

# Introduction to the IMI2 Antimicrobial Resistance (AMR) Accelerator programme

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## Background and problem statement

The discovery and development of new preventions and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge that is compounded by a low return on investment (RoI) for the pharmaceutical sector driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: [https://ec.europa.eu/health/amr/sites/amr/files/amr\\_action\\_plan\\_2017\\_en.pdf](https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf)). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on par with subjects such as HIV and Ebola. Additionally, drug resistant tuberculosis (TB), the largest single contributor to AMR health, mortality, and economic impact.

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no novel mechanism antibiotics for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life threatening multi-drug resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017 Executive Summary at the following link, [http://www.who.int/tb/publications/global\\_report/Exec\\_Summary\\_13Nov2017.pdf](http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf)) there is an acute need for the development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options. This applies to all types of TB (drug-sensitive (DS), multi-drug resistant (MDR) and extensively-drug resistant (XDR-TB)). A pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB has provided and will continue to lead to learnings that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

## Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines, including but not limited to new antibiotics, to treat patients with resistant bacterial infections in Europe and across the globe or to prevent them. Specifically, if successful, projects in the Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'phase 2-ready' assets over a roughly seven-year period.

The AMR Accelerator will provide, under one operational structure, a wide-ranging series of projects that will address many of the scientific challenges in AMR. The scientific scope will be broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the Accelerator will develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator will complement and augment the capabilities of the IMI ND4BB programme.

Progression of successful assets beyond the scope of the Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (<https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf><sup>1</sup>) should be taken into account.

The Accelerator will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: [https://ec.europa.eu/health/amr/sites/amr/files/amr\\_action\\_plan\\_2017\\_en.pdf](https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf)). The Accelerator will also directly address the IMI2 JU objective of 'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557>)

## AMR Accelerator programme structure

The AMR Accelerator programme consist of three pillars under which multiple actions are expected:

- **Pillar A:** Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C will be a maximum of EUR 237 230 000.

The EFPIA and Associated Partner in-kind contribution will be matched by IMI2 JU funding across the whole of the Accelerator and not necessarily 1:1 on an individual project or pillar basis.

The two-stage IMI2 JU Call 20 includes one topic (topic 7) under Pillar B to complement the actions funded under IMI2 JU Call 15 and IMI2 JU Call 16.

Future call for proposals could be launched at a later stage to select under each pillar additional research projects or networks depending on developing scientific needs and objectives in AMR research.

### **Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.**

The CBN will: 1) create a coordination and support group to assist in the effective management of projects across the Accelerator and; 2) deliver pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN will include projects to further basic science and discoveries to enable future drug discovery and development in the

<sup>1</sup> For example, points 3 and 4 from the 'Roadmap for Progress'.

prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the Accelerator related to TB will be conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial action in the CBN resulting from topic 7 in IMI2 JU Call 15 will implement a coordination and support group that will support operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also will focus on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

**Pillar B: Tuberculosis Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.**

The TBDDN will work to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform will be self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA please visit: <http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program>). It will provide ready-to-use services for rapid progression of available (1<sup>st</sup> line) new and innovative candidates. The platform will be partly supported by the coordination and support group from Pillar A but will include management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

Topic 8 of IMI2 JU Call 15 will result in an action that will create a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it will address the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Topic 7 of IMI2 JU Call 20 will result in an action that will develop and implement innovative, state of the art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. Additionally, it will exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

**Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.**

As in the CBN, the overall scientific scope in the PBN will be broad, including prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment (new antibiotics, non-antibiotic alternatives, formulation strategies, and combinations). Within this broad scope, the PBN will provide a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed or studied, including both pre-clinical work and potentially phase 1-3 clinical development. The PBN will also potentially be useful to generate new clinical/regulatory phase 3 pathways for pathogens such as NTM and to conduct phase 2 trials in TB.

Consortia selected under this pillar may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner)<sup>2</sup>. IMI2 JU Call 16, the first call under Pillar C, is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

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<sup>2</sup> See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").

## Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (which is under finalisation<sup>3</sup>) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 7 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement<sup>4</sup> will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE- 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for the first CBN action to provide day-to-day support of projects in the Accelerator, and will ensure exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN actions (IMI2 JU Call 15 topic 8 and Call 20 topic 7) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 (grant agreement under finalisation) to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable in each action resulting from topic 8 of IMI2 JU Call 15 and topic 7 of IMI2 JU Call 20. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions, as well as the IRP action of IMI2 JU Call 15 topic 1, with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

## Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the coordination and support group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the 'call to action' to address HIV/AIDS and on par with the public health threat. Consequently, public-private partnerships (PPPs) such as the framework provided by the IMI2 JU continue to be critical to that effort.

Excellent examples have been the previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio)). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge of maturing the TB pipeline from the selection of candidates to progression through phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

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<sup>3</sup> For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.

<sup>4</sup> See: [https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi\\_en\\_v5.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf)

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines on an area of critical scientific need.

The development of the Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- **Capability Building Network:**
  - play key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
  - enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
  - opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- **Tuberculosis Drug Development Network:**
  - enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
  - enable SME and/or academic groups to progress potential drugs from pre-candidate status through to 'ready for phase 2' status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
  - opportunity to work within a broad network on researchers focused on TB drug discovery.
- **Portfolio Building Network:**
  - opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value, and sharing risk. There will be potential to further extend such partnerships with EFPIA companies beyond the scope of the Accelerator following completion of project;
  - will allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at

[https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions\\_and\\_answers\\_on\\_the\\_AMR\\_accelerator\\_programme.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf).

## Topic: Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)

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### Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Antimicrobial resistance

### Specific challenges to be addressed by public-private collaborative research

Tuberculosis (TB) is the leading infectious cause of death worldwide.[1] To achieve the target of TB elimination by 2035, the WHO estimates that there is a funding shortfall of over USD1 billion per year in TB research. The treatment of drug-sensitive TB is an onerous regimen of four drugs for two months followed by two drugs for four months (six-months total), and multidrug-resistant TB may require treatment for up to two years. Many patients find adherence difficult, and the current drugs are associated with significant tolerability issues. Shorter and safer treatment regimens are urgently needed. Tuberculosis has a low or negative expected return on investment and therefore fails to attract funding: this call addresses this high unmet medical and public health need.

Currently, TB drug development involves 14-day monotherapy trials for early bactericidal activity (EBA) to identify the maximally efficacious dose for a new chemical entity (NCE). The standard trial design contains no option to change doses or de-escalate in-stream in response to emerging Pharmacokinetic-pharmacodynamic (PKPD) or safety data, resulting in a flat dose-response.[2] In Phase 2B, the efficacy of treatment combinations is then studied in eight weeks of dosing, with time-to-sputum-culture-conversion as the primary endpoint. This paradigm has multiple weaknesses: inadequate exploration of dose response; lack of innovative study designs to empirically determine optimal duration of therapy as well as inability to study multiple regimens in parallel. Moreover, there is a lack of Phase 2 biomarkers that adequately predict phase 3 outcome (relapse-free cure).[3][4][5]

Therefore, there is a critical need for innovative trial designs in TB. Efficient adaptive trial designs would accelerate clinical development in Phase 2, but cannot be implemented currently due to the lack of in-stream biomarkers for sterilising cure/relapse. Several RNA expression, cytokine, bacterial and radiological biomarkers have been proposed in the literature, but to date there has been neither comparison nor prospective validation of these biomarkers. A biomarker that predicts relapse at an individual level may further create opportunities for individualised medicine, or even permit creation/validation of trial simulations. These trial simulations could help optimise trial design, and facilitate in-stream decision-making in adaptive trials.

Private and public investment has been made in the discovery of NCEs but there is at present no mechanism for clinical exploration of these NCEs in innovative combinations. The collaboration of industry academics, clinicians and SME partners pooling resources and NCE's, developing adaptive trial designs alongside implementation of biomarkers, diagnostics and digital technology will make this a unique partnership. It will accelerate the development of combination regimens for the treatment of

the world's biggest cause of mortality in infectious disease, aligned with the World Health Organisation sustainable development goals.

## Scope

The objectives of this Call Topic are to develop and implement innovative, state of the art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. The funded action will define the duration and composition of novel treatment combinations that will shorten or simplify the standard of care, for drug resistant Tuberculosis, as well as prospectively validating biomarkers against the relapse endpoint. In addition, the funded action is expected to develop clinical trial simulations, evaluate new technologies to monitor and enhance treatment adherence, and develop an understanding of population pharmacogenomics, in all forms of active TB.

The funded action will develop a portfolio of ten NCEs that have completed first-in-human studies from a pool of existing NCE's supplied by EFPIA/Associated partners, and carry out Phase 2A (EBA) studies followed by Phase 2B/C efficacy and relapse assessment. The funded action will also study high quality NCEs that are either owned or controlled by (with the right to further develop) EFPIA, academics or SMEs that wish to perform TB Phase 2 studies performed by the consortium on their compounds (in monotherapy (Phase 2a) or combination (Phase 2b/c)). It is expected that minimum requirements for compounds entering the consortium would include lack of pre-existence resistance in the field (focus on drug resistant tuberculosis), a suitable safety and efficacy profile alongside suitable supplies of formulated product. Only molecules with a novel mechanism of action, not already existing within the portfolio, or with proof of a substantial improvement over existing compounds, would be accepted for Phase 2A EBA studies (please refer to EFPIA/AP contribution for pipeline current target classes). Acceptance of suitable molecules will be subject to due diligence by the governing bodies of the consortium. These NCEs will be studied alone in early clinical efficacy EBA studies and in combinations for relapse studies, including with recently approved drugs in innovative Phase 2 trials designed to accelerate drug development and maximise the chance of success in Phase 3. These trials may include innovative ways of combining drugs and new formulations in different phases of a regimen

The funded action will develop innovative trial designs able to define optimal treatment duration against endpoints that better predict the current Phase 3 endpoint of relapse and will improve efficiency by comparing multiple regimens in parallel within the same study.[6][7] Early interims will stop failing/futile arms, resulting in even greater efficiencies.

The funded action should also prospectively validate biomarkers against a relapse endpoint. The primary objectives of the biomarker work is to validate i) biomarkers able to accurately prioritise regimens for evaluation in phase 3, ii) biomarkers that are able to predict sterilizing cure/relapse at the individual patient level, and iii); a third, more ambitious objective, is to identify biomarkers that permit the building of a clinical trial simulation platform.

A combination of biomarkers that predicts relapse and guides treatment duration alongside innovative adaptive trials, would greatly accelerate drug development in TB by enabling in-stream adaptation of a clinical trial to prioritise evaluation of the most promising regimens. The simulation platform should embrace and validate data-driven technologies such as artificial intelligence/ machine learning (AI/ML) to set criteria for stopping arms and to determine treatment duration.

Clinical data generated in one population are not always applicable to other populations. The understanding of how host genetics influence TB outcomes are critical, but are often missing in early stage development. This can result in failures when therapies which have been validated in one population are then implemented in other populations. The applicant consortium is expected to study the influence of host genomic factors on drug factors, such as drug exposures and clearance in the patient, and to match these against a relapse endpoint. This would permit the selection of drugs and doses that are appropriate to particular populations or even to specific patients. It is anticipated that a proportion of the data generated in the funded action will be generated outside of Europe and this pharmacogenomic activity will therefore be critical to ensuring the applicability of that data to a European population.

Adherence is critical for efficacy of a treatment regimen. The proposed activities should exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

The consortium will develop and execute innovative adaptive trial designs to evaluate approximately ten NCEs and approximately ten combination regimens. To complete recruitment within relevant timeframes, the trial network should be able to enroll about one thousand TB patients annually. To achieve this level of recruitment, a proportion of patients may have to be recruited from highly endemic countries outside Europe. The consortium should propose a mechanism for the allocation of financial resources matched to actual patient recruitment costs which ensures meeting the objectives.

## Collaboration agreement(s)

The action funded under this call topic will be 'Pillar B, (Topic 2)' of the AMR accelerator. Please refer to Call 15 and 16 topic texts regarding 'collaboration agreements', and 'Questions and answers'<sup>5</sup> associated with both calls. This topic will be complimentary to the actions funded under Pillar A and B of the AMR accelerator.:

- IMI2 JU Call 15 topic 8, for using the generated pre-clinical regimen prioritisation to guide regimen selection for Phase 2B/C studies.
- IMI2 JU Call 15 topic 7 AMR Pillar A on selection of biomarkers for validation, standardisation and quality control of assays that are in common between AMR consortia

Moreover, this action will seek collaboration agreements with the actions that are funded under the following topic

- **IMI2 JU Call 15 topic 1**, the proposed phase 2 trial designs will be presented to the EMA and FDA for scientific advice and the proposed biomarker development framework will be presented to the EMA and FDA for biomarker qualification advice in co-ordination with this action and TB Drug Translational Development Collaboration (TDTDC) as necessary
- Individual-level patient data will be made publicly available through a sustainable data-sharing platform developed in co-ordination with **the projects arising from IMI2 – Call 15, topics 1, 7 and 8**.

When reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

The options regarding 'complementary grants' of the IMI2 JU Model Grant Agreement and the provisions therein (Articles 2, 31.6 and 41.4) will be enabled in the corresponding IMI2 JU grant agreements for all AMR accelerator projects.

## Expected key deliverables

The proposed activities will be expected to achieve the following deliverables for the implementation of innovative state of the art adaptive clinical trials, the development of biomarkers and the development of Artificial Intelligence

- Innovative, adaptive clinical trials
  - To develop strategies for adaptive dosing (escalation/de-escalation) and trial stopping criteria based on in-stream pharmacokinetic, efficacy and safety read-outs while building a pharmacokinetic-pharmacodynamic model, as appropriate.

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<sup>5</sup> [https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions\\_and\\_answers\\_on\\_the\\_AMR\\_accelerator\\_programme.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf)

- Successful submission of documents to EMA and FDA for scientific advice on proposed innovative trial designs by the end of the first year, and for innovative trials with novel endpoints, designs and analysis plans prior to study start as required.
  - An approved plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance.
  - A strategy for the standardisation of sample collection, laboratory assays, imaging protocols, radiation safety for subjects across a global study. This should include a plan for collaborating with **IMI2 JU Call 15 topic 7 AMR Pillar A**
  - Established clinical trial capacity with the ability to recruit approximately 1000 patients per year, spanning at least two WHO regions able to deliver regulatory trials in TB by the end of the first year.
  - An established Target Product Profile (TPP), Target Regimen Profile (TRP), aligned with that described by WHO, and due diligence criteria for the progression of assets within the consortium.
  - Applicant consortia should publish a Phase 2A (EBA) design that permits in-stream adaptation of dosing in response to pharmacokinetic and pharmacodynamic readouts, so as to permit the full characterisation of the dose-response curve.
  - Applicant consortia should publish a Phase 2B/C design that evaluates multiple regimens in parallel against novel endpoints related to the current Phase 3 endpoint (relapse and poor outcome), an ability to determine the optimal duration for a regimen, and interim(s) for futility that permit efficiency to increase as arms are dropped.
  - Establish a plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance.
  - Completed clinical trial data: Dose selection criteria for the UNITE4TB portfolio of Innovative NCEs based on completion and results from Phase 2A EBA, and Phase 2B/C combination studies Identification of at least one viable regimen for Phase 3 clinical trials, or a ranked list of viable treatment regimens (maximum four NCEs each), capable of shortening therapy and/or with a safety/tolerability/accessibility profile better than the current standard-of-care, and which are ready to enter Phase 3.
  - An established data sharing platform where individual level patient data are FAIR (Findable, accessible, Interoperable and Recoverable) and publicly available beyond the life of the consortium.
  - Reporting outcomes in compliance with the European Clinical Trial Directive. The applicant consortia must present a publication strategy that does not delay the external availability of individual level patient data beyond the lifetime of the consortium.
- Innovative biomarkers
    - A strategy for how published biomarkers will be prioritised and selected for evaluation and validation . For the avoidance of doubt, novel biomarker development is outside the scope of this action.
    - A strategy for early scientific engagement with the EMA and FDA, prior to clinical study start, to obtain regulatory buy-in for the proposed biomarker validation framework
    - A methodological framework to prospectively validate biomarkers to be used in adaptive trial designs to shorten drug development and expand clinical trial capacity, and ideally used as a surrogate marker of sputum culture conversion and sterilising cure.
    - Data package of prospectively validated model/panel of biomarkers to be used in clinical trials to shorten TB drug/regimen development duration, and ready for submission to the EMA and FDA for regulatory qualification.
- Pharmacogenomics

- Pharmacogenomics strategy for exploring how host genetic variation may influence drug absorption, target exposure, clearance, and patient outcomes resulting in pharmacogenomic PKPD models for individual NCEs.
- Clinical trial simulation tool
  - Developed clinical trial simulation tool(s) incorporating AI/ML to inform trial design, facilitate in-trial adaptation and, possibly, phase 2 trial waiver.
- Digital health technologies
  - A strategy for the evaluation of the impact of these technologies on adherence, and the impact of varying treatment durations on adherence in the field
  - Technology to evaluate the impact of treatment duration on adherence. Implement and validate digital health technologies to improve adherence to TB regimens within the currently proposed studies.
- Artificial Intelligence/Machine Learning
  - A strategy for regulatory agency advice and alignment with proposed AI/ML-based models.
  - Establish models that describe the role of individual biomarkers suitable for regulatory acceptance
- Biobank. Establish a sustainable biobank to make samples with linked de-identified clinical data collected from the consortium clinical trials publicly available beyond the life of the consortium.
  - Human biological samples collected as part of the clinical studies should be banked and made available to external researchers beyond the lifetime of the consortium. Samples provided to researchers should be linked to de-identified demographic and clinical study data in a manner compliant with GDPR.
  - The applicant consortia should provide a strategy for human biological sample tracking, access and management that is compliant with relevant European legislation.
  - A strategy for granting access to samples should also be presented (e.g., an independent panel for evaluation of proposed research plans).

## Expected impact

The objectives, deliverables and impact of the resulting action are well aligned with the mission and goals of IMI2 JU to deliver increased success rate of biomarkers and priority medicines in innovative clinical trials. The expected impact of the funded action will also help attain 2030 UN Strategic Development Goals and 2035 End TB Targets by:

- Providing new tools and understanding on how to progress TB science for the discovery and development of new clinical candidates and combinations thereof across the TB R&D landscape with special emphasis on innovative clinical trial design and development of novel biomarkers;
- contributing to the EU's ambition of being a 'best practice region' for addressing AMR, and profit from its medical capacity to individualize and implement into medical practice combination therapies addressing MDR/XDR;
- developing new knowledge and tools, innovative clinical trial designs, imaging technology, biomarkers and pharmacogenomics diagnostics and exploiting artificial intelligence for the development of new clinical candidates and combinations;
- enabling the progression of potential new safe, efficacious, shorter and affordable treatment solutions for TB patients worldwide, with the intent to improve the quality of life and life expectancy of TB patients;

- contributing to the development of a vibrant TB research environment in the EU, fostering private-public collaboration across EFPIA, Academia, NGO's and SME's and strengthening the competitiveness and industrial leadership of Europe;
- providing a legal frame and agreement on IP terms and exploitation, as paradigm of public and private international collaboration in the development of combination regimes;
- Implementing agreement with other consortia facilitating prompt data sharing and data exploitation to accelerate TB drug regimen development.

In addition, the following additional exploitation<sup>6</sup>/dissemination<sup>7</sup> obligations must be considered to maximise impact: The applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. These strategies aim to ensure fast access and uptake in high TB burden countries to secure maximum impact on the TB epidemic.

A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure, for example, qualification advice on the proposed methods for novel methodologies for drug development.

The major outputs of the proposed activities, such as innovative clinical trial designs, biomarker evaluation and the evaluation of novel technologies to monitor and enhance adherence must be disseminated in peer-reviewed open access journals. Any clinical trial simulation created must be made available via an open access platform to external researchers beyond the lifetime of the funded action.

Clinical samples must be made available to researchers outside the consortium and beyond the lifetime of the consortium through a sustainable biobank.

In their proposals, applicants should outline how the proposed activities will:

- Manage research data including use of data standards and a fully developed strategy for FAIR storage and access to data and models beyond the lifetime of the consortium;<sup>8</sup>
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;<sup>9</sup>
- Communicate the project activities to relevant target audiences.

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures<sup>Error! Bookmark not defined.</sup>) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding. Applicants should specifically consider synergies with partnerships that have existing TB clinical trial networks, TB drug discovery consortia, or with relevant not for profit organisations in the field.

The funded project also is expected to seek collaboration and establish a data sharing framework agreement with the TB Drug Translational Development Collaboration (**TDTDC**) to ensure complementarity and sharing of results particularly with regards with efficacy, safety and experimental biomarkers.

<sup>6</sup> Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

<sup>7</sup> Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

<sup>8</sup> Guidance on data management is available at [http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management\\_en.htm](http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm)

<sup>9</sup> <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

## Industry consortium

The industry consortium (EFPIA and Associated Partners) plan to contribute the following expertise and assets:

- **NCEs.** To ensure a working portfolio of ten assets, it is anticipated that EFPIA and Associated Partners will contribute a substantial number of assets to the pipeline. It is expected that in the region of eight NCEs will be made available to the consortium in the first year, consisting of ATPsynthase inhibitors, Nitroimidazoles, Decaprenylphosphoryl- $\beta$ -d-ribose 2'-epimerase (Dpre1) inhibitors,  $\beta$ -lactams, Leucyl-tRNA synthetase (LeuRS) inhibitors and cholesterol catabolism inhibitors. Approximately seven additional NCE's may be included the years that follow, with at least four additional mechanisms of action including novel oxazolidinones, protein synthesis inhibitors, transcriptional repressors affecting the metabolism of medicines and new generation ATP synthase inhibitors. Molecules may become available via EFPIA partners, TB Alliance, Gates MRI, ERA4TB or through other initiatives. Selection of molecules will be subject to due diligence by the governance bodies of the consortium
- The Sponsor for each clinical trial within the consortium will be chosen from among the asset owners contributing NCEs to a study and will assume all legal and regulatory Sponsor accountabilities. In this capacity Sponsors will retain full responsibility only for the investigation and reporting of SUSARs and serious GCP breaches occurring within a trial. Other pharmacovigilance responsibilities will be agreed at the second stage of application.
- EFPIA members and Associated Partners will provide expertise and advice on core clinical trial activities and minimum standards expected as outlined in relevant regulatory guidelines which will be the responsibility of the applicant consortium including, but not limited to:
  - Clinical: protocols and informed consents, for data collection and quality management, privacy, reporting and disclosure. Minimum standards for monitoring and audit plans.
  - Statistical analysis plans and quality control processes.
  - Provision of regulatory documents such as investigator brochures and IMPD will be provided by asset owners. Asset owners will also be responsible for the creation of annual regulatory reporting for each asset (INDSR, DSUR, PSRI) using data provided by the applicant consortium. Asset owners will provide guidance on the construction of regulatory packages.
  - Pharmacovigilance: requirements for safety reporting within trials.
  - Laboratory and imaging: requirements for assay standardisation/imaging protocol standardisation, results reporting and quality control and assurance. Legal obligations for tracking of human biological samples.
  - Clinical pharmacology: standards for model building, quality assurance and reporting.
  - Sample collection and banking protocol and standards for biomarkers and diagnostics. Assay protocol, reagents and equipment standardisation. Collaboration with applicants regarding selection of biomarkers and their validation/approval from regulatory agencies.
  - Investigational product: requirements for storage, transport, tracking and destruction of investigational product (both NCEs and licensed medicines).
  - Agreements and contracting: requirements for transfer of Sponsor responsibilities, and compliance with relevant European regulations and legislation when contracting third parties or vendors.

### Contribution of Data by industry and associated partners as “in-kind”

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data/collecting samples in prospective activities that are part of broader clinical studies independent from but carried out in connection with the action and contributing results necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The estimated in kind contribution for the prospective activities to generate these data and samples will constitute a substantial proportion of the EFPIA based in kind contribution

The prospective data and samples are planned to include preclinical and clinical studies with assets from the EFPIA partners that will be carried out to prepare assets to be potentially included as part of UNITE4TB asset pipeline. These data and samples are essential for achieving all the objectives of the project as they will provide a basis for inclusion on compounds within the studies and access to data on the disease per se. Significant scientific contributions are also being delivered in the other pillars of the AMR accelerator and outputs from these activities are transferable to this project. The EFPIA and Associated Partner in-kind contribution will be matched by IMI2 JU funding across the whole of the Accelerator and not necessarily 1:1 on an individual project or pillar basis

## Indicative duration of the action

The indicative duration of the action is 84 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

## Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

Applicant consortia wishing to include their own NCE(s) will be subject to the same governance and acceptance criteria as other assets in the existing portfolio as determined by the decision-making bodies within the consortium. Any NCE brought into the consortium must be novel and clearly differentiated from any asset existing in the funded action pipeline according to guidelines proposed by the governing bodies.

- **Innovative clinical trials.** Applicant consortia should include experienced TB investigators and sites with proven trial capacity (the number of sites should be limited to a reasonable number to facilitate management and coordination), capitalising on sites from previously established European-funded networks, or from sites within endemic countries outside of Europe. The consortium should not attempt to set up a trial network *de novo* nor attempt to build capacity at sites with no previous TB clinical trial experience. Quality of data generated by the trials must be adequate for inclusion in a regulatory file, delivered in a timely fashion, and with appropriate cost efficiencies. The consortium may subcontract specific activities to CROs to seek for efficiency or additional expertise. Applicant consortia must have the expertise needed to execute and collect and analyse efficacy and safety data from an EBA study and for the analysis of data from phase 2B/C efficacy and relapse studies;
- **Innovative Biomarkers.** Expertise in the implementation of already identified biomarkers and regulatory buy-in for the proposed biomarker validation framework;
- **Clinical trial simulation.** Experience in building clinical trial simulations and regulatory qualification. Understanding of regulatory requirements for model specification and interrogation, with a specific understanding of the issues around black-box versus white-box approaches. Any AI/ML algorithms deployed to prioritise regimens and/or to predict sterilizing cure should be complementary to existing mechanistic models;
- **Artificial Intelligence/Machine Learning** The applicant consortia should have access to AI/ML expertise and its application in drug development/clinical trials;
- **Digital Health Technologies** The applicant consortia should have knowledge of digital health tools/technologies and expertise in deployment in resource-poor settings;

- **Pharmacogenomics** The applicant consortia should have expertise in pharmacogenomic techniques, collection, assay and analysis techniques.

### **This may require mobilising, as appropriate the following expertise:**

- Experience in running clinical trials of a standard sufficient to support inclusion in a regulatory file in the field of TB. Including a deep understanding of relevant clinical trial guidelines, regulations and legislation and previous experience of engagement with the EMA and FDA;
- Expertise in analysis and interpretation of relevant biomarker modalities, including, but not limited to, the host response, bacterial antigens and radiology;
- Operational expertise around the transport and management of clinical trial supplies and human biological samples;
- Understanding of scientific and regulatory requirements for biomarker validation and qualification, appropriate to build a plausible validation/qualification strategy acceptable to the EMA and FDA, including an awareness of the scientific and regulatory issues around clinical trial simulations;
- Expertise in digital health technologies relevant to treatment adherence;
- Pharmacogenomic expertise in collection of host DNA, ability to sequence and identify relevant pharmacogenomic variations in different populations. Ability to de-identify data and to store it in compliance with relevant guidelines and legislation. Analyse genomic data and correlate this to drug PK and trial endpoints.

### **It may also require mobilising, as appropriate, the following resources:**

- Access historical data archived by Critical Path to TB Drug Regimens (CPTR).

### **Considerations for the outline of project work plan**

In their stage 1 proposals applicants should

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Present a strategy for ensuring the translation of the projects results to drug development: a key deliverable will be qualification advice from the EMA and FDA for the biomarker validation strategy.

### **Suggested architecture**

The applicant consortium would be expected to have a structure that address the following areas:

**Administration.** In view of the complexity and size of the action, the applicant consortium should make provisions for project management, general administration (including project co-ordination, communication strategy for consortium partners and between consortia, meeting management), compliance with IMI requirements (reporting and financial audit). Including a suitable mechanism to adjust funding for clinical sites based on successful recruitment strategies. Applicants should refer to reflection paper EMA/121340/2011 [8].

**Compliance and quality control.** Compliance with relevant guidelines and regulations (ICH GCP, European Clinical Trial Directive, GDPR, human biological sample tracking and other sponsor obligations), selection of trial Sponsor, pharmacovigilance and safety reporting, mechanisms for oversight, clinical data quality, laboratory/radiological assay standardization and internal and external quality control strategy, management of clinical trial supplies/investigational product.

**Clinical trial design.** Co-ordination of regulatory activities and designs with **IMI2 JU Call 15 topic 1**, protocol development, statistical analysis and quality plans, publication plans.

**Clinical operations.** Implementation of consortium strategies for compliance and quality assurance, sites selection (including provisions for flexible allocation of resources by recruitment rate) and set-up, logistics plans (transport of samples and consumables), equipment purchase, preparation of regulatory and ethics packages, annual regulatory and ethics reports, training of monitors and sites, creation of site files, creation/review of clinical and laboratory SOPs, evaluation of innovative technologies for adherence.

**Biomarkers.** Create biomarker validation strategy, create infrastructure for transfer of samples and data between consortium partners, validate biomarkers against relapse endpoint and report results, create clinical trial simulation, prepare package for FDA/EMA biomarker qualification.

## **Additional considerations to be taken into account at the stage 2 full proposal**

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

**Decision-making.** Following the first stage of the IMI2 JU Call process and selection of partners to receive IMI2 JU funding, it is expected that the consortium preparing the full proposal for the second stage of the IMI2 JU Call process will agree on a robust decision-making process (including escalation procedures) for progression of different NCEs, combination regimens and biomarkers. Overall plans and go/no-go milestones will be established during the stage 2 application that will assist in the decision-making process to help ensure that the overall portfolio remains dynamic and work on NCEs is appropriately prioritised across the portfolio. For the avoidance of doubt, any decisions directly affecting an existing NCE shall always require consent of NCE owner.

Such decisions will be made by a committee that includes representatives from all project partners. The composition of this committee will be detailed and agreed by all partners in the Consortium Agreement. A fair and efficient decision-making process will be presented in the full proposal at the second stage of the IMI2 JU Call process. This committee will track the progress of the project against its own internal milestones and will be empowered (to be outlined in the Consortium Agreement) to make progression/termination decisions based on pre-agreed go/no go milestones in a regular, streamlined, single-meeting process. The decision-making process by the committee may result, in case of a 'no-go' decision, in the recommendation from the committee/consortium to IMI2 JU for terminating the grant based on Art. 50.3.1 (h) of the IMI2 JU MGA. The final decision on project continuation or termination will be taken by IMI2 JU in line with the provisions of the Grant Agreement. However, the JU may also make such a decision without prejudice to any decision-making process at the level of the consortium, that is, even without the aforementioned recommendation.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/Associated Partners, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project co-leaders from among EFPIA beneficiaries/Associated Partners shall facilitate an efficient negotiation of project content and required agreements. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed EFPIA co-project leader from among EFPIA beneficiaries/associated partners shall facilitate an efficient negotiation of the required legal consortium agreement. Project content and science shall jointly be facilitated by both co-project leaders.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at

[https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/opencalls/Questions\\_and\\_answers\\_on\\_the\\_AMR\\_accelerator\\_programme.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/opencalls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf).

## Data Management

A significant part of data generated in the funded action may be exploited in the development and, on the long term, market launch of new therapeutics against tubercular infections (validating targets, confirming lead compound candidates, developing and testing new drug regimens, further clinical trials). In particular, such data may have a significant commercial value since an important subset of the data will be needed for filing regulatory documents. Consequently, preliminary sharing of data outside of the consortium could hinder the exploitation of the project results and hence the overall objectives of the AMR Accelerator (bringing new TB/NTM drugs on the market). Thus, the selected consortium should propose a strategy for access to data, which would be in addition or alternative to the H2020 policy for Open Access to Data under Art 29.3 of the Grant Agreement. Such a strategy should be presented in the funded action Data Management Plan (DMP)."

## Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.<sup>10</sup>, and updated during the project lifetime. It could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).<sup>11</sup>

## Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

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<sup>10</sup> As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

<sup>11</sup> <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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