility is limited because the majority of MBL-producing pathogens co-express serine- β -lactamases that inactivate aztreonam. Combining aztreonam with avibactam, a β -lactamase inhibitor, is expected to restore the clinical utility of aztreonam as avibactam inhibits multiple types of serine-based β -lactamases, including Ambler Class A extended-spectrum β -lactamases (ESBLs), Class A *Klebsiella pneumoniae* carbapenemase (KPC), Class C (AmpC) enzymes, and some Class D enzymes (notably OXA-48).

Infections caused by pathogens carrying MBLs are currently relatively rare in the United States (US) and most countries in the European Union (EU); however, there have been outbreaks noted and the prevalence of these pathogens is increasing globally. Within the medical community, there is significant concern that, like other MDR pathogens (such as those producing KPCs), MBL-producing pathogens are associated with increased mortality and morbidity for patients and increased treatment burdens on healthcare systems. Together, the global emergence of MBL-producing pathogens and the expected consequences point to a significant emerging unmet need for new therapy options to treat serious Gram-negative infections proven or strongly suspected to be caused by MDR pathogens producing MBLs. AZ-FC consider that ATM-AVI could address this need; however, as MBLs are currently rare in many countries, there are significant challenges to generating the clinical evidence needed to show activity against these pathogens.

AstraZeneca and Forest-Cerexa (AZ-FC) are proposing development of the combination product aztreonam-avibactam (ATM-AVI) for the treatment of serious Gram-negative infections proven or strongly suspected to be caused by multiple-drug resistant (MDR) pathogens producing metallo- β -lactamases (MBLs) in addition to other resistance mechanisms. . In preclinical *in vitro* and *in vivo* models, ATM-AVI shows promising activity against the most common types of MBL now in circulation.

The clinical development plan is being developed based on current AstraZeneca interpretation of regulatory advice. This is subject to change and could impact the extent of development work that is suitable to be conducted within the IMI JU ND4BB programme. Elements of the development plan that are currently identified as being suitable for the IMI ND4BB programme are outlined below.

Programme overview. The combination of aztreonam and avibactam provides an unusual opportunity to combine two very well understood molecules. Aztreonam is a monobactam antibiotic with > 25 years of on-market experience. It has a well-established pharmacokinetic, safety, and efficacy profile. Avibactam (formerly known as

NXL-104) is a novel beta-lactamase inhibitor that protects aztreonam from the most common circulating beta-lactamases (See References). Avibactam is being studied in parallel by AZ-FC in separate combinations with ceftazidime and ceftaroline.

The aggregate pharmacokinetic, safety, and efficacy profile of avibactam from these studies now exceeds 600 exposed subjects and in particular includes Phase 2 efficacy data with both the ceftazidime-avibactam and ceftaroline-avibactam combinations. By building on the aggregate database for these molecules, AZ-FC is able to propose the highly abbreviated and focused development program outlined below.

PART B overall budget: €64.1M (EFPIA €39.5M/ IMI €24.5M)

WP 4: Phase IIa pharmacokinetic/pharmacodynamic analysis of ATM-AVI in patients with serious infections caused by Gram-negative pathogens

Prospective Start date: Early Q1 2014 for a first subject inclusion (FSI) target of late Q2 2014

Study Rationale:

This is a prospective, randomised, multicentre, assessor-blind, parallel group, study to determine the PK, safety, tolerability and efficacy of ATM-AVI versus meropenem in the treatment of hospitalised adults with cIAI or NP including VAP. The study will randomise approximately 75 patients in a 2:1 ratio (ATM-AVI: meropenem.)

The fundamental rationale underlying this study is to investigate and understand the PK of ATM-AVI in a patient population similar to the intended target population for the ATM-AVI product and to support, in terms of empiric evidence, the extensive PK modelling assessments based on the prior Phase 1 study in healthy volunteers and existing knowledge with regard to ATM and AVI in the target patient population from other development programmes.

Study objectives:

Primary objective:

Assess the safety and PK of ATM-AVI patient population with serious Gram-negative infections.

Study design:

The proposed study is a phase 1b/2a randomised (2:1), active controlled study in patients with serious bacterial infections known or suspected to be caused by Gram-negative bacteria. 75 patients, from approximately 35 sites, with serious infections caused by Gram-negative pathogens with cIAI anticipated to be the predominant clinical infection.

Patients will be randomised to ATM-AVI + metronizadole or meropenem in a 2:1 ratio. Patients will be treated for a minimum of 5 days and a maximum of 15 days. PK samples will be taken on day 1 and day 5. Additional objectives include test of cure at day 25 and microbiological response rates.

Indicative budget: €13M (EFPIA €6.5M/ IMI €6.5M)

WP 5: Phase III randomised, multicentre, clinical study to evaluate the efficacy and safety of ATM-AVI in the treatment of serious infections caused by Gram-negative pathogens proven or strongly suspected to be caused by multi-drug resistant pathogens including metallo- β -lactamase producers.

Prospective Start Date: Depending on final agreed development plan with regulatory agencies and internal governance but the possible start date is 2H 2014.

Study rationale

AZ-FC propose conducting a randomized, multicentre, approximately 400-patient, assessor-blinded study in regions known to be endemic for MBLs to assess the efficacy and safety of ATM-AVI compared with meropenem plus colistin in the treatment of selected serious Gram-negative infections proven or strongly suspected to be caused by MDR pathogens producing MBLs. With a target enrolment goal of at least 20 patients with infections proven to be caused by pathogens producing MBLs per treatment group, AZ-FC estimate that approximately 200 patients identified at risk for these infections will be enrolled per treatment group. Enrolment may continue beyond 400 patients if at least 20 patients confirmed to be infected with MBL-producing pathogens have not been randomized into each of the two treatment arms.

The proposed study design reflects the importance of gaining experience with ATM-AVI in the treatment of patients who have infections caused by pathogens producing MBLs in a manner that (1) permits comparison with best available therapy, (2) minimizes the practical difficulties of recruiting patients with rare Gram-negative infections caused by pathogens producing MBLs, (3) maximizes the potential for completing the study in a manner that addresses the urgent medical need caused by the emergence of pathogens producing MBLs, and (4) produces meaningful clinical data that can be interpreted relative to preclinical data and human PK/PD data.

The indications chosen for study, cIAI and HAP/VAP, are both serious infections and are likely to be caused by the bacterial species that produce MBLs. The proposed primary objective is to evaluate efficacy at test of cure (TOC) in the modified intent-to-treat (MITT) population. Clinical cure rate at the TOC visit is proposed as the primary efficacy variable. Cure is defined as complete resolution or significant improvement of signs and symptoms of the index infection such that no further antimicrobial therapy, drainage, or surgical intervention is necessary.

Study objectives:

Primary objective:

- Efficacy of ATM-AVI compared to meropenem - colistin at test of cure (TOC) in MITT population

Secondary objectives:

- Efficacy in the Clinically Evaluable (CE) population
- Microbiological response at end of therapy (EOT), TOC and Late Follow Up (LFU) in the modified intention to treat (mITT) and microbiologically evaluable (ME) populations
- PK of ATM-AVI and relationship between exposure and clinical and microbiological response
- Safety and tolerability profile of ATM-AVI compared to meropenem-colistin.
- 28-day mortality

Study design

300 patients globally with known or suspected MDR Gram-negative pathogens randomized to ATM-AVI or meropenem plus colistin (2:1). Patients will be included with a cIAI or hospitalized acquired pneumonia/ventilator acquired pneumonia (HAP/VAP). The

target enrolment of 200 patients in the ATM-AVI – treated arm is intended to include at least 20 patients with infections proven to be caused by pathogens producing metallo- β -lactamases.

European involvement in Global Phase III:

AstraZeneca needs to ensure that the study provides at least 10% of the total patients/arm with known MBL infection. Therefore the majority of sites will be located in regions that are endemic for MBL infections (e.g., Indian Subcontinent). Sites within Europe must not dilute but be additive to the goal of achieving these numbers of MBL infections. AstraZeneca is expecting surveillance data that will inform the extent of involving IMI qualifying countries such as Greece, Israel, Turkey, UK, Balkan states, Spain, Italy, etc. Currently the expectation is that there could be approximately 20 sites in EU with a target patient number of approximately 125. This is subject to change based on emerging data.

In addition to the main objectives of the study, patient samples will be analysed via selected rapid identification platforms and compared with classic microbiology results to determine degree of correlation. This work would be in partnership with a diagnostic manufacturer and would include analysis of samples from study patients with cIAI and nosocomial pneumonia.

Indicative budget: €49 (EFPIA €32M/IMI €17M)

WP 6: Management of ATM-AVI Clinical programme and integration with overall Topic 5 and ND4BB programme

Estimated Start: 3Q 2013

Estimated Study Duration: 5 years

The governance and decision-making as it relates to clinical development and progression of the ATM-AVI asset is the responsibility of the sponsor. As sponsor, AstraZeneca, is legally accountable for the safety of all patients on the trial, and will retain the right and responsibility for all decisions.

The overall purpose of WP6 is to:

- 1) ensure effective coordination of the clinical trial operations and management across WP 4 and 5 and integration with the AstraZeneca project team Programme Management
- 2) collaborate with other partners outside Europe involved in the global development of ATM-AVI
- 3) integrate with the overall Topic 5 (via WP3).
- 4) ensure adequate product and GCP training and qualifications of investigators within the Consortium conducting WP4 and WP 5.

The main purpose of this WP will be to ensure effective programme management of the ATM-AVI clinical programme within ND4BB, ensure collaboration with the overall Topic 5 programme and support WP3 in its alignment and collaboration with COMBACTE

Additional tasks include;

- Arrangement of training meetings among all Sub-topic 5B investigators; at least one face-to-face training prior to initiation of the project, and subsequently follow-up training (possibly via webcast, teleconference, etc)

- Coordination of clinical trial operations and management, including data management, as appropriate

Experienced clinical investigators, in collaboration with EFPIA partners, will function as coordinators and mentors within the consortium, facilitating information-sharing among the Consortium investigators and providing training to new investigators. Training will align where possible with the certification and training programme for the emerging COMBACTE Clin-NET investigator network.

EFPIA Partner Contribution: Project/Alliance Management personnel, meeting facilities, communication expertise. Provision of workshops/seminars/Q&As. Providing training and oversight for ensuring GLP standards for Consortium laboratories, especially those serving as central laboratories for WP 4 and WP 5. Providing training and oversight to ensure clinical and laboratory sites remain “audit ready.” Sharing of learning from clinical networks and the conduct of clinical trials in emerging economies. Information/expertise in clinical trial design, epidemiologic methods, infectious disease surveillance, regulatory requirements, quality assurance monitoring, clinical microbiology requirements and data quality standards.

Indicative budget: €2.1M (€1.05M EFPIA; €1.05M IMI JU)

INDICATIVE EXPECTATIONS FROM THE APPLICANTS:

The applicant consortium applying for this project should include the following:

Overall, the successful Applicant Consortium for Topic 5 must document in the EOI the capability for conducting observational non-interventional and therapeutic clinical trials in both the clinical indications of interest and also in the identified geographic areas. Applicants should be able to fulfil within the indicated time frame the patient recruitment and study personnel resourcing requirements of all studies described under Topic 5.

Participating sites must conduct studies in accordance with the ethical principles in the Declaration of Helsinki, and consistent with ICH GCP and the applicable local regulations.

Other requirements of successful Applicants include:

- Expertise in current standard of care for patients with complicated intra-abdominal infections, nosocomial pneumonia and nosocomial bloodstream infections.
- Expertise in observational study design and conduct
- Expertise in providing clinical project management, including cross-functional collaborations, budget/timeline management, and regular status reporting
- Expertise in establishing and complying with standards for data extraction, data recording, database architecture, data analysis, and data privacy principles
- Ability to provide bacterial isolates and associated microbiological and epidemiologic data to a central regional laboratory
- Experience in supplying on-site training to ensure compliance with clinical study protocols
- Expertise in GCP and local and global regulations as they pertain to clinical trial design
- Expertise in understanding the pathogenesis of the hospitalized infections due to MDR Gram-negative bacterial pathogens and in developing and performing relevant serologic assays on samples from clinical subjects, preferably under GLP conditions¹⁷
- Proposals for novel biomarkers and diagnostics to both identify patients with infections due to MDR Gram-negative pathogens and predict clinical outcomes for patients to be utilized in clinical trial designs.

¹⁷ Special consideration will be given to laboratories capable of acting as a central regional laboratory to provide serologic testing support to other member sites

Requirements Specific to WP 1 and WP2

- Member networks and sites that have experience of designing and implementing patient-based modules, observational retrospective and prospective research and or similar epidemiology protocols.
- Demonstrated ability to collect and report observational data on indications and patient infections of interest to the scope required.
- Observational research experts to create study protocols and to determine the relevant pathogens, antimicrobial agents, clinical correlates, and analyses.
- Ability to collect relevant samples for allied biomarker analysis.

Requirement specific to WP4 and WP5

The applicant consortium should ensure the expression of interest describes their ability to recruit and retain the targeted patient population in addition to describing recent clinical experience conducting randomized comparator controlled antibacterial studies. Sites should conduct trials in accordance with the ethical principles in the Declaration of Helsinki, and be consistent with ICH GCP and the applicable local regulations.

- Each hospital and healthcare institution engaging in ND4BB clinical studies should have the expertise and facilities (including quality clinical microbiology labs and expertise) to address all aspects of the outlined protocols. .
- Hospital and healthcare institutions with expertise in running clinical trials for hospital based infection to GCP standards.
- Have participants with the ability to fulfil the recruiting requirements of the studies **within the indicated time frame.**

The optimal sites should possess the following characteristics as a minimum (when specified only for studies targeting a specific indication) and preferably exhibit an ability to contribute multiple investigators who have expertise in different target disease indications that could be the focus of future Calls:

1. Clinical study experience with antibacterial treatments and the ability to follow patients upon discharge.
2. Demonstrated ability to recruit patients with the target characteristics (e.g., nosocomial pneumonia [including ventilator associated bacterial pneumonia] and or complicated intra-abdominal infections). For the Phase 3 trial, centres must have a reasonable likelihood of enrolling patients with infections caused by pathogens carrying MBLs based on previous experience of treating this type of patient.
- 3 In order to ensure recruitment goals for the trial can be met, the clinical research sites potentially to be recruited must demonstrate capacity to recruit and provide follow-up care in the proposed clinical trial, to at least 5 eligible patients over a 12 month period. Preferentially the site should have no other clinical studies that may compete for the target patient groups. Qualified sites that do have potentially competitive studies should be assessed to determine if they have sufficient patients and appropriately qualified and trained staff to participate in multiple studies. Sites should be able to comply with procedures for data recording, reporting and retention.
 - Minimum clinical microbiology laboratory requirements include Laboratory accreditation by a country specific agency
 - Documentation of appropriate quality control/quality assurance programme
 - Ability to process (inoculate appropriate media and incubate) all respiratory specimens
 - including sputum, endotracheal aspirate, bronchoalveolar lavage, deep surgical specimens, and blood cultures within 2 hours from collection time if specimen is kept at room temperature or within 24 hrs of collection if stored at 2-8°C

- Ability to perform Gram stain on respiratory specimens and report number of white blood cells (WBC) and epithelial cells per 100x field, and bacteria (semi-quantitation and morphology) per 1000x field
- Ability to report the growth of bacteria semi-quantitatively as growth per corresponding quadrant on agar media (i.e. 1+, 2+, 3+, etc.)
- Ability to perform minimal antimicrobial susceptibility testing (eg, disk diffusion tests) using CLSI methodology
- Ability to subculture any isolated pathogens and send to a central laboratory for further testing (i.e. identification confirmation, susceptibility testing, etc.)
- Ability to properly store any isolated pathogens and Gram stain slides until instructed by study monitor to discard
- Other study specific laboratory requirements (e.g., a study may require the ability to store specimens)
- Laboratory results reported to the investigator via electronic data capture, hard copy or fax

GENERAL PRINCIPLES FOR ALL STUDIES CONDUCTED UNDER ND4BB

Study Management

All clinical studies conducted in ND4BB will be conducted to Good Clinical Practice (GCP) standards to ensure that no process or data quality issues arise to jeopardize the outcome of the studies. In the case of the clinical trials, protocol compliance data quality and data integrity are essential to avoid the risk of a failed regulatory process. Noncompliance can severely jeopardise regulatory approval and pose ethical issues related to informed consent agreements with patients.

Due to the complexities of designing a global clinical trial to support regulatory submissions, it is common for both industry-funded and FP7 projects that a clinical research organization (CRO) is engaged to implement the study design and monitor clinical sites to ensure compliance. While this is the preferred approach, in some instances it may be preferable for a SME/CRO in collaboration with the sponsoring company's internal operations groups to implement these clinical trials.

There are two possible scenarios for the selection of the CRO:

- 1) The public entities recruit subcontractors under full respect of all applicable rules and regulations. In order to make up the funding gap arising out of the maximum 75% reimbursement of research activities, EFPIA companies foresee to provide a direct financial contribution to concerned beneficiaries.
- 2) In the event that the EFPIA fund the CRO in its entirety as part of their contribution in kind, the CRO will be appointed directly by the sponsoring EFPIA company according to normal internal procurement practices. The EFPIA company must be able to demonstrate 'value for money' to satisfy external auditors; otherwise, this cannot be counted as contribution in kind.

The criteria for the selection and identification of the CRO will be agreed upon during the formation of the full project proposal and project negotiation phase in accordance with the applicable rules, with the intention of having the contract with the CRO in place as soon as the project agreements are completed. This CRO will be accountable for delivering the operation of the clinical trial, including monitoring of all investigational sites operating under Good Clinical Practice (GCP) standards. This CRO, depending on its global capabilities, may be responsible for ensuring coordination across all clinical trial sites (ie, those funded directly by the sponsoring EFPIA company as well as those engaging as part of the Applicant Consortium). This relationship will be governed through a specific Clinical Trial Agreement among the sites, Sponsor and CRO. Where CRO

activities reside outside of the EU, this will be funded directly by the EFPIA Sponsor. In some clinical trials it may be possible that the EFPIA Sponsor may also recruit a CRO to manage non-EU based sites as part of a global study; in these situations an agreement between the EFPIA CRO and the consortium CRO will be established to ensure effective overall management of the trial. In all circumstances, only those hospital and healthcare institutions shown via site visits to be sufficiently compliant to be able to fulfil all aspects of the protocol to GCP standards will be permitted to recruit patients into the study.

Monitoring

Site Compliance

The EFPIA company that owns the asset will act as study trial Sponsor and as such will remain accountable for regulatory filings, pharmacovigilance, and all aspects of trial conduct. If a CRO is used, it will be responsible for ensuring effective monitoring of all sites with respect to medical governance, data management, and GCP requirements.

Trial-related decision making

Standard decision-making processes will apply to progression of clinical trials and will be the responsibility of the Sponsor. As the sponsoring company is legally accountable for the safety of all patients on the trial all decisions regarding trial progression or termination due to emerging safety issues will remain the responsibility of the sponsoring company. The Principal Investigator will be notified of any decisions to terminate or change a study in response to emerging safety data. In accordance with the requirements of the trial sponsor, the CRO will perform site inspections of investigator sites as needed to confirm the ability of the site to function up to GCP standards and to be capable of processing microbiology and serology specimens to laboratory certification requirements. Should a site fail to pass this inspection they would not be allowed to participate in the study, unless corrective measures can be taken by the site to address all critical insufficiencies.

Data Sharing in ND4BB

Data sharing is paramount to the success of ND4BB. Applicants Consortium will be expected to contribute data to the ND4BB Information Centre, as developed in the ND4BB project Translocation, and to participate in cross-project team meetings as appropriate to ensure learnings, knowledge, and skill sets are maximized across the ND4BB teams.

Clinical Trial Data

Disclosure of data from all ND4BB clinical trials supporting regulatory filings is subject to specific regulatory requirements with which EFPIA partners must comply. These regulations ensure that all data are presented and communicated in a responsible way by ensuring that efficacy data are presented with a balanced understanding/communication of the adverse event profile or other safety risks. Strict adherence to these regulations also ensures that data sharing activities will not be misrepresented as 'promotional activities,' as the conduct of such activities is prohibited prior to drug approval. While respecting these strict regulations, Sponsors of clinical trials conducted under ND4BB intend to disseminate results from trials conducted under the ND4BB programme as broadly as possible.

The goal of data sharing is to disseminate knowledge that is generally useful for others planning clinical trials. Examples of data sharing might include:

- Issues with specific inclusion criteria or endpoints
- Techniques for facilitating rapid enrolment of subjects at study sites
- Insights regarding pharmacodynamic markers/drivers of efficacy

Conversely, some data are very compound specific, may have special handling and reporting requirements due to regulatory concerns, and do not provide generalized

insight useful for other development programmes. The most obvious such data are the safety and adverse event data for a particular product.

To address all of these concerns, ND4BB-related work will be shared in several ways. First, protocols and summary results from studies conducted under the ND4BB programme will be posted on internet registers, and clinical trial Sponsors will aim to publish results as journal manuscripts in searchable, peer-reviewed scientific literature, ensuring the accurate and balanced presentation of data. As such, for all clinical trials conducted under the ND4BB programme, Sponsors will ensure that:

- Protocols and informed consent documents clearly outline the intent to post a protocol summary on a publicly available protocol register and the clinical trial summary results on a publicly available results register, and to publish the results in searchable, peer-reviewed scientific literature.
- Primary publication of the study results, whether positive or negative, preferably as a journal manuscript (including primary and secondary efficacy endpoints and safety results and, when medically informative, exploratory analyses) will be mandatory. Publication of trial results will also be accompanied by public disclosure of the full study protocol (which may be redacted for proprietary content) on the Sponsor's Clinical Study Register.
- Proposals for additional analyses and reporting of either aggregate or subject-level data pre- or post-approval are assessed for scientific merit, impact, and reporting concerns by the Principal Investigator and EFPIA Sponsor and will only be undertaken following final approval by the Sponsor. As noted above, reporting is legally required to be presented and communicated in a responsible way such that efficacy data are presented with a balanced understanding and communication of the adverse event profile or other safety risks. Such work is generally undertaken as collaborations between the clinical trial Sponsor and the proposer, with all analyses being reviewed and approved by the Sponsor prior to publication to ensure Sponsor policies regarding responsible communication are regarded (i.e. to ensure that the data is being used for appropriate scientific purposes in line with the original informed consents in addition to all local and national data privacy and data transparency policies).

In general, summary data from all clinical trials conducted under the ND4BB programme must be publicly posted within a reasonable period following study completion (typically considered the date of the last subject's last visit) or completion of the clinical study report. Once a clinical trial has been completed and the database locked for subsequent statistical analyses and reporting, data collected from study subjects at a specific investigator site can, at the Sponsor's discretion, be disclosed only to that specific investigator. Broad dissemination of any clinical trial data to investigators or other public entities will occur only as outlined above, as such data dissemination conducted "pre-approval" is considered as promotional and violates regulatory statutes.

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