A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases

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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	Target validation and biomarker research (efficacy and safety)
IMI2 Strategic Research Agenda - Health Priority	Neurodegenerative diseases

Specific challenges to be addressed by public-private collaborative research

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), represent a huge economic and societal burden.

One of the key barriers to the development of treatments for neurodegenerative disease is an insufficient toolbox of biomarkers and associated clinical progression data to easily screen populations, diagnose patients, monitor progression and response to treatment, all of which would improve the efficiency of clinical trials.

Significant investment by both funders and pharmaceutical companies created significant amounts of data and samples that could be used to significantly accelerate biomarkers discovery and development. However, these valuable resources remain in silos, hard to be shared and accessed by the research community.

Key unmet needs limiting the use of samples and data for the discovery, development and validation of neurodegenerative disease biomarkers today include:

- Sample and data access for research use: There is currently insufficient access to high-quality, longitudinal, and well-characterized samples (including clinically well diagnosed and controls) and accompanying clinical data to meet current and future demands.
- Sample Quality: A lack of standardization in collecting on and processing of samples and linked datasets causes large disparities in sample quality and decreases the utility of banked samples for researchers.
- Transparency: There is currently no centralized resource documenting what sample types and accompanying clinical datasets are available across different organizations (public and private), and what access restrictions may be in place.
- Data sharing: Platforms and processes for sharing clinical data to accompany samples and then to enable reutilization of derived data are lacking or inadequate in terms of interoperability.

Enabling the sharing of, and access to, high quality samples and data for accelerating biomarker discovery and validation has a twofold public health benefit. First of all, it would foster more efficient and effective translation of research into public health relevant outputs by boosting cooperation, reproducibility of research, and its cost-efficiency. Secondly the availability of validated biomarkers would both speed up the development of novel therapies and their effective deployment at scale, decreasing the significant burden on public health of neurodegenerative diseases. This should be seen with a focus on the development of early detection diagnostic

tools, that leverage potentially peripheral biomarkers in combination with a digital signature which are easy to access and use. It would be needed to do this, while building a platform for sample sharing and broader data access.

The fields of bio-banking, data sharing, and biomarker analysis are in constant and rapid evolution from technological, legal and ethical perspectives. Many different stakeholder groups have the relevant experience, know-how and resources but these are not currently shared or leveraged at scale. A public-private partnership synergistic effort is needed to successfully tackle these challenges, and solve the current fragmentation, dispersion and lack of sustainability. A concerted initiative to create a scalable and self-sustaining public-private federated bio-banking infrastructure has never been tried before nor have all the elements necessary for its success, such as upscaling and sustainability, been previously identified. The Innovative Medicines Initiative (IMI) framework offers an ideal model to create such an initiative at the necessary scale in term of resourcing and integration of all necessary stakeholder groups.

Scope

At the short proposal stage, applicants should address all the five objectives of this Call topic, providing the outline and strategy for implementing them as analysed below. These will be fine-tuned and fully developed at the full proposal stage jointly with the industry consortium.

1. Create a set of agreed principles to enable sharing and access to data and samples taking into consideration all relevant barriers (e.g. General Data Protection Regulation (GDPR), legal, intellectual properties (IP), ethical, regulatory, societal).

Applicants should address all considerations (e.g. operational, GDPR, national legislation, ethical, intellectual properties, social) for delivery, sharing and access of both the retrospective and prospective data and samples with the whole research community including the drug developers. In particular they should convincingly formulate how to ensure best practices and to enable effective use of samples and data, respecting the wishes, intent and privacy of research participants. A first set of agreed principles should be available by the end of Phase one of the project (end of year one), to be further worked upon during the project duration, with an aim to agreeing on a final version of principles by the end of the funding period. These should to be effectively disseminated to the broader research community.

2. Establish a network that can house high quality data and samples, which could have federated and centralised elements. The overall solution has to be interoperable (e.g. with other global data platforms), scalable and suitable for a broad variety of both data types (including digital), and of samples, from public and private (e.g. proprietary clinical trials) sources, whether they be part of the consortium or provided from external donors.

Applicants should demonstrate in their proposal the strategy and capacity to build, grow and deliver by end of the funding period a self-sustainable platform for high quality samples and data, sharable and accessible by the broader research community, including drug developers.

Applicants should be aware that activities related to building a biorepository or data management and sharing platform from scratch are out of scope for this topic. Instead, they should build upon existing resources (including ongoing longitudinal cohorts or studies), knowledge and infrastructures to deliver a novel solution able to seamlessly incorporate existing retrospective samples and data with prospective samples and data collections. The industry consortium will make available a data platform (e.g., Alzheimer's Disease (AD) Workbench[1] via the Gates Ventures Alzheimer's Disease Data Initiative), which will soon start. The AD Workbench provides not just for storage but also for computational needs, tools, and a virtual analytics environment, among others. Thus, applicants should propose solutions for adapting AD Workbench to create an instance of the data platform in

[1] To register as a user of the Alzheimer's Disease Workbench please go to the following site https://addilogin.b2clogin.com/addilogin.onmicrosoft.com/b2c_1_signup_signin/oauth2/v2.0/authorize?response_type=id_token&scope=openid%20profile&client_id=e5ef93e7-8825-4b74-bc58-5f1cd2999fc9&redirect_uri=https%3A%2F%2Fportal.addi.ad-datainitiative.org%2F&state=c82cea5e-ac71-4ac3-9c65-a75c836e145f&nonce=91b6bb2d-9828-46ac-bb2d-65f5dd076b58&client_info=1&x-client-SKU=MSAL.JS&x-client-Ver=1.1.3&client-request-id=4d79bb93-16d5-44cd-ad99-7a48cf1bcbe0&response_mode=fragment and follow the steps in this guide: https://knowledgebase.aridhia.io/article/registering-for-a-workspaces-account/

Europe to achieve the objectives of the topic. Any data platform to be used in addition to and/or in combination with the AD Workbench should be open source and fully interoperable.

Ideally the starting infrastructures for sample and data hosting would have been successfully utilized in international public-private multi-stakeholder settings and must be scalable and interoperable. The final platform created by the project could be based on a primary solution from the applicants, which needs to be interoperable with existing other solutions (and in particular AD Workbench) or could be primarily based on AD Workbench. In developing the final platform applicants should also consider that it has to be fit for purpose i.e capable of incorporating samples and data contributed by the industry consortium from previous clinical trials plus, and importantly, samples and paired data collected in future clinical trials. Applicants should demonstrate how the know-how and experience of the industry consortium and the industry-provided data platform is integrated for optimal operation of the network platform and to become self-sustainable.

The value of the datasets should be maximised through the creation or utilization of e.g. a data environment in the cloud, which collects and harmonizes existing data from academic cohorts and pharmaceutical studies that are already available with newly created ones. This should facilitate uniform data sharing and reutilization with interoperability, for data analysis, Artificial Intelligence (AI) and machine learning applications. The platform should enable secondary use of data acquired on samples including high-dimensionality data such as genomes, proteomes and metabolomes.

It is expected that under the "agreed principles to enable sharing and access to data" in this network, components of data sharing and data return for partners or external research collaborators will be included, to ensure that those novel/derived data are generated based on data or samples provided.

3. Establish fair and transparent governance and processes specifically to enable sharing and access to data and samples.

Applicants should establish a credible sample and data access committee. They should identify and apply clear and transparent rules of appointment of its members and ensure that there is relevant stakeholder representation (including patients).

In addition and starting from the agreed principles (see objective one) the consortium should develop an agreed charter to be followed by the access committee to enable consistent access to samples and data. The applicant should also formulate a strategy to efficiently and effectively dynamically incorporate the learnings from the project activities in the governance and processes for data sharing and access, to keep it fit for purpose.

4. Test the above with the defined case studies and apply the learnings to fine-tune processes and use the outcomes to grow the platform.

To demonstrate the utility of the established entity, case studies should be proposed using data and samples to support biomarker discovery and validation. These should include (but are not limited to) (1) the Amyloid-Tau-Neurodegeneration (ATN) system, which has been proposed as a very suitable staging and prediction system, but whose measurement still relies on complex markers which do not lend themselves easily to screening testing of large numbers of elderly people; (2) the complement pathway, which is a specific component of the inflammation response that is now recognized as a key factor in a wide range of chronic neurodegenerative conditions and has been genetically linked to Alzheimer's Disease; furthermore, there continues to be increasing attention towards (3) digital biomarkers with the potential for monitoring neurodegenerative diseases given the ubiquitous nature of consumer electronics and powerful computational platforms. As such, successful proposals should include pilot case studies that at minimum target all the above described.

Applicants should include the well substantiated description of (1) cohorts with early Alzheimer's disease, which will allow the evaluation of the ATN system, comparing more complex and expensive markers like cerebrospinal fluid amyloid β (Aβ) & tau, Amyloid-positron emission tomography (PET) and magnetic resonance imaging (MRI) with potential blood-derived markers as alternate biomarkers and (2) cohorts with Parkinson's disease to investigate the impact/relation of the complement system on diagnosis, severity and progression.

Since high quality is of paramount importance, applicants should demonstrate 1) that the retrospective samples are of high quality and accompanied by high-quality, curated, standardized, and interoperable datasets, and 2) they have a strategy and robust methodology for ensuring high quality of the prospective data and sample collection. Prospective collection should be based on well-defined clinical cohorts, with bio-samples and digital biomarker data. This should build on state-of-the-art standards and processes with updates and new development to allow moving to the next level and achieving the project objectives. It is critical that they show how the know-how and

experience of the industry consortium is leveraged in the full consortium to ensure the consistency and quality of samples, accompanying assays/standard operating procedures (SOPs) and data. In view of the expected use of samples and data for regulatory biomarker validation, the perspective of regulators should be included from day one of activities.

Applicants should document that both samples and data described in their proposal are accessible and sharable with the whole public-private partnership from the start of the project activities, with the potential for broader availability by the end of the project. In addition, it should be addressed how the retrospective sample and data collections will be further expanded and enriched both in size and type as a result of the activities of the project. This should importantly include digital data and longitudinal follow up at individual level, which is both sharable and scalable.

5. This platform must be a self-sustainable entity by the end of the project.

Applicants should formulate how the network platform will achieve self-sustainability by the end of the project. Considering the challenges and demands for achieving this objective, relevant activities should be in place from the beginning of the project and it is expected that approximately one third of the total IMI2 JU funding should be allocated to this work-stream. To demonstrate self-sustainability, first of all applicants should address how the established network will be able to handle the logistics required to receive, handle, process, store, and deliver samples at scale, both existing ones as well as new sample sets as the initiative reaches maturity.

To respond to the rapid changes in the field, the consortium should perform an analysis of gaps and requirements to efficiently build and operate the platform and make it self-sustainable. This is to be part of a white paper, concluded by the end of the first year of activities (the first phase of the project). With the support of an advisory board (to be in place by month three of activities and including all necessary expertise and stakeholder representation, e.g. regulators, industry, patients, among others) the consortium will appraise original plans, available assets and expertise to adapt them as necessary. This may require some re-tuning in areas and activities of critical need and related budgeting to ensure achievement of the project objectives and progress to self-sustainability by end of the funding period. Significant changes will be taken on-board according to the relevant grant agreement procedure.

Applicants should present a strategy and plan of activities to further grow the platform and ensure steady sample availability by attracting and integrating data and samples from novel cohorts and clinical trials beyond those provided by consortium members. The plans should be documented by previous record of success. These plans should be based on a thorough analysis of both blocking factors and success ingredients for making the platform attractive to the donors of data and samples. These latter should/could also be the end-users, to create a virtuous self-sustaining cycle. Starting from multiple neurodegeneration indications (Alzheimer's disease and other tauopathies, Parkinson's disease) the potential for future expansion to other indications, beyond the funding period, should be considered. Applicants should also demonstrate the suitability of the platform for integrating unusual samples (e.g. faeces, saliva) and unusual data sets (e.g. dietary surveys, microbiota profiles).

Applicants should propose and develop a business model for a sustainable network platform. Development should reach a first concrete application. This should include all important considerations for making the platform attractive for its users, usable, useful and thus used. A strategy has to be implemented both for maintaining a constant stream of data and samples from external donors and for attracting samples users. This should include a mechanism for integration of data obtained from the sample analysis back into the platform for secondary use by the research community. Implementation of a fee system for access to data and samples might be considered to secure continued operation. A mechanism for making the model sustainable should be developed from the start including e.g. potential revenues / income (via sample and data access fees) should be developed from the start of the project and be operational already within its lifespan.

To enable the achievement of the project's ambitious objectives the applicants should propose a strategy for effective public-private governance and management of activities within timelines and budget. The proposed governance will have to agree on and deliver the complete project work-plan in two consecutive phases; a preparatory one (first year) and a subsequent full implementation phase (second phase of four years). This includes the initial allocation, monitoring and necessary adaptation of resources to work-streams during the course of the project.

Timing of activities should be proposed considering that the project shall consist of two phases: a first starting phase of one year and a further full implementation phase of four years. Applicants are expected to propose key

activities to reach the milestones for both phases at the time of submission of their short proposal, to be further refined by the full consortium in the stage 2 full proposal.

Considering the overall objectives and the challenges implied for their achievement, it is expected that the Phase 1 activities will require around 15% of the budget, with the remaining amount for the activities of Phase 2. Applicants should also ensure sufficient budget is allocated to the key activities supporting the objective of self-sustainability by end of the project (approximately one third of the total IMI2 JU contribution).

The fundamental components of the proposed business model need to be clearly outlined and tested in the second phase to enable sustainability beyond the 60 months. The results of such testing should provide tangible evidence to illustrate that the business model can then be deployed successfully to enable continuation of the platform and services specifically beyond the lifespan of the funded project.

In Phase 1 of the action, the consortium is expected to achieve critical milestones that will inform Phase 2 activities, including any relevant change in areas and activities of critical need and related budgeting. Therefore, the work-plan of Phase 2 may have to be adapted in light of the outcome of the activities of Phase 1.

Starting Phase 2 activities (and final allocation to activities of relevant IMI2 JU contribution) will be endorsed by an internal review by the consortium supported by the advisory board of the project (milestone review).

Thus, for the success of this initiative, it will be paramount to have mechanisms that allow integrating novel elements and knowledge identified by the gap analysis in Phase 1. This will allow for upscaling and operational validation to ensure successful self-sustainability during the action duration. This will be enabled by the Phase 1 & Phase 2 milestones-based approach for activities and their budgeting.

To enable such a process, each of the work-streams must define critical milestones as a minimum at the end of the first year of activities (phase 1 of the project), mid-term (will be assessed by the reviewers in the mid-term review organised by IMI2 JU) and at the end of the funding period. Milestones have to be clear decision points for go/no go decision and re-orientation on specific activities and their resources. They must be based on measurable and time-bound deliverables. Robust mechanisms for check and correct have to be agreed across the public-private partnership and be in place from the beginning of the project, both at overall project coordination level and work-stream level.

Expected key deliverables

It is expected that applicants already address all deliverables in the Short proposal (within the available duration and budget) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium. These will be fine-tuned by the full consortium to lead to a final set of agreed deliverables in the full proposal.

The listed key deliverables link directly to the topic objectives as listed below. The applicants should propose complementary additional relevant and measurable deliverables well aligned with the activities described in the scope section and considering the two-phase, milestone-based strategy.

Associated with objective 1) Create a set of agreed principles to enable sharing and access to data and samples, taking into consideration all relevant barriers (e.g. IT, GDPR, legal, ethical, regulatory, societal)

- Establish an advisory body: this body should represent diverse experts (e.g. in bio-banking, data sharing, information technology and artificial intelligence, regulatory advice, GDPR, ethical and societal issues, the patient voice, intellectual properties, national legislations across Europe and globally, business models and sustainability) within and outside the consortium;
- Delivery of an initial white paper that addresses gaps and requirements (including European regulatory considerations, as part of the above described areas of expertise) to establish a network that can house high quality data and samples and enable sharing and access for supporting discovery and validation of biomarkers;
- Delivery of final white paper with updated agreed principles to enable sharing and access to data and samples with clear identification of the cohorts participating. This should incorporate all learnings generated by the project activities including relevant regulatory guidance in the context of validation of biomarkers.

Associated with objective 2) Establish a network that can house high quality data and sample, which could have federated and centralised elements

- Establish a framework to leverage (or integrate with) existing/proposed data platforms, which need to be scalable to accommodate retrospective and prospective data, and a strategy for its dynamic fine-tuning as the initiative grows;
- An established interoperable scalable network of biobanks to accommodate retrospective and prospective samples and a strategy for its dynamic fine-tuning as the initiative grows.

Associated with objective 3) Establish governance and processes to enable sharing and access

- Establish a credible sample and data access committee:
    - with clear and transparent rules of appointment;
    - including relevant stakeholder representation (including patients);
    - with an agreed charter (from the overall consortium) to enable consistent access to samples and data.
- Establish a process for efficiently linking to regulatory procedures (e.g. Innovation Task Force and/or Scientific Advice by European Medicines Agency (EMA)) for maximum impact on drug development and/or biomarker validation. Include the consideration of regulators or, at minimum, a regulatory expert in the advisory committee.

Associated with objective 4) Test the above with case studies

- Produce reports on the performed case-studies testing the established network, and demonstrating the utility of the data, biomarkers and biorepository. These should appraise the value of leveraging samples and data towards 1) demonstration of utility of samples with a standardized assay of current neurodegenerative disease biomarkers, and towards 2) new biomarker identification and analysis interrogating the complement system for neurodegenerative diseases. This should include an appraisal on the utility in the regulatory context considering as relevant e.g. Innovation Task Force and Scientific Advice.[2]
- Case studies should:
    - Evaluate the ATN (Amyloid-Tau-Neurodegeneration) system in cohorts with early Alzheimer's disease, to allow comparison of the more complex and expensive markers like cerebro-spinal fluid (CSF) amyloid β (Aβ) & tau, Amyloid-PET and MRI with potential plasma markers as alternate biomarkers;
    - Interrogate the Complement pathway biomarkers across a panel of neurodegenerative diseases. This could start potentially using first a discovery stage Complement proteomics unbiased approach, that could be followed by confirmatory studies with standard lab-based assays on larger sample panel, in order to identify potential patient subgroups. This should include regulatory advice e.g. from EMA Innovation Task Force[3];
    - Include at least one cohort with longitudinal collected digital biomarkers.
- Generation of harmonized sample and datasets: Novel, prospective sample and datasets should be incorporated in the platform and must be harmonized and interoperable with data resources already included from start of operation.

Associated with objective 5) This network must be a self-sustainable entity by the end of the project

- Draft sustainability plan: A first draft of a detailed sustainability plan (financial and business) should be developed to demonstrate sustained operation after funding period;

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development
[3] https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section

- Finalized and Implemented sustainability plan: Self-sustainability of the entity should be demonstrated via a finalized and implemented sustainability plan.

Suggested allocation to Phase 1 of activities (thus to be achieved by end of 1st year of activities):

- Associated with objective 1) Create a set of agreed principles to enable sharing and access to data and samples taking into consideration all relevant barriers (e.g. GDPR, legal, ethical, regulatory, societal):
    - Establish an advisory body: This body should represent diverse experts (e.g. in bio-banking, data sharing, information technology and artificial intelligence, regulatory advice, GDPR, ethical and societal issues, the patient voice, intellectual properties, national legislations across Europe and globally, business models and sustainability) within and outside the consortium.
    - Deliver a white paper that addresses gaps and requirements to establish a network that can house high quality data and samples, and enable sharing and access (see objective 1)
- Associated with objective 4) Test the above with case studies:
    - Gauge the ATN (Amyloid-Tau-Neurodegeneration) system in cohorts with early Alzheimer's disease, to allow comparison of the more complex and expensive markers like CSF Aβ & tau, Amyloid-PET and MRI with potential plasma markers as alternate biomarkers

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact.

In particular short proposals should address:

- How the self-sustainable network platform composed of a European biobank operation, and accompanying data platform, will positively fuel and impact basic research and development and drug development campaigns;
- How the public-private partnership providing infrastructure to enable worldwide sample and data sharing will have substantial impact on development and regulatory validation of biomarkers/diagnostics, and how in turn this would likely have a cascading effect on accelerating therapeutic development.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

In addition, applicants should describe how the project will impact on competitiveness and growth of companies including SMEs;

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards.[4]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research Infrastructures.[5]
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[6]/dissemination[7] obligations must be considered to maximise impact:

[4] 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
[5] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[6] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[7] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

Dissemination needs to include (1) publication and actively engaging community to implement the agreed principles for data/sample sharing and access and (2) demonstrating the value of the platform (key to support its sustainability) as impact of the enabled data/sample usage.

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) in order to incorporate resources, past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium will contribute the following expertise:

- Project leadership, governance and project management resource and capabilities;
- The identification and transfer of samples into the biorepository will be supported, including accompanying patient / participant data;
- Provide the necessary scope of legal, technical, and other required resources (FTEs) to enable successful transfer of samples and subsequent utility of the platform for users,
- Testing of the consistency and quality of sample handling, storage, and distribution using some of the now standard biomarkers used in the field such as Aβ40, Aβ42, Tau, phosphorylated Tau (p-Tau), synuclein, neurofilaments (NFL) etc;
- Interaction to ensure banking of samples will aid in disease understanding and modelling. For example, existing sample collections from previous clinical trials entertained by EFPIA-companies may be used to:
    - Define and refine criteria to incorporate, use, distribute samples and return obtained data back into the database for further use by third parties;
    - Refine legal requirements and documents (ICFs, etc) to standardize how samples will be retrieved in future trials to be incorporated in such repositories.
- Support for research activities focusing on the utility of the biorepository to identify biosignatures related to the dysregulation of as-yet under-researched mechanism in neurodegeneration, e.g. the complement system (see case studies appraising biobank operational scheme);
- Supporting validation of biomarkers to accelerate the development of diagnostics;
- Supporting development of sample collection, QA/QC, sample storage and handling protocols;
- Facilitation of transfer of capabilities and knowledge to reach the ultimate goal of self-sustainability of the Biobanking entity;
- Providing expertise and real-life experience about integrating unusual samples (e.g. faeces, saliva) and unusual data sets (e.g. dietary surveys, microbiota profiles) to clinical studies.

The industry consortium plans to contribute the following assets:

- Existing samples from clinical trials including accompanying data and information. The transfer of such samples into the biorepository will be supported;
- Assays, standard operating procedures, and necessary material (e.g. antibodies) to perform diagnostics;
- Research assay with CSF and Plasma markers of neurodegeneration and neuroinflammation including but not limited to:
    - CSF: Aβ42, total Tau (tTau), (pTau), Aβ40, neurofilaments (NFL), soluble triggering receptor expressed on myeloid cells 2 (STREM2), tyrosine (Y), lysine (K) and leucine (L)-40 glycoprotein (YKL40), glial fibrillary acidic protein (GFAP), Alpha Synuclein, Neurogranin, interleukin-6 (IL-6), S100b;

- Plasma/ Serum: Aβ42 high sensitivity, Aβ40, tTau, NFL, STREM2, YKL40, IL-6, S100b, GFAP, brain derived neurotrophic factor (BDNF), growth differentiation factor-**15 (**GDF-15), Insulin like growth factor binding protein 7 (IGFBP7), neuron-specific enolase (NSE).

These assays are high-performance, non-commercial assays, and would be made available fee for service at a contract research organisation (Covance) and would require advance planning to ensure capacity and availability (> 6 Months).

- Contribute datasets from retrospective (and ongoing) interventional and/or observational studies to the data platform;
- AD Work bench – access and leverage AD Work bench data platform for the project;
- In addition the consortium will provide synergy and point of contacts with other initiatives.

Indicative duration of the action

The indicative duration of the action is 60 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 applicant consortium will be selected on the basis of the submitted short proposals.

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.

This may require mobilising, as appropriate the following expertise:

- All relevant areas of expertise that are necessary to deliver on all of the project deliverables. This should include entities with a proven track record of successful experience in the following or equivalent areas of experience, including key considerations of SMEs :
  - Technology and solid understanding of technical architecture for biobanks and bio-repository know-how for long-term collection, storage and distribution of large numbers of samples, including:
    - Capacity to allow online identification and ordering of samples including infrastructure to accept, add, and retrieve data obtained with and attached to samples; this includes modalities for covering handling, maintenance, and distribution costs of the repository which shall support the transformation of the action into a self-sustainable operation in a European and worldwide context;
    - Legal expertise;
    - Data/ Information technology Infrastructure expertise;
    - Expertise and networks to procure samples through existing or to be-established (clinical) networks
    - Experience in standardization procedures (e.g. via European Committee for Standardisation (CEN)) including QC of samples
    - Experience with federated and/or centralised Laboratory Information Management System (LIMS) architecture, security and standards to monitor status of repository and maintain and amend information available to each specimen
  - Expertise regarding establishing and managing a data platform that:
    - Utilises requisite standards and common data models;
    - Facilitates data access;

- Can incorporate new data generated using samples from the repository;
- With appropriate protections and security to protect sensitive healthcare data;
- Is suitable for a public-private partnership context.

- Knowledge in establishing and maintaining a harmonized online data portal / interface that:
  - Can interrogate available datasets and samples via federated approaches to unify available clinical datasets;
  - Is interoperable between biobanks, clinical data systems, and across the biorepository network involved in the action, including requesting samples for analysis.

- Experience relevant to biomarker discovery and validation, ideally including the expertise below to ensure the success of the described pilot case studies:
  - Experience with early AD biomarkers;
  - Experience in complement pathway biomarker analysis both unbiased (such as large-scale targeted proteomics) and more standard biomarker assays for large scale analysis of larger case panels;
  - Experience in digital biomarkers and digital signatures via connected devices and wearables e.g. for early detection and/or disease progression.
- EU & Worldwide legal, ethical and regulatory expertise pertaining to:
  - Legal requirements specifically to sharing, access and usage of health data in Europe at a minimum;
  - The use of human samples (sampling, storage, distribution across regions), bio-banking and patient consent/secondary use / ethics;
  - Data sharing, access and consent related to sensitive health-related data and their secondary use;
  - Regulatory expertise in how to engage and influence outcomes with regulators in line with targeted project deliverables.
- Business, financial, and economics experience to transform the bio-sample repository into a self-sustainable business:
  - Experience and expertise in developing a strategy for ensuring the translation of the project results / bio-sample analysis to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes
  - General project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

Applicants are also encouraged to consider having a patient group involvement within the consortium to ensure that the input of patients is covered including not limited to, but including consent and other aspects e.g. 'Henrietta Lacks' representation.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

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

- A pre-existing and functional sample repository, preferentially with background in Neurodegenerative Disease Therapeutic Area (Alzheimer's disease and related tauopathies, Parkinson's disease), that could already be made available for distribution at the beginning of the action;
- Active cohorts with early stage neurodegenerative disease (e.g. Alzheimer's disease and Parkinson's disease);
- An established distribution pipeline to deliver samples to customers and being operational at within first year of the action;
- Existing sample and data sets (provided e.g. from industry partners or provided by third parties) that will be contributed to this network.

Considerations for the outline of the 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;
- Propose a work plan that efficiently enables the implementation of activities following the two Phases as in the Scope section;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Please consider a work-plan that includes all activities and elements related to scope and deliverables.

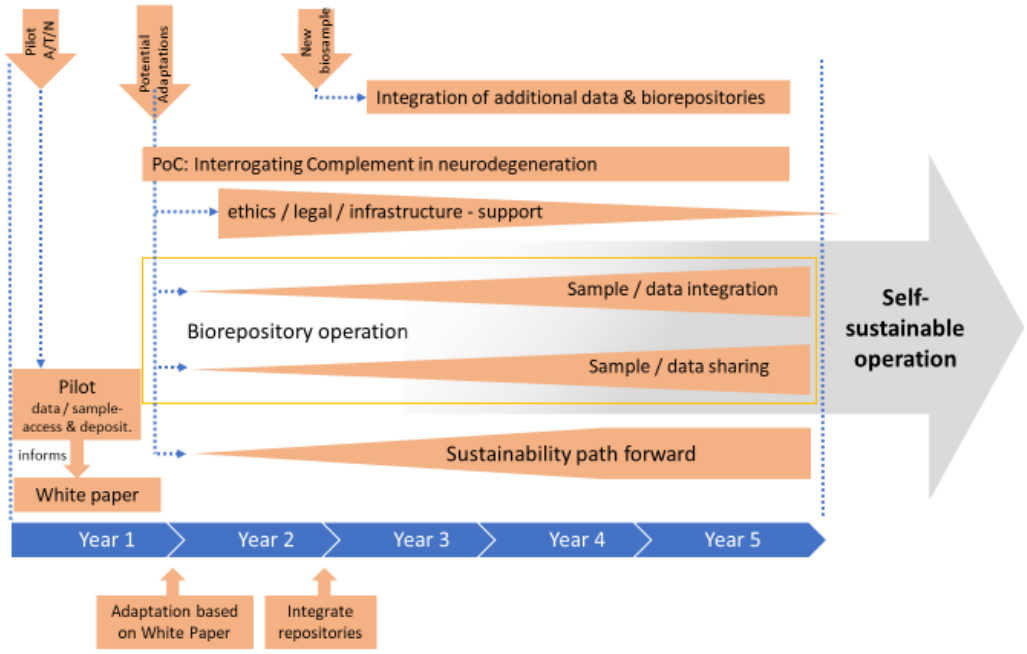

Figure 1 – draft structure of activities

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

At stage 2 of the IMI review process, 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.

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/large industrial beneficiaries, 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 leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[8]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[9], and updated during the project lifetime and 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).[10]

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.

[8] 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
[9] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply.
[10] http://www.corbel-project.eu/about-corbel/research-infrastructures.html