IMI2 821513 – NEURONET

Efficiently Networking European Neurodegeneration Research

WP1 – Projects and Impact Analysis

D1.2 Integrated Programme Analysis v1

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Definitions and abbreviations

Partners of the NEURONET Consortium are referred to herein according to the following codes:

1. **SYNAPSE**: Synapse Research Management Partners SL
2. **NICE**: National Institute for Health and Care Excellence
3. **AE**: Alzheimer Europe
4. **JANSSEN**: Janssen Pharmaceutica NV
5. **LILLY**: Eli Lilly and Company Limited
6. **ROCHE**: F. Hoffman – La Roche AG
7. **TAKEDA**: Takeda Development Centre Europe LTD
8. **SARD**: Sanofi-Aventis Recherche & Développement
9. **PUK**: Parkinson's Disease Society of the United Kingdom LBG

Grant Agreement: The agreement signed between the beneficiaries and the IMI JU for the undertaking of the NEURONET project.

Project: The sum of all activities carried out in the framework of the Grant Agreement.

Work plan: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.

Consortium: The NEURONET Consortium, comprising the above-mentioned legal entities.

Consortium Agreement: Agreement concluded amongst NEURONET participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

IMI: Innovative Medicines Initiative

ND: Neurodegenerative Disorders

WP: Work Package

Publishable summary

NEURONET is a Coordination and Support Action (CSA) aiming to support and better integrate projects in the Innovative Medicines Initiative (IMI) Neurodegenerative Disorders (ND) portfolio. WP1 *Projects & Impact Analysis* is a descriptive and methodological work package (WP) that collects information (e.g. scope, deliverables, funding etc.) about IMI ND projects to enable an integrated view of the IMI ND project portfolio in terms of relative specialisation, timelines, expertise and outputs. As part of WP1 activities, NEURONET conducted an integrated analysis of IMI ND projects at the programme level in order to obtain a first integrated view of the portfolio. This deliverable reports on the approach, methodology and results of the exercise carried out.

1 Introduction

NEURONET is a Coordination and Support Action (CSA) aiming to support and better integrate projects in the Innovative Medicines Initiative (IMI) Neurodegenerative Disorders (ND) portfolio.

WP1 Projects & Impact Analysis is a descriptive and methodological work package (WP) that collects information (e.g. scope, objectives, deliverables, partners, funding, results, obstacles, etc.) about the IMI ND projects, analysing their workplans and outputs, and establishing measures for impact appraisal.

In this report, we describe the analysis conducted at the programme level by WP1 in order to obtain a first integrated view of the IMI ND portfolio. Due to the significant volume of information gathered, as a first step, NEURONET decided to focus on the main assets developed by the 15 IMI projects of the ND portfolio currently taking part in NEURONET (the list of projects is provided in Annex I). For the purposes of this deliverable, *assets* are defined as any significant outputs, resources or results that are susceptible of being disseminated, shared or sustained over time due to their worth, impact and potential for leverage.

Furthermore, we have embarked on an exercise to map existing collaborations between IMI ND projects, aiming to identify potential synergies that could be exploited in new collaborations. The approach used for the collaboration mapping exercise is also outlined in this report, as well as initial ideas for collaboration and synergy that can amplify the II ND programme's impact.

Figure 1 shows the initial 'landscape' for NEURONET, depicting the IMI projects and other initiatives to which direct or indirect connections were existing and could be leveraged from the NEURONET Consortium.

2 Methods

2.1 Project information gathering

The set of measures to be collected from projects (described in deliverable D1.1) was designed to provide NEURONET with a solid understanding of the IMI ND projects, including their scope and relative specialisation, funding, expertise, outputs, assets and achievements, as well as any potential unmet needs or difficulties they may have encountered in key project areas (e.g. ethics, data sharing, etc).

The strategy used to obtain such information relied heavily on NEURONET partners' links to the fifteen IMI ND projects included in this exercise (figure 1). A subgroup of NEURONET partners formed a "data collection team" that collected the necessary data to allow for an integrated analysis of the portfolio, including the identification of potential synergies, dependencies or best practices that could be shared between projects.

As depicted in figure 2, there were three phases in the data collection process:

- **Phase 1:** In the first phase of the data collection process, NEURONET consulted public sources of information, such as the IMI website, the CORDIS portal (i.e. the primary source of results from the projects funded by the EU's framework programmes for research and innovation) and the project websites.
- **Phase 2:** In the second phase of the data collection process, NEURONET extracted information from the projects' Descriptions of Action (DoA), project newsletters, deliverables and other project reports. Using this information and the data collected in Phase 1, a dossier for each project was created (see Annex II).

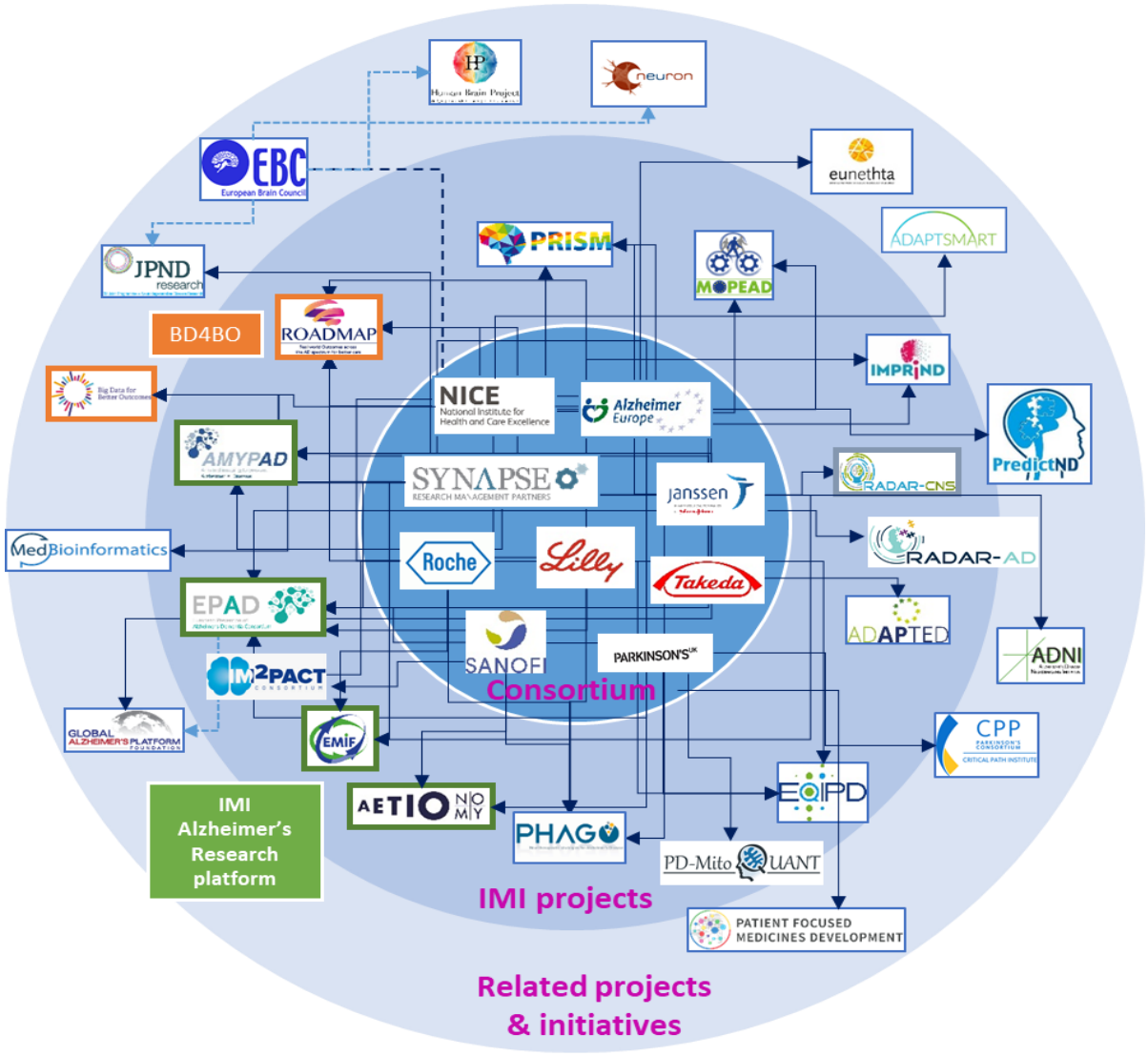


Figure 1. Initial NEURONET landscape: links between NEURONET partners, IMI ND projects and related initiatives

- **Phase 3:** In the third phase of the data collection process, information was primarily obtained using qualitative methods. NEURONET project coordinator and project leader, Carlos Díaz and Lennert Steukers, conducted personal interviews with project leaders. Many were carried out during the second face-to-face SCB meeting & NEURONET Annual Event at the Alzheimer Europe Conference, held in The Hague (The Netherlands) from 23 to 25 October 2019, and additional phone or in person interviews were subsequently carried out. Moreover, to map and evaluate inter-project collaborations identified during face-to-face interviews with project leaders, a survey was devised (see Annex III) to gauge how successful those collaboration attempts were, which obstacles were found, etc. Finally, the NEURONET data collection team analysed the contents of project presentations from the NEURONET Annual Event at the Alzheimer Europe Conference in order to complete the information collected for each project with the most updated status.

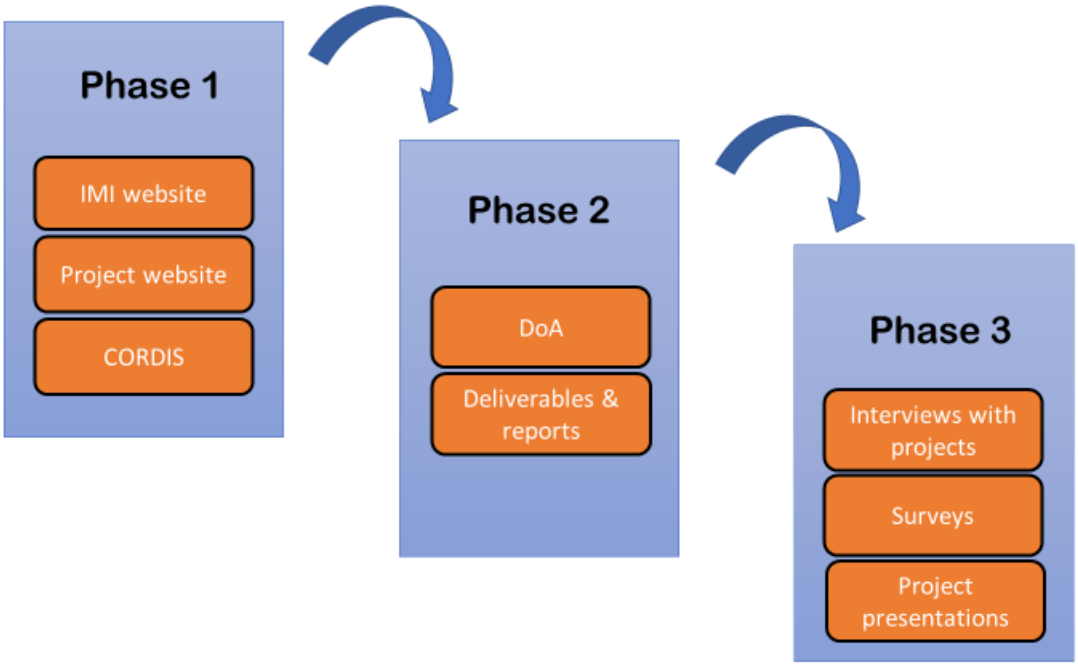


Figure 2. Data collection approach

2.2 Integrated programme analysis

To collate and discuss the information obtained from the various sources during the data collection process, a face-to-face meeting was organized in Madrid on 20th November 2019. As previously explained, due to the volume of information gathered, and upon recommendation of the SCB, NEURONET decided to identify the key results and outputs developed by the 15 IMI projects of the ND portfolio and focus the integrated programme analysis on the so-called 'project assets'. It was decided to display all the assets in a map, along two axes:

- Type of asset (cohort, dataset, knowledge, disease models, taxonomy, platform, tool, stakeholder engagement models, biological samples, other)
- Drug development stage (non-clinical, clinical, RWE, regulators)

By displaying all the assets in this format NEURONET aims to:

- to showcase the wealth of the IMI neurodegeneration portfolio – it is hoped that the asset map can be useful for example when discussing sustainability and addressing potential funders (e.g. EFPIA, philanthropy, etc).
- to provide SCB members with information on the assets that could form the basis of new projects and collaborations.
- to aid the identification of gaps in the portfolio.
- to support impact analysis of the IMI neurodegeneration portfolio, to be reported in deliverable D1.4.

Additionally, results from the survey on attempted cross-project collaborations were analysed qualitatively, focussing on obstacles found and recommendations for the future.

Similarly, results from project information collection, interviews and the asset map were analysed and used to suggest potential new synergistic collaborations and new research initiatives that could underpin current and future projects in the portfolio, maximise impact or cover existing gaps.

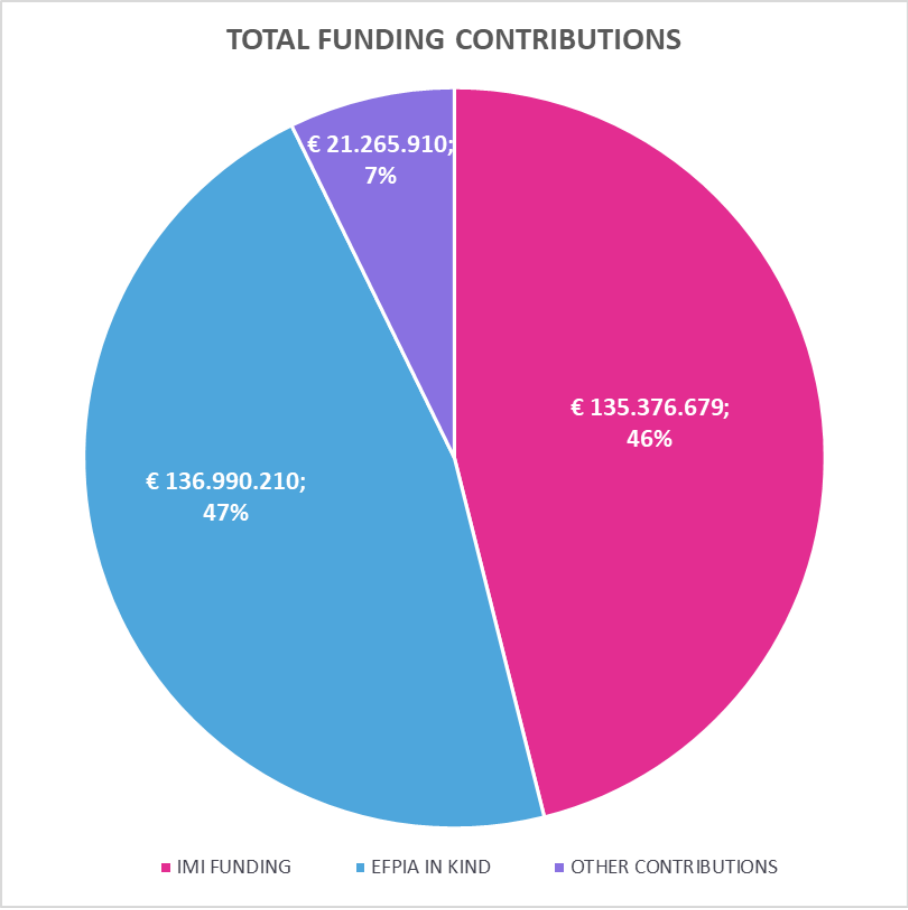
The preliminary results reported in the next section must be considered as a first iteration of the integrated programme analysis, an exercise that will expand and further develop as new projects are added to the constantly expanding IMI ND project portfolio and as current projects continue to deliver their planned results.

3 Results

3.1 Summary metrics of the IMI ND portfolio

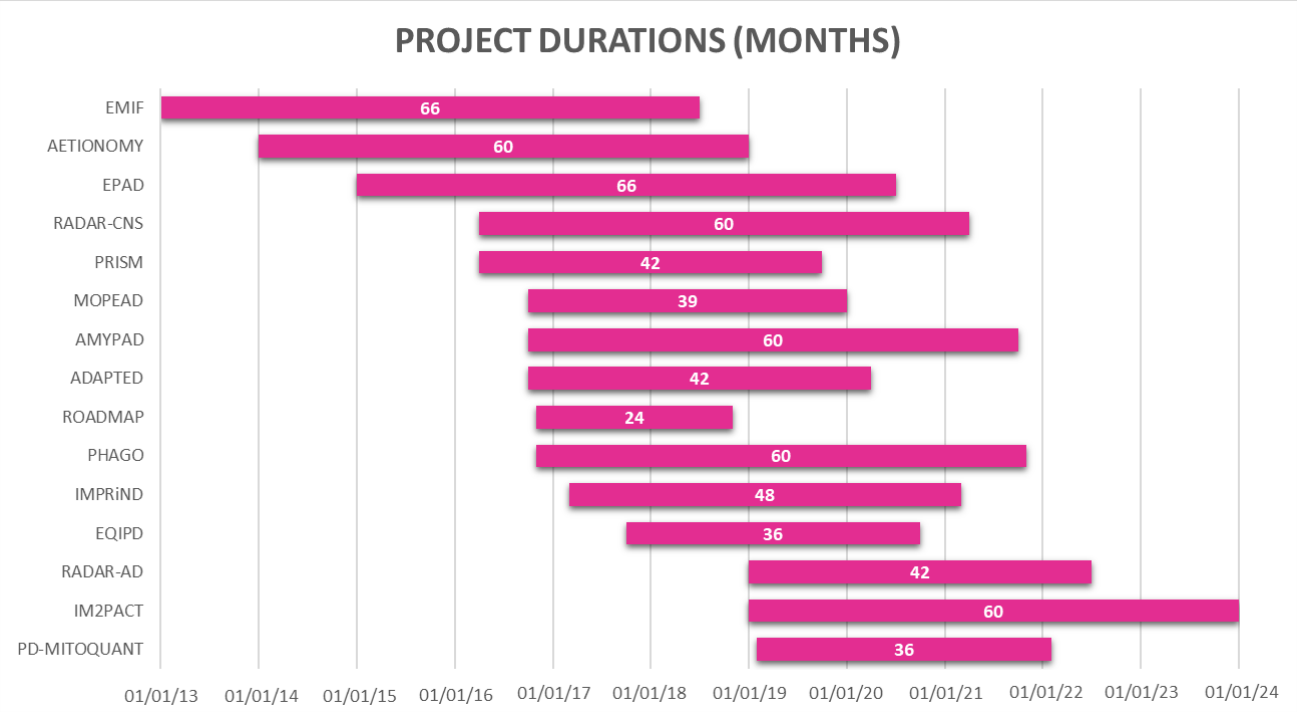
In this section we will provide summary statistics and metrics about the IMI ND portfolio according to the data gathered by NEURONET.

Looking at total funding invested in the IMI ND portfolio, we see that 46% of funds (€ 135.376.679) come from IMI JU, 47% from EFPIA in kind contribution (€ 136.990.210) and 7% (€ 21.265.910) from other sources, e.g. in cash contributions from EFPIA or other associated partners, etc. In total, 293,6 Million Euro are mobilised thanks to IMI for neurodegeneration research, with mean funding per project being € 19.575.519,93 (median € 16.195.875,00).

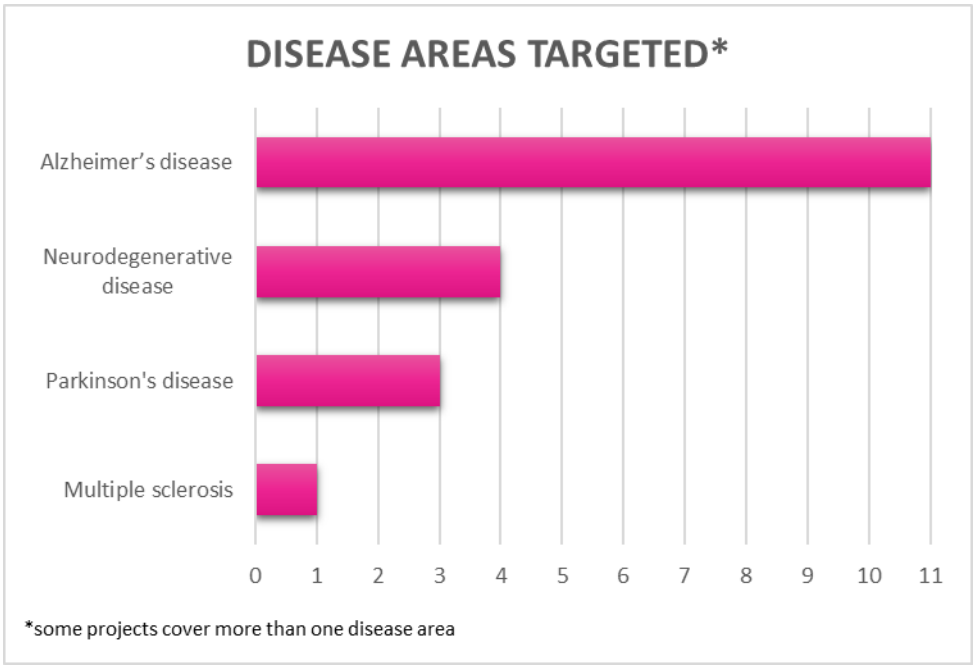


We were interested in obtaining estimates for the actual size of the workforce involved in IMI ND projects, so we decided to use the total number of contacts included in the consortium mail distribution list (including researchers, project managers, admin staff, legal staff etc.) as a proxy. We obtained the total number of contacts included for 12 of the projects and used those figures to calculate the mean number of contacts per partner (6,48 contacts). Then we imputed this value for the remaining projects for which we did not have data to estimate the total number of individuals working in IMI ND projects, which could be around 2.368.

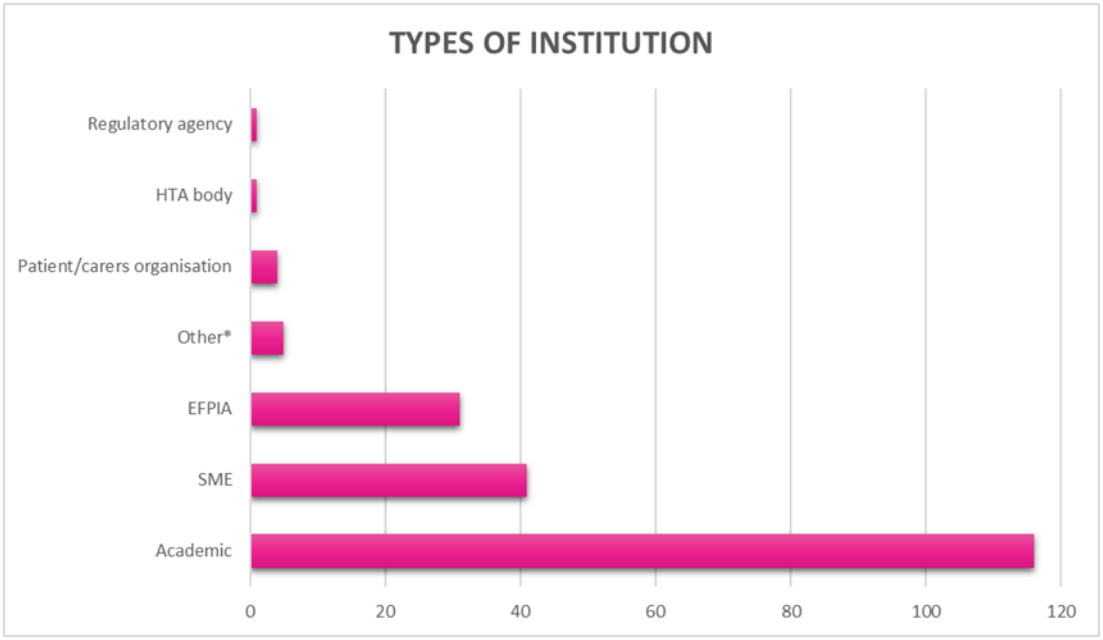
If we look at the duration of IMI ND projects, it can range from 24 months in the case of ROADMAP to 66 months for EMIF or EPAD. The average project duration is 49,4 months.



Regarding the disease areas targeted, there are 11 projects to Alzheimer's (ADAPTED, AETIONOMY, AMYPAD, EMIF, EPAD, IMPRIND, MOPEAD, PHAGO, PRISM, RADAR-AD, ROADMAP), 3 projects devoted to the study of Parkinson's (IMPRIND, PD-MITOQUANT, AETIONOMY), and 1 to Multiple sclerosis (RADAR-CNS). In addition, there are 4 projects that are not focused on a particular neurodegenerative disease or have more general objectives (AETIONOMY, EQIPD, IM2PACT, IMPRIND).

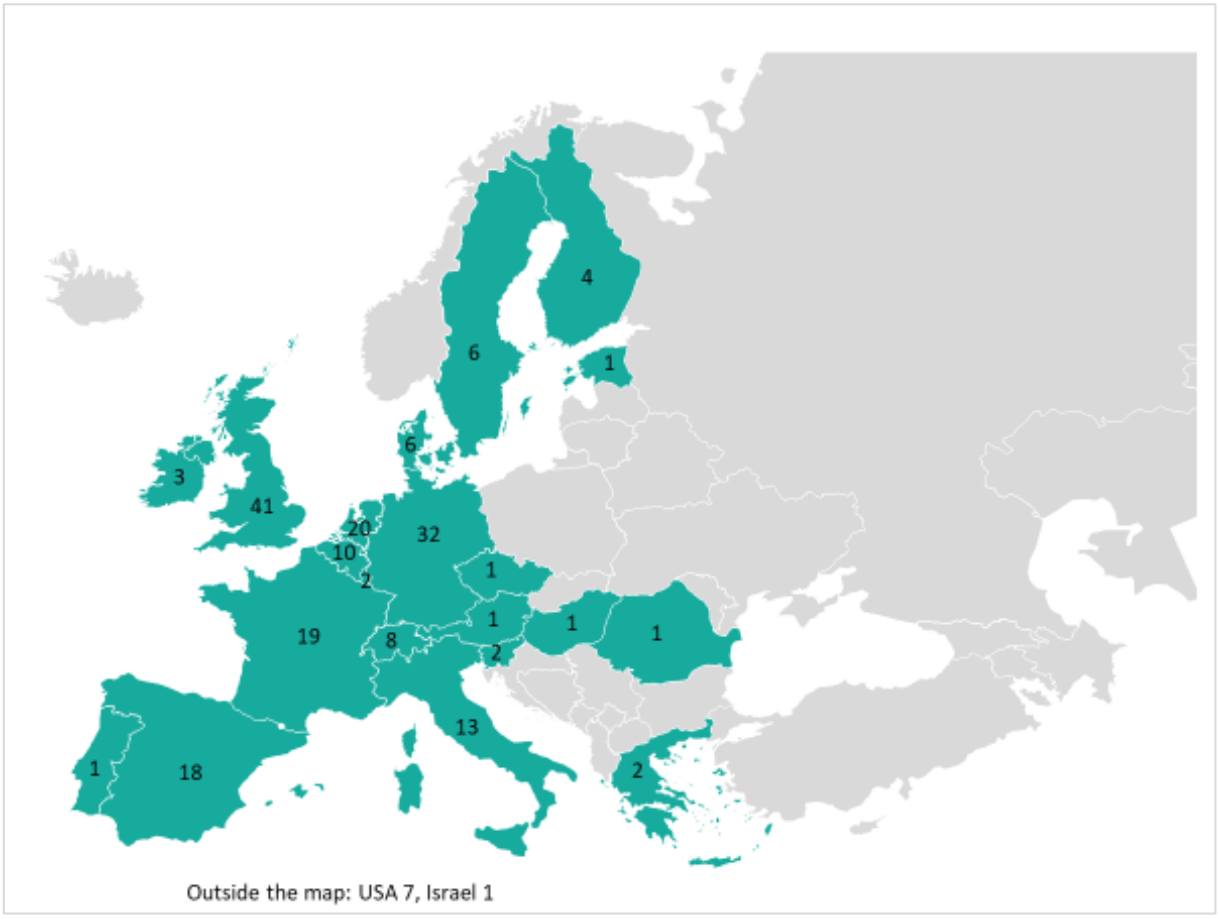


When looking at the different types of institutions involved in IMI ND projects, there are 116 academic institutions, 41 SMEs, 31 EFPIA partners, 4 patients or carers organizations, 1 HTA body, 1 regulatory agency and 5 organizations that fall under other types (non-SME, non-EFPIA, CRO, public body), for a total of almost 200 different institutions actively participating in the IMI ND portfolio.

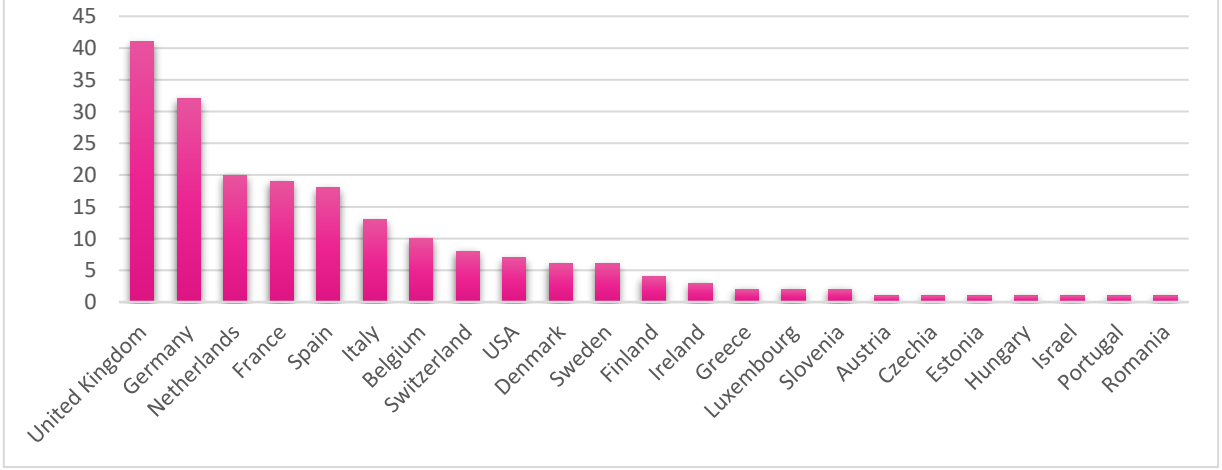


In relation to the countries of the institutions participating in IMI ND projects, 41 are from the United Kingdom, 32 from Germany, 20 from the Netherlands, 19 from France, 18 from Spain, 13 from Italy and 10 from Belgium; followed by smaller numbers of partners coming from other European and non-European countries (see figure below).

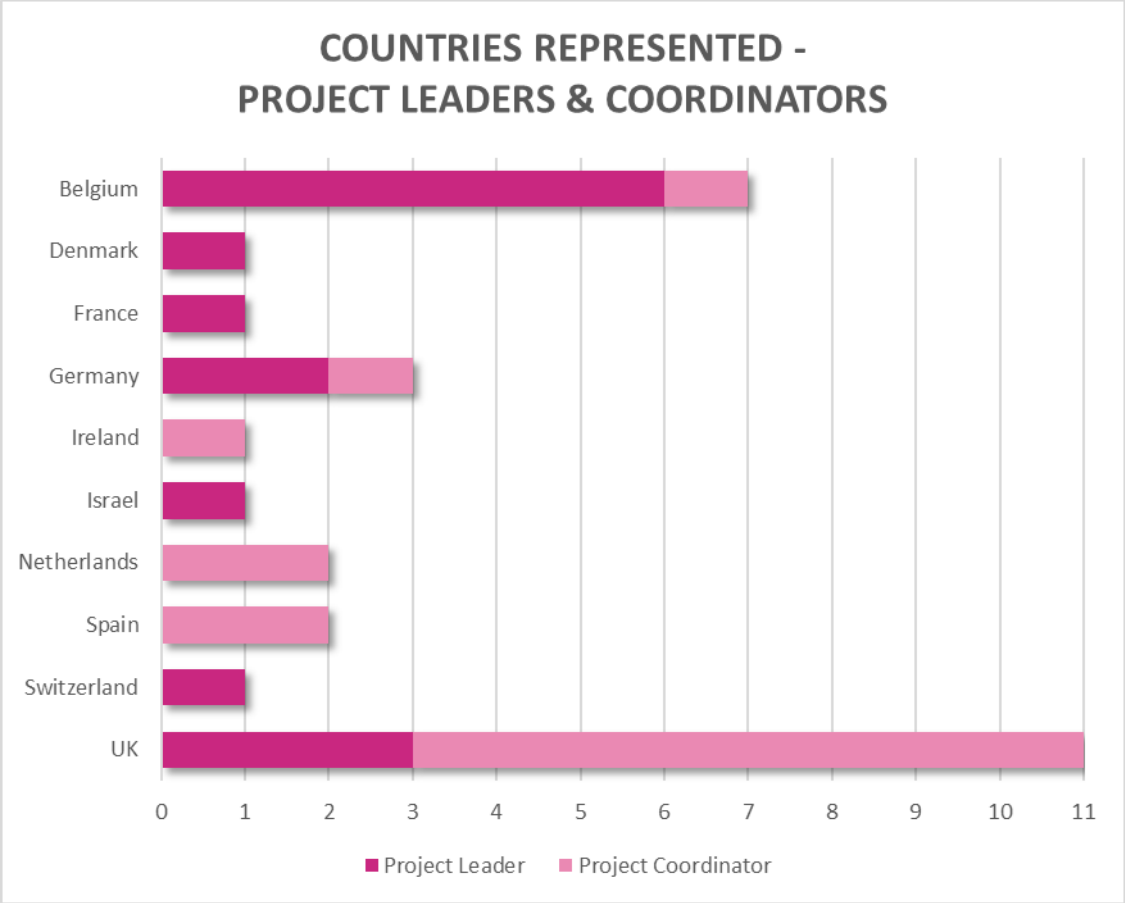
MAP OF REPRESENTATIVE COUNTRIES OF INSTITUTIONS



REPRESENTATIVE COUNTRIES OF INSTITUTIONS



Finally, we looked at the countries of the institutions leading the projects, considering both the academic leader (i.e. the project coordinator) and the EFPIA leader (i.e. the project leader). There are 11 from the United Kingdom, 7 from Belgium, 3 from Germany, 2 from Spain, 2 from the Netherlands and 1 from Switzerland, France, Denmark, Ireland and Israel.



3.2 Learnings from past collaborations & recommendations for the future PPP

NEURONET conducted a "lessons learned" exercise, as part of the ongoing integrated programme analysis of the IMI ND portfolio. An effective "lessons learned" process is one that allows an organization to learn and prevent it from repeating mistakes and enables it to perpetuate successes. NEURONET applied two methods for capturing lessons learned:

1) Unmediated face-to-face interviews with project leaders, with 11 interviews done by end of February 2020; and
2) A survey about past cross-project collaboration attempts (including 16 different collaborations), sent to project leaders and coordinators for completion (see Annex II).

Regarding the latter, projects were asked to provide information on:

1) the topic of the collaboration;
2) whether the results of the collaboration were satisfactory or not;
3) whether legal support was required to materialise the collaboration, and
4) whether there were any specific obstacles hindering the collaboration.

NEURONET collected data on the following past collaborations:

Project 1	Project 2
AMYPAD	EMIF-AD
AMYPAD	EPAD
PHAGO	ADAPTED
PHAGO	EBISC
PHAGO	EPAD
PHAGO	IMPRIND
EMIF-AD	EPAD
EMIF-AD	AETIONOMY
AETIONOMY	EPAD

Out of the 9 collaboration attempts, 6 were materialized (totally or partially) and 3 were unsuccessful. The main obstacle for collaboration reported by the projects were the long delays due to the nature of preparing a collaboration agreement and collection of signatures. As a consequence of such delays, the data had been available only at the end or, in some cases, even after the end of the project that wanted to analyse it, or the animal models that were to be shared were already too old.

The responses received to the survey, together with the feedback we had from project leaders during the face-to face interviews, allowed NEURONET to describe the key lessons learnt from past collaborations and provide recommendations that the IMI JU and EFPIA may wish to take into consideration when shaping the next calls and framework programmes. These include the following important positive aspects:

- IMI is the world's biggest public-private partnership in life sciences, and it has been an engine and a driver of innovation in European health research, spearheading in many cases worldwide advances. The research, industry and societal sectors involved in IMI benefited from the cooperation and knowledge sharing that take place in IMI projects. Thanks to IMI there is now a much greater interaction and coordination across industry, academia and other sectors. This has yielded a situation where collaboration across competing companies and researchers is seen as a natural thing and not as an exception.
- The power of IMI projects in terms of supporting early career researchers cannot be overestimated, including scientific training, exposure to world-class international leaders and collaborative environments.
- IMI research and innovation efforts have opened new commercial possibilities based on new services and products, but it has especially been beneficial in terms of scientific progress and publishable results.
- IMI projects have contributed to the development of tools, standards and approaches to address the high unmet medical need for effective disease-modifying as well as symptomatic interventions in neurodegenerative disorders in general, and Alzheimer's disease in particular.
- IMI supported the development of platforms and infrastructures (e.g. EMIF, EPAD) to speed up clinical development, including strategies for early generation of more patient and payer-relevant data (e.g. ROADMAP).

Many challenges and opportunities for improvement were also detected, which are summarized as follows:

Before the Call launch - Topic development

1. Topic definition – Well suited for the framework

The legal framework with regards to the Intellectual Property (IP) of IMI projects and financial rules have not always been found to be most suitable for all topics spanning the target identification and drug development pipeline. Pure fundamental research projects in the precompetitive space seem more feasible to execute compared to projects in the grey zone between precompetitive and competitive space. An example is the IMI project EPAD (European Prevention of Alzheimer's Dementia) under the IMI 1 framework. EPAD is pioneering a novel, more flexible approach to clinical trials of drugs designed for secondary prevention of Alzheimer's dementia. This project was designed to have different IP holders to run drug trials under a single academic sponsor. The operational set-up of the site network, cohort study and trial platform (both legal as financial) within the IMI 1 legal and financial framework proved to be quite time-consuming resulting in delays and not meeting the timelines from IP holders. An example of a financial hurdle was the 75% reimbursement rate for R&D costs hampering swift expansion of the site network to non-partner clinical sites. Also, it became clear quite early during the project execution that running a PoC platform within an 'at-cost' financial framework would be impossible.

RECOMMENDATION: To facilitate the operational setup of IMI projects, the existing IMI IP and financial guidelines could be adapted. As the IP clauses in the IMI2 model Grant Agreement leave some room to manoeuvre (e.g. 23a.1, "Beneficiaries…must take measures to implement the principles set out in points 1 and 2 of the Code of Practice"), NEURONET would advise to create specific, but adaptable template documents for IMI projects in precompetitive and competitive spaces, and leave enough flexibility to projects to be creative in how financial structures/flows serve project progress best. Any risks that this flexibility create could be managed by e.g. clearly set milestones or go/no-go points defined in advance.

2. The IMI Neurodegenerative Disorders portfolio richness – Innovation does not always require novelty or high-risk

Within the IMI Neurodegenerative Disorders (ND) portfolio, there is a richness of obtained assets in each IMI project, which are not always shared within the research community. The reflection on the obtained assets within the IMI ND portfolio could be immensely improved in order to de-risk investment being made in duplicative efforts as well as to inform the projects about critically taking lessons learned into account before embarking on a new journey. More specifically, an example in which efforts were duplicated in IMI projects, is related to the setup of research participant/patient cohorts in IMI ND projects for clinical studies or generation of clinical samples. For some IMI ND projects, it would have been useful to interlink with the EPAD project and make use of the EPAD longitudinal cohort instead of creating new ones. This example clearly shows that most of the IMI ND projects are still working in silos.

Another point of discussion is the fact that the call for topics in IMI ND projects are currently focused on innovative technologies and not focused enough on incremental innovations. One could also question the paradigm that disruptive, new-to-world or new-to-market ideas are a prerequisite for research innovation and growth. A good analogy would be Apple iPhone, which had one big new-to-market innovation in the first iPhone – it was not new-to-world – but obviously Apple figured out how to do it better and make it more usable and appealing. But since then, one could argue it has all been incremental and continuous innovation – nothing radically new – which nonetheless has had a substantial impact on the markets, as well as on society as a whole. Similarly, a notion that all projects need to always represent true breakthroughs and offer complete, final solutions may be detrimental in terms of practical implementation and impact on daily work.

RECOMMENDATION: To de-risk duplicative efforts in new IMI ND projects, NEURONET would advise a better communication between IMI ND projects (in order to avoid that all projects are working in silos) and a more prominent connection with the IMI ND Strategic Governing Group (SGG), responsible for instigating new call topics. Concerning IMI projects with less innovative technologies, a balanced approach could be to place huge bets on high-risk, disruptive or discontinuous innovation whilst also funding sustainable and continuous innovation. For example, this could be done by building on or maintaining valuable portfolio assets that have already been developed. For high-value portfolio assets, IMI could play an important role in helping projects bridge the gap towards sustainability, for example through conditional funding mechanisms that allow for extended grants renewable under the condition of tangible results being obtained.

3. EFPIA resource contribution: ensuring that commitment is matched by engagement

The intended resource contribution of some EFPIA partners in IMI projects does not always equal active engagement. Several projects have reported no active involvement of EFPIA/Associated partners with minimal resource contribution (e.g. 0.1 FTE/year or 100k in-cash contribution). A meaningful commitment should be sought from EFPIA partners in order to make them part of an IMI project.

RECOMMENDATION: To ensure that the commitment of some EFPIA partners in IMI projects is meaningful, more strict rules should be defined (e.g. by ensuring more specific/balanced task allocation, or by adapting the IMI mid-term review process to detect and remedy "absent" EFPIA partners).

4. Collaborations – Organically grown vs imposed

Too many interdependencies with other calls/projects are being written in Topic texts as well as in Short proposal (SPs) posing severe risks for project execution, because it is not clear whether such collaborations are a critical dependency, or merely something desirable. If the former case is true, separate Grant Agreements with distinct timelines, budget and objectives are typically difficult to reconcile. A clear example is the AMYPAD-EPAD collaboration whereby the AMYPAD prognostic study was devised as highly associated to the EPAD cohort study. Both legal as well as psychological/social aspects across Consortia can severely impact project timelines/goals. There is a general danger in issuing 'letters of support', commonly done but that can be interpreted as a 'Yes, we will collaborate' (when no real assessment of feasibility of doing so has been performed, and when resources are not available at either end to actually implement any collaboration).

RECOMMENDATION: NEURONET would recommend having Memorandum of Understandings (MoUs) in place between IMI projects (which will replace the "letters of support") at the design stage, coupled with more precise collaboration agreements before signature of Grant Agreements. It may also be advisable to encourage more detailed contingency planning, extending to the identification of alternative datasets, and sources of material in case collaboration cannot be implemented, to avoid extreme dependency. This should be done in a way that doesn't hinder any potential partnerships, and that doesn't impose an unmanageable administrative burden at the application stage and at the delicate initial stages of implementation. It may also need identification of mutual incentives for collaboration ex ante to avoid excessive name-dropping in call texts that may be interpreted as pre-requisite. An additional recommendation might therefore be to be clearer about why other projects are mentioned in call texts and what is exactly expected of applicant consortia in that respect.

5. Sustainability-by-design – More burden than blessing

Despite the huge success in terms of research collaboration and innovation across multiple stakeholders, the ultimate impact of most IMI projects on society depends on the capacity of each project Consortium to guarantee uptake of its results and ensure continuity of the necessary activities beyond the funding period of the IMI project, to fully leverage the value of its assets. However, most consortia struggle to come up with credible plans for sustainability. These, generically labelled as "sustainability" activities, are challenging for several reasons, including, among many other factors:

- Consortia are not legal entities themselves (and must therefore respect autonomy of their participants).
- Sustainability activities after the project period do not fall under the Grant Agreement and therefore require a *de novo* commitment from interested parties beyond the original commitment, subject however to ownership, access rights and other legal conditions imposed by the Grant Agreement and that survive the project phase.
- The long period (typically 7 years) between conception and conclusion of implementation, which sometimes implies quite radical changes in the scientific, business and institutional contexts.
- A lack of incentive for consortia to honestly appraise the true value of their generated assets.
- A general disconnect within institutions between the principal investigators and decision-makers in terms of long-term commitment.
- A general lack of knowledge and experience within consortia about business planning, assessment and set up, which hampers an appropriate analysis of value of assets and of the ways in which these could be sustained and expanded.

In this context, the general trend to alleviate these problems seems to be to advance as much as possible consideration of sustainability aspects, even to the point that it is recommended that this is done at the beginning of projects, or even before that. Unfortunately, this only may help intra-Consortium reflection and consensus, but not necessarily buy-in or uptake by potential funders or customers, particularly because the inherent risks of collaborative, distributed research efforts prevail until results are solid enough to gauge their exploitation potential (typically during the second half of any project).

RECOMMENDATION: NEURONET would have several suggestions regarding to the sustainability of assets of IMI projects. A first option could be to formalise the requirement for a "sustainability fund" to be set aside by a consortium for each new IMI project. The amount of sustainability fund for each new project should be determined by the anticipated value of the assets. Another possibility might be to create a central "sustainability fund" at IMI. The central sustainability fund at IMI could be dedicated to the asset maintenance of IMI projects, enabling a transition from project to self-sustainability status. Similarly, central structures (databases) for data assets could be set up, including mechanisms for access to federated resources, data discovery, etc. that act as reference point for current and future projects Finally, NEURONET would suggest the possibility of a separately funded IMI virtual incubator for innovations to objectively appraise assets and their sustainability prospects, to cover the transition to the 'market' phase, and act as a magnet for external funders and investors (see section 3.4.1 below), also taking advantage of complementary and synergistic results from different projects that could be mutually reinforcing and enhance value.

Stage 1: Call launch, 2-stage submission and evaluation of project proposals

1. Selection Process – Not always most fit for purpose

The selection process between EPFIA and Academic partners results in forced marriages that are not always fit-for-purpose. The selected applicant consortium (academic partners) should be taken 'as such' although maybe not all academic partners truly have the best skill set or are perfectly suited (or sufficiently committed) to deliver.

> *RECOMMENDATION: In case that the selected applicant consortium* generates doubts about future performance, more flexibility for enhancing the Consortium at the Stage 2 application would be desirable. In addition, the process should allow critical analysis of partner capabilities and balance essential vs. nice-to-have experiences/assets, with most efficient completion of project objectives in mind.

2. Stakeholders – Too many fish in the pond

Having too many stakeholders in a consortium not only creates an enormous internal overhead (e.g. administrative), it also creates the risk of having many absent or silent partners and not getting true value for money. The IMI system should allow for more flexible switches in terms of partnership, and the possibility to reallocate tasks and/or responsibilities. This is possible through Grant Agreement amendments however this is not very frequently implemented, generating expectations of permanence that are somewhat independent of performance. Participating organisations should also take the actual capacity for Work Package (WP) leaders to manage workstreams into consideration. WP leaders do not always have the ability, time and resources required to continually ensure the progress of workstreams, which can negatively impact project delivery. This 'Consortium entropy' problem also applies to external stakeholders which sometimes are requested in the call (regulatory authorities, patient organisations, etc.). This kind of relationships could be managed at the portfolio level instead of leaving it to each project to 'fight their war' alone.

3. Public Private Partnership participant – Yes, this means sharing in some way or another

Stepping into a Public Private Partnership (PPP) requires a level of willingness to share amongst both public and private partners, something that does not always materialise in practice. A pertinent example here is that partners are not always fairly acknowledged when sharing data with others. This acknowledgement should reflect their efforts in collecting the data, as well as the efforts required to manage the burdensome administrative and legal processes that underpin secure, ethical data sharing. A duality between project-level and partner-level commitments may create problems.

> *RECOMMENDATION: NEURONET would propose that the legal and practical terms for sharing of resources, data and know-how should be formalised from the start of a project (e.g. endorsing the Data Citation Principles, ensuring that data DOIs are appropriately used, providing specific guidance for biobanking and data storage, etc*). Higher flexibility to manage partnership during the proposal and project stages would allow consortia to continuously strive for efficiency. Milestone-based payments (as opposed to cost reimbursement) could benefit performance-based assessment of participants.

Project preparation & execution

1. Administration – Unavoidable necessity

In general, administrative requirements when stepping into the IMI framework are generally considered as being quite cumbersome. Legal documents/procedures (e.g. preparing, negotiating and finalizing a fully

executed Grant and Project/Consortium Agreement) are very time-consuming, leading to excessive use of templates and default conditions that are not adapted to the project's reality.

During the project execution, it might be that two IMI projects are formally willing to collaborate by means of a collaboration agreement. However, this is often an administrative hurdle. In order to share results, assets, confidential information and/or other solutions between two IMI projects, all beneficiaries of both projects frequently need to approve and sign a dedicated collaboration agreement, leading to a very time-consuming process causing major delays and sometimes completely undermining timely collaboration. As an example, due to major delays on concluding the PHAGO-IMPRiND collaboration agreement, the mice were aged too old and could not be used anymore leading to a waste of resources. In general, the perception is that a strategic move from 'project' to 'asset' value consideration, and from 'bureaucracy fulfilment' to 'tangible result obtainment', would be beneficial for all.

RECOMMENDATION: NEURONET would propose to simplify the procedure of a formal collaboration agreement by changing the signature procedure which will not require the signature of the legal representative of all beneficiaries of both consortia, but only those directly affected or owning the assets in question.

2. Non-performers – Easy way out?

There is a general feeling that having an easier way out for non-performing partners would be beneficial in an IMI project. There is a social/psychological aspect to it, but the Coordinators or Leads do not always have enough leverage to do this. The budget and task reallocations are not always straight-forward, and Grant Agreement amendments require time to formalise. Due to their inherent limitations, IMI official reviews only assess consortia as a whole, and not individual participants.

3. Common elements - Centrally managed project aspects

Some project elements could potentially be managed centrally (by IMI) by providing tools to the IMI projects for communication (e.g. communication plan, templates, etc), by providing technical solutions (e.g. website platform, data hosting, etc) and by providing also project management tools (e.g. Sharepoint for projects, etc). This would not only allow more efficient use of resources but would also centralize project information, project datasets, etc. without the risk of losing track of this information when individual projects end.

4. Project Extension – Just not there yet

Request for extra time and/or extra resources at the end of the initial IMI project are quite common. A project extension will buy the consortium some extra time (no cost extension) but in certain cases an extra award of resources could secure the finalization of the development of a certain asset or to make the asset sustainable. The IMI programme foresees such extensions (e.g. IMI 1 ENSO and IMI 2 restricted calls) but this could benefit from a more transparent award process, as well as no limitation on whether the possibility of a later restricted Call was already included in the original topic description.

3.3 Map of assets

One of the main outputs from WP1 resulting from the data collection strategy described in section 2 above has been the design and development of a first version of an "IMI ND asset map", i.e. a comprehensive view of the different assets resulting from IMI ND projects. Currently, an interactive version of it is accessible through the NEURONET Knowledge Base, which allows users to click through the different project logos and obtain more detailed information about the asset they represent. The complete list of assets, which undergo validation by the respective projects is:

PROJECT	ASSET
ADAPTED	Omics data from iPSC cells, humanised ApoE mouse models
ADAPTED	Omics data from CSF/plasma from MCI patients
ADAPTED	Biosamples from people with AD, MCI, or healthy individuals
ADAPTED	iPSC-derived cell models of ApoE risk alleles
ADAPTED	Role of the ApoE gene in AD
AETIONOMY	AETIONOMY PD cohort
AETIONOMY	Clinical, neuroimaging and -omics datasets from AETIONOMY PD study
AETIONOMY	DNA, CSF, plasma, serum and fibroblasts samples from the AETIONOMY PD study
AETIONOMY	AETIONOMY Knowledge Base
AETIONOMY	NeuroMMSig server
AETIONOMY	In silico model of neurodegenerative disease mechanisms
AETIONOMY	Mechanism-based taxonomy of AD and PD
AETIONOMY	Mechanism-based pathophysiology of AD and PD
AMYPAD	Diagnostic and Prognostic study (DPMS)
AMYPAD	Prognostic and Natural History study (PNHS)
AMYPAD	Neuroimaging datasets from the AMYPAD PNHS and DPMS studies
AMYPAD	AD neuroimaging data risk prediction model
AMYPAD	Value of amyloid imaging in AD diagnosis, prognosis, and potential for treatment monitoring
EMIF	EMIF-AD multimodal biomarker discovery study (MBD)
EMIF	EMIF-AD 90+ study
EMIF	EMIF-AD PreclinAD study
EMIF	EMIF platform EHR resource
EMIF	Clinical, neuroimaging and -omics datasets from EMIF-AD MBD, 90+ and PreClinAD studies
EMIF	Plasma, DNA and CSF from the EMIF-AD Multimodal biomarker discovery study (MBD)
EMIF	Blood samples, CSF and skin biopsies from participants of the EMIF-AD 90+ study
EMIF	Blood and CSF from participants of the EMIF-AD PreclinAD study
EMIF	EMIF Platform and Catalogue
EMIF	DTA Templates
EMIF	Risk factors for amyloid pathology, predictors for cognitive decline: clinical biology of AD
EPAD	Clinical, biomarker and neuroimaging data from the EPAD LCS study
EPAD	Longitudinal Cohort Study biosamples
EPAD	Trial Delivery Centre (TDC) network
EPAD	The EPAD Register
EPAD	Proof of Concept Trial Platform
EPAD	Participant Registry in EPAD (PREPAD) tool
EPAD	Ethics work on biomarker disclosure
EPAD	Procedures for trial delivery centre certification, agreement template, etc.

EPAD	Understanding of earliest stages of AD
EPAD	Research Participant Panel
EPAD	EPAD Academy
EQIPD	Animal data from multi-site experiments
EQIPD	EQIPD Training Platform
EQIPD	Ontology for describing animal experiments
EQIPD	EQIPD Quality System
EQIPD	Variables in preclinical AD research that influence outcomes
EQIPD	Living systematic review
IM2PACT	Omics data on patient tissue and cellular disease models
IM2PACT	In vitro and in silico models of the blood-brain barrier
IM2PACT	Biology of the BBB and transport mechanisms
IMPRiND	Pre-clinical modelling of protein aggregation in PD and AD
MOPEAD	Engagement approaches for different patient groups
MOPEAD	Protocols for patient engagement
PHAGO	Neuroimaging data from the KCL neuroimaging study
PHAGO	Data and Knowledge platform from Fraunhofer
PHAGO	CSF samples from the TREM2 variant cohort of KCL
PHAGO	Tools and assays for targeting and analysing TREM2 & CD33
PHAGO	Function of TREM2, CD33 and related immunomodulatory pathways in AD
RADAR-AD	Real-world data from RADAR-AD study of multiple wearable and digital devices
RADAR-AD	Technology and device guidelines for evaluating ADL
RADAR-AD	Digital biomarkers to evaluate functional decline in AD
RADAR-AD	Patient Advisory Board
ROADMAP	Data Cube
ROADMAP	EXAG Advisory Agreement Template
ROADMAP	Knowledge on how to approach data sources
ROADMAP	Relevant functional outcomes for different stakeholder groups
ROADMAP	EXAG model for regulatory interaction
ROADMAP	Outcome Definition Team, including the European Working Group of People with Dementia

For graphical representation, assets are classified according to their nature (datasets, disease models, cohorts, etc.) and according to their position along the drug development pipeline (non-clinical, clinical, etc. – see figure 3).

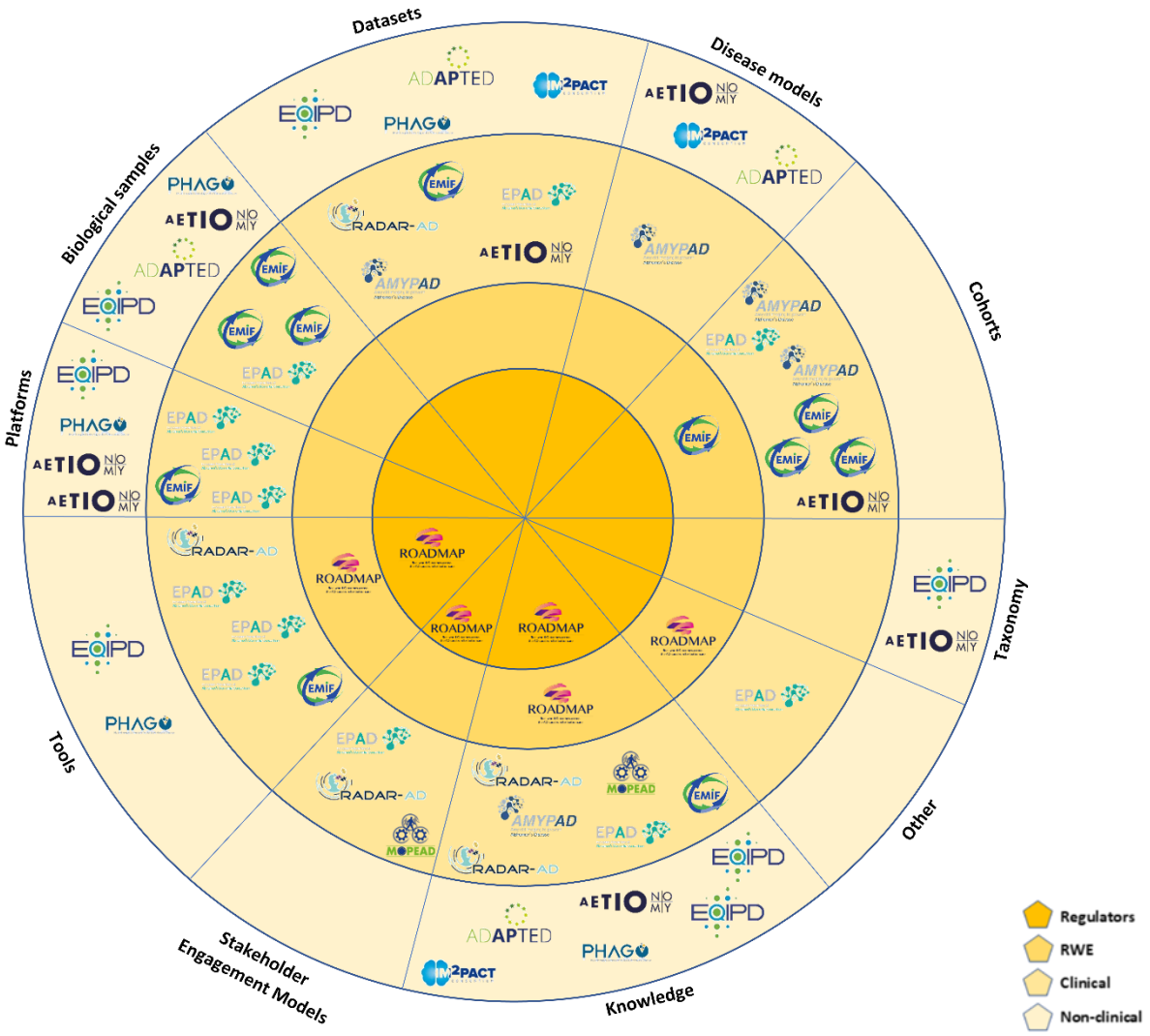


Figure 3. Asset Map

A preliminary analysis of the asset map offers some hints at the current results of the IMI ND portfolio:

- There seems to be a general lack of outputs relevant for regulatory purposes and real-world evidence studies. In that space, the programme seems to have relied on the ROADMAP project, however this was by design a short exploratory project lasting only two years. Admittedly, recent failures in Alzheimer's trials and general negative mood across industry may have hindered creation of new projects in those critical areas that will be essential when new therapies arise.
- There seems to be a lack of outputs in terms of taxonomies/vocabularies, although most projects have to deal with issues related with such outputs. This may indicate that the field is assumed to be adequately covered in terms of taxonomies and therefore 'off-the-shelf' solutions are generally used. This however clashes somewhat with known difficulties in terms of interoperability of data sets.
- Areas relative to platforms, data sets, samples and cohorts seem to be covered by several projects.
- Not many tools seem to be developed in the preclinical space.
- As could be expected, outputs that can be defined as "knowledge", are abundant.

The asset map is undergoing review and validation by the different projects. It is expected that a continuously updated asset map will allow to better illustrate the results and impact of the IMI ND portfolio, and devise new projects that address unmet areas of research. It may also help to devise flagship projects that specialise in solving common challenges to allow repetition of efforts and overlapping objectives, leading to more efficient use of resources.

3.4 Potential synergies and new ideas

One of the objectives of NEURONET is to proactively detect and propose actionable items to enact specific synergies and collaborations (e.g. re-use of results) between IMI ND projects. As a result of the integrated analysis, NEURONET identified the following links and potential collaborations between projects. These are not formal proposals and are not to be understood as real possibilities, because many factors may affect their feasibility or logic. They are just intended to depict the potential benefits of the holistic view across the programme that NEURONET represents.

MOPEAD: The project developed several educational videos and infographics for people worried about memory loss. These materials for public education should be disseminated across the portfolio to be used for raising awareness, educating citizens and promoting patient engagement in research studies and clinical trials. Moreover, they also developed a factsheet with recommendations for policy makers and regulators. All materials are available on the project website, however there is no apparent use of those by other projects dealing directly with patients or citizens in general.

EQIPD: The project aims to support and improve the quality of the work done in preclinical research by developing e-learning materials (and organizing a summer school) to promote preclinical research rigour and robustness in study design, data analysis and reporting of results. The EQIPD training materials could immediately be disseminated to all projects conducting preclinical research studies (**ADAPTED, IM2PACT, IMPRIND, PHAGO and PD-MITOQUANT**) or become a new requirement in future IMI calls.

IM2PACT, ADAPTED, IMPRIND and **PHAGO** use bioinformatics, iPSC-derived cell models, animal models and brain tissue samples to gain a better understanding of AD biology and pathological mechanisms for target identification and drug discovery. Samples and data generated by these projects could be shared or combined for integrated analysis or development of new research projects or validation studies. The cell lines generated could be submitted to the **EBiSC** bank, and the experience of **AETIONOMY** in data integration and management could also be useful for these projects.

IMPRIND and **PD-MITOQUANT** study the biology and pathological processes implicated in PD (misfolded protein propagation and mitochondrial dysfunction) to discover innovative therapeutic targets that can be further developed by the pharmaceutical companies. Samples and data generated by these projects could be shared for integrated analysis, which could facilitate the identification and validation molecular drivers and finding new strategies to prevent PD (e.g. investigating the role of a-syn in mitochondrial dysfunction, and its interaction with tau).

EPAD and **RADAR-AD** both have engaged patient representatives in their activities: The Research Participant Panel in EPAD and the Patient Advisory Board in RADAR-AD. The two groups could work together to produce a report with recommendations for successful patient involvement in European research studies from the patients' perspective (e.g. how can they best contribute, what must be improved etc).

AMYPAD, RADAR-AD and MOPEAD focus on the identification of tools and strategies for earlier diagnosis of AD from three different perspectives: PET imaging, remote assessment using digital technology and sensors and patient engagement models. The results and combined learnings from these projects could be become the basis for future research projects delving into the prevention and early diagnosis of AD. Rather than an 'active' collaboration this could be seen as a post-hoc exercise to integrate their results.

RADAR-AD, RADAR-CNS, MOBILISE-D and IDEA-FAST focus on the use of mobile and digital technologies for the continuous assessment of patients with neurodegenerative diseases. All these projects are heavy on data management therefore sharing the need for a robust and secure database and digital management platform that is compliant with legal and data privacy requirements to support data acquisition, storage and analysis of information. Furthermore, they all need to develop protocols for data integration, analysis, storage and sharing. Of the four projects listed, RADAR-CNS is the oldest (started in 2016) and could share the technical and computing knowledge acquired, and the data analysis expertise developed with the three newer projects that started in 2019-2020.

PRISM, **MOBILISE-D and IDEA-FAST** are projects that superseded the traditional approach in research studies, i.e. to focus on a particular disease or diagnosis, and instead followed an innovative approach: the study of symptoms or signs that are common to different pathological conditions (in this case, social withdrawal, gait abnormalities and sleep disturbances). The aim is to predict adverse medical outcomes regardless of underlying disease and to liaise with health authorities and regulators so novel clinical readouts or digital endpoints can be accepted for use in clinical research and clinical practice. This approach might contribute to a new classification or taxonomy of ND conditions, and has clear links with **AETIONOMY,** a project that used computational models to identify underlying disease mechanisms and to propose a rational disease taxonomy for AD and PD.

PD-MIND will carry out a RCT across multiple centres in different countries to test a nicotinic agonist drug for PD-MCI. Moreover, patients and other stakeholders will be involved from the start to ensure their viewpoints are taken into account in the design and execution of the trial. Although PD-MIND seems to have their 10 study sites already identified, the experience of **EPAD** in establishing the TDC network and the role of the Research Participant Panel could be of interest for them.

IMPRIND studies propagation of misfolded tau considered the main culprit of neurodegeneration in AD. Data generated by IMPRIND could be combined with clinical data and samples (e.g. PET scans, CSF, brain tissue) for an integrated analysis to improve our understanding of the pathological role of tau (e.g. propagation cycle, tau tangle spread, toxicity, cognitive defects, etc.). **AMYPAD** have expressed an interest in collecting tau scans (a highly innovative approach, as tau PET imaging has only been available for approximately the last 5 years) although this is not part of the project workplan and currently there is no budget for these scans. However, these two projects share an interest in tau protein so maybe in the future their common interest could be pursued in novel research studies investigating not only AD but also other tauopathies (e.g. FTD, PSP, CDB, etc).

EPAD has developed during the last 4 years a longitudinal cohort study of some 1600 participants that are followed up regularly through a network of 30+ centres across Europe, with standardised assessments and regulatory-level practices. With the end of the project foreseen in 2020, there is a risk that such a precious resource is lost and only collected data and samples remain. These would be valuable in themselves for other projects in the portfolio, but the EPAD cohort could also be transformed into a jointly-owned, wider European neurodegeneration cohort that uses a simplified protocol but includes assessments relevant to other ND beyond AD. This cohort could then become a common 'resource' across projects so that recruitment needs of current (such as **AMYPAD**, **PD-MIND** or **RADAR-AD**) or future projects can be streamlined and facilitated thanks to the existing network of centres, which could be expanded.

In addition, NEURONET has also been working closely with the SCB to promote synergies and develop completely new ideas of interest for the portfolio that could potentially become new research projects or initiatives. These are being reported to IMI and the Neurodegeneration SGG, although their funding doesn't have to solely rely on IMI. They showcase the benefit of creating a forum across leaders of the different projects that can act as a cradle and brainstorming space about needs that may not ordinarily be detected by funding agencies. These new ideas resulting from discussions at the SCB are described in the following sections.

3.4.1 Virtual incubator for sustainability

A Virtual Incubator for IMI projects (VIP)

A proposal for consideration towards future IMI calls

Prepared by: Carlos Díaz

The IMI project portfolio represents an unprecedented wealth of public-private partnerships carrying out research and development activities on biomedical sciences, with huge potential impact on patients, industry, health professionals, governmental agencies and many other stakeholders. Anchored on industry needs, and therefore extremely pragmatic in nature, IMI projects typically take 1 to 2 years to conceive and design, and 3 to 6 years to implement. More than 100 projects have been funded under both IMI-1 and IMI-2 programmes to date, with hundreds of institutions and thousands of researchers involved, both in the EU and beyond, representing a large variety of stakeholder groups.

Despite this huge success in terms of research collaboration and innovation across multiple stakeholders, the ultimate impact of most IMI projects on society depends on the capacity of each project Consortium to guarantee uptake of its results and ensure continuity of the necessary activities to fully leverage the value of its assets. These, generically labelled as "sustainability" activities, are challenging for several reasons, including, among many other factors:

- Consortia are no legal entities in themselves (and must therefore respect autonomy of their participants).
- Sustainability activities after the project period do not fall under the Grant Agreement and therefore require a *de novo* commitment from interested parties beyond the original commitment, subject however to ownership, access rights and other legal conditions imposed by the Grant Agreement and that survive the project phase.
- The above-mentioned long period between conception and conclusion of implementation, which sometimes implies quite radical changes in the scientific, business and institutional contexts.
- A lack of incentive for consortia to honestly appraise the true value of their generated assets.
- A general disconnect within institutions between the principal investigators and decision-makers in terms of long-term commitment.
- A general lack of knowledge and experience within consortia about business planning, assessment and set up, which hampers an appropriate analysis of value of assets and of the ways in which these could be sustained and expanded.

As a consequence, most consortia struggle to come up with credible plans for sustainability, and the most practical solutions tend to recurrently fall into two basic options: instigate a follow-up, publicly-funded project, or have industry fund directly any follow-up activities. Both solutions are generally difficult and sub-optimal and may ultimately fail to actually deliver value or maximise uptake by the appropriate stakeholders.

In an attempt to ameliorate the problem, funding agencies are increasingly requesting consortia to advance sustainability activities as much as possible during the project life. This is useful in terms of creating "sustainability-aware" projects already from the initial stages. However, the problems listed above remain – most notably, the fact that, by definition, the vast majority of these projects are research and development activities, for which risk and uncertainty are inherent characteristics, and where the actual results are yet to be obtained or produced during years before any serious appraisal is possible in terms of basic elements such as what is of value, how it will be delivered, why such delivery will be better than any alternatives or competition, who will want to pay for such value, etc. The danger is that any sustainability deliverables are only theoretical and not grounded on real potential for success in the market.

Despite current efforts, an impending need still exists to maximise and demonstrate return on the huge public-private IMI investment in terms of real impact on society, better products and solutions that ultimately help citizens get access to better healthcare.

In this context, a Virtual Incubator for IMI Projects (VIP) is proposed to help projects bridge the gap towards sustainability in a consistent manner. Business incubators have been widespread over the last decades in Europe and elsewhere into the thousands, as a way to support new and start-up companies in their critical initial stages in order to maximise their chances for successfully enter the market, grow and develop until they're ready to fly on their own. Incubators are typically developed by local and national authorities, and more recently as well by big corporations as part of open innovation programmes. In essence, incubators try to compensate for the archetypical lack of resources of start-up companies in areas such as office space, fundraising, access to loans and guarantees, logistics, computing and internet facilities, mentoring, business knowledge, marketing assistance, networking, technology appraisal, etc.

Obviously not all of these are needed or applicable to IMI projects, but on many aspects they do resemble start-up companies when they try to make the shift from a 'project mindset' to a 'sustainability mindset'. They need to select their most valuable assets, consider ownership of those (thereby maybe not extending sustainability efforts necessarily to the whole Consortium), prioritise business logic over scientific-political considerations, honestly assess their competitive advantage, obtain sound financial projections well beyond the "wishing well", devise the most appropriate organisational structure for value delivery, etc.

A VIP could act as neutral party to:

- Objectively assess the assets resulting from each project and their true chances of succeeding in the market, including technology maturity appraisal.
- Support projects with expert knowledge on business planning and development, marketing, financial projections, project management, legal and IP issues, organisation, etc.
- Offer mentoring and assistance services to continuously support the initial steps of the project until full sustainability is reached.
- Training of project teams on key aspects related to sustainability and business development.
- If needed, help projects with fundraising by facilitating channels to the appropriate sources (venture capital, business angels, charities, philanthropy, national and international grants, etc.).
- Offer networking possibilities and economies of scale thanks to a wider perspective on all projects.

The existence of such incubator could be a perfect complement to the current sustainability plans developed by each project, which could go beyond the mere 'declaration of intentions' to actually serve for an initial appraisal. Admittedly, not all projects should be able to benefit from the incubator, and some assessment and filtering may be necessary to be able to focus incubators resources where the potential benefit is highest. Resulting from such initial assessment, successful project teams should commit to a clear plan of action and key performance indicators that would act as kill-points at regular intervals to evaluate the impact of the VIP,

the maturity level reached and renewal of incubator support. It is estimated that incubator support may range from a minimum of one year to a maximum of four years, and it could start already during the project phase, so that transition into sustainability is accelerated if a good basis and sound business case is present already.

The VIP team should consist of experts in the above-mentioned areas, preferably with knowledge on EU and particularly IMI private-public partnerships, and governance should include a variety of stakeholders, including funding agencies and potential investors.

3.4.2 High level neurodegeneration summit

High level neurodegenerative disease summit

Prepared by: Craig Ritchie

BACKGROUND

Across the world there are numerous major research initiatives who share very similar objectives; namely to deliver an enhanced understanding of disease mechanisms that lead to and accelerate the course of neurodegenerative brain disease. Insights gained if these objectives are met will have several clinical benefits: [1] early disease detection, [2] risk profiling early in the course of disease, [3] empirically based precision therapeutics (and prevention strategies) and [4] new target elucidation driving drug discovery and development. Unfortunately, these major research initiatives only communicate and learn from each other though the traditional routes of academic publication and conferences.

The science underpinning these developments ranges from fundamental sciences, data science, translational epidemiology, clinical trials (experimental medicine, Phase 2 and Phase 3) as well as social sciences research.

The investment from the public, philanthropic and commercial purse is massive so much so that the lack of progress over 20 years should mediate a serious review of the approach. It is not considered that the scientific approach is erroneous but rather that left to the traditional routes of non-strategic, multi-player academic and commercial delivery we will most likely continue to fail to deliver on the 4 clinical benefits noted that are so evidently needed.

To this end the IMI programme developed NEURONET to create the environment for the IMI Neurodegenerative disease projects to coordinate activities to help generate greater knowledge more effectively, more efficiently and more rapidly. The NEURONET model has yet to yield tangible success but has already started to make progress in identifying project synergies within the IMI portfolio and shared objectives that can be leveraged between projects.

Therefore, NEURONET seeks to expand this model to a global scale. This would be by establishing a high level forum for programme leads to ultimately develop a global research strategy for neurodegenerative disease research developed by the programme leads in isolation of the pressure from funders, commercial drivers and other stakeholders with vested interests in a specific approach. Specifically, this should not include funders because it should be the scientists involved in programme delivery who should map out the critical steps to which the funders should respond. This is a reverse of the existing situation which empowers funding organisations to set the research agenda rather than the researchers.

PROCESS

The key programmes which NEURONET will convene leaders from are:

- DIAN (Dominantly Inherited Alzheimer's Disease Network)
- EPAD (European Prevention of Alzheimer's Dementia) Programme
- A4 Programme
- JPND (Joint Programmes on Neurodegenerative Diseases)
- API (Alzheimer's Prevention Initiative)
- ADNeT (Australian Dementia Network)
- UK-DRI (UK Dementia Research Institute)
- DZNE (German Centre for Neurodegenerative Diseases)
- ADDI (Alzheimer's Disease Data Interoperability) Initiative
- ADDF (Alzheimer's Drug Discovery Fund)[1]
- DDF (Dementia Discovery Fund)[1]
- GBHI (Global Brain Health Institute)
- DPUK (Dementias Platform UK)

Scientific Leads/Directors from each of these programmes will be contacted to gauge interest in the principal of the meetings as well as to provide insights into other programmes that may have been overlooked in the initial scoping exercise. Moreover, where the leads of the programme as a whole fail to cover crucial topics e.g. data sciences – then experts can be brought into the group as full members.

The final list of Scientific Leads/Directors will then be invited to a 2-day initial research summit to generate a white paper on the scientific needs of the field. NEURONET will coordinate this meeting and provide all logistic and administrative support. Consideration will be given to identifying a journal e.g. NEJM/Lancet to carry the white paper and provide editorial assistance in developing it.

The key objectives of the meeting are:

[1] To set a series of high-level objectives for the neurodegenerative research field with a view to improving clinical care and prevention.

[2] To identify key roadblocks to achieving these objectives.

[3] To formulate an action plan for between programme research.

The group will meet every 2 years to review the 'progress against plan' as well as adapt the 3 objectives in light of progress or otherwise. To facilitate the meeting a steering committee and chair will be developed from the non-neuroscience field e.g. oncology, cardiovascular medicine or HIV where there has been tangible success against these major diseases.

SUMMARY AND NEXT STEPS

This meeting must set up in such a way that it avoids as far as possible being a short-lived political body releasing well-meaning statements with no downstream actions – rather the scale of the issues being faced mean that the group must position itself as an ideally informed, experienced and influential group which will take responsibility for an ambitious action schedule.

[1] We need to collectively decide whether ADDF and DDF are funders.

3.4.3 Harmonisation of ND datasets across Europe

Global NDD model and virtual cohorts

Prepared by: Sebastian Schaaf, Sumit Madan, Holger Fröhlich & Martin Hofmann-Apitius

Problem statement

In the neurodegenerative disease field, patient-level data appear to be highly scattered across different studies, organizations and information systems. However, integrated, high-quality data is a prerequisite for precision medicine, a paradigm that bears the promise of breakthrough in this challenging scientific domain. Unfortunately, strong barriers exist that prevent us from sharing and integrating data to a degree that we could use it for precision medicine research. In particular, concerns on data privacy seem to repeatedly impose major roadblocks to research. Even if sharing is made possible, practical issues on combining data from different sources hinder broad-scale research and secondary use of data. Namely, formatting of data, the syntax of transmission protocols, and, notably, the exact semantics of variables. As a consequence, combining data in most cases boils down to a mainly manual, pair-wise, error-prone and single-use process on the data itself, less using explicit metadata.

Vision for a solution

A possible solution to overcome these obstacles would need to address issues of integrative data semantics by formalizing a semantics-driven, field-specific, but generalizable data space or model. Its core obviously comprises a global variable catalogue, including a description of the values used to measure them and the relationships existing between variables. Such model could be represented with an ontology and a schema that together formalizes, represents knowledge about variables and their relationships and that supports mapping and normalization to equivalent variables. If the representation of such model is semantically rich, it will map to other existing ontologies and variable catalogues relevant for the neurodegeneration research domain. Representation as an ontology and a schema will enhance semantic interoperability, effectively rendering the possibility for graph models of related knowledge. According to the general nature of such graph representations, not only neurodegeneration research could be represented, but also related areas, such as psychiatric conditions.

Extending the approach for use as a referential data model for population-based, observational studies is straightforward: variables present in observational studies are integrated in the ontology and allow for mapping to entities in instances like the Dementia platform UK (DPUK), UK Biobank and other population studies. These could serve as wide-spectrum controls. In addition, placebo arms of clinical studies coming from EFPIA partners could be used to gather additional variables (and values) from highly relevant data collections. Technically, implementations of those efforts have to be in alignment with top-level standards like FHIR, CDISC, and OMOP.

Beyond preparing and using previously developed generative AI models, providing the opportunity to generate synthetic data within each data-hosting organization is feasible in such a broad and standardized data landscape. Synthetic data (virtual cohorts), constituting computable fingerprints, can then be shared with the outside world in a privacy preserving manner.

Usability and benefits

A global and consistent model for longitudinal, high-dimensional neurodegeneration data would allow to map existing data (and entire studies) to that model. A global model would greatly facilitate fundamental assessments of patient-level data, such as dimensionality, statistical power, limitations, imputations etc. in a much faster and efficient manner than separately going (often manually) through each study and mapping them pair-wise. Comparative and integrative modelling and mining of different studies becomes a realistic option.

In particular, the AI-generated synthetic data from each study would allow us to quantify the bias we may encounter with data from highly stratified studies (e.g. ADNI, PPMI, AddNeuroMed, AIBL). Moreover, combining different AI-generated synthetic datasets can result in a data-privacy-preserving "global cohort", which can be instantiated as a "global virtual cohort", i.e. a synthetic data set representing all relevant variables and a wide spectrum of observed distributions of variables enhanced with their dependencies. EFPIA partners could turn (part of) their clinical trial data into virtual cohorts and release them inside of their own organization; they could also "publish" part of their clinical trial data as completely virtualized, synthetic data sets, receiving synthetic data sets from other organizations in return.

This fundamental work lays the ground for future "true data science" in neurodegeneration research. It is noteworthy at this point that our approach outlined here can be ported to other adjacent and even more remote indication areas. We could even imagine that – based on the approach described above – the co-morbidity aspects of separate disease areas, e.g. neurodegeneration on one side and diabetes / metabolic syndrome on the other side, could be addressed.

Requirements

While a common data space developed as pure top-down approach may end in an excess of width and depth while lacking touch with clinical reality, we need input from major stakeholders in the "data science for neurodegeneration research" arena. In particular from those stakeholders, who have either controlled or observational study data (UK Biobank; Scandinavian EHR collections; Rotterdam cohort etc.). By content, a systematic collection of longitudinal cohort data and systematic comparative as well as integrative modelling of these study data sets are crucial. This applies to topics, variables, their specifications and relevance to wider audience of domain experts. The later have to be included from the US and Japan as well as other Asian countries, forming a research collaboration across the Atlantic and the Pacific. By introducing extension modules and integrating local concepts fragmentations following national or continental borders should be countervailed.

Technologically, an information system is required to make the global schema, the locally aligned datasets and the resulting virtual cohorts widely accessible and usable. On the one hand, rapid prototyping environments like Jupyter notebooks deserve a closer inspection, as providing functional libraries here could address several users from a broader audience, enabling them to handle and visualize data with high-level commands. On the other hand, dedicated server infrastructure needs to be developed and instantiated in order to serve as powerful backends. Ultimately, such an information system should comprise an interface that allows researchers all over the world to run "patients-like-me" scenarios, e.g. compare their own cohort against the global virtual cohort.

On a deeper level, we need to track the virtual cohorts synthesized - most likely by the use of "blockchain-like" technologies. Opposingly, there is an intrinsic need to perform constant "privacy / re-identification tests" on the virtual cohorts to ensure that virtual patients cannot be traced back to existing patients from the template real-world cohorts.

Taken together, we head for an infrastructure that manages the use of the global cohort: we want a widely used, ubiquitous available system for in silico experimentation, but we do not want un-ethical use of that system. We want to make this system accessible to scientists from all countries, but we want to know what is being done with this resource, e.g. we foresee the need of a citation reference policy similar to ADNI. We want people to publish their results and to share their experiences; therefore, we may need an open source model that allows people to work with the resource, to modify it and to improve it … but we do not allow commercialization of the common good of this resource.

3.4.4 Integration of registers and prospective data collection across Europe

Dementia platform Europe

Prepared by: Pieter Jelle Visser

Background

The development of treatment for Alzheimer's disease is progressing slowly. In order to speed up treatment development there are the following needs:

- Estimation of prevalence of preclinical, prodromal and dementia AD at local memory clinics. This will facilitate recruitment of individuals for trials;
- Insight in disease progression. This will help disease modelling and inform trial design;
- Infrastructure to measure treatment response in future Phase 4 trials;
- Access to samples for validation novel biomarkers.

In Europe there is an extensive network of specialised memory clinics. The connection of databases of local memory clinics in a federated database structure could be an efficient approach to obtain estimates on prevalence and disease progression. In addition, there are many prospective cohort studies with high quality data for disease modelling and biomarker validation. Some of these cohorts host their data on data sharing platforms but there is no central access point which limits visibility of these cohorts and their data and samples.

Aims and objectives

Aim of the project is to:

1. Set-up a federated database in order to obtain information on prevalence and course of AD using data routinely collected in memory clinics across Europe
2. To facilitate access to data from research cohorts.

Objectives:

- Select memory clinics with suitable data;
- Set-up a local database or web-based database if a memory clinic has no database;
- Connect memory clinic database to a federated database;
- Estimate prevalence of amyloid positive individuals on a bimonthly basis;
- Track rate of decline on MMSE, CDR of boxes and standardised memory tests using memory clinic data;
- Improve access to existing research cohort data and samples.

Approach

1 Technical approach

The intention is to make use of existing technical solutions that have been developed as part of other IMI and related projects.

1.1. Federated access

- EMIF-AD data model for harmonisation across memory clinics. This minimal dataset includes 40 variables
- Software for distributed data access: The memory clinics will be offered several possibilities to share data given the local technical and legal situation. Available options are EPAD-PREPAD, EMIF-AD switchbox, Dutch Personal Health Train and Human Brain Project Medical Information Framework.

1.2 Access to research cohorts

- EMIF-AD data platform: this platform provides data from 8 harmonised research cohorts, which can be downloaded for local analysis;

- Dementia Platform UK provides access to 30 research cohorts from the UK. The platform provides data analysis possibilities on the platform and data cannot leave the platform. (A copy of the DPUK instance will implemented in Europe- pending Brexit or an alternative solution with similar functionalities will be used);

Both platforms have a catalogue of meta-data from cohorts. These need to be merged.

2 Cohorts

2.1. Memory clinics: Memory clinics will be included that routinely collect data on amyloid positivity, cognition, function, and imaging. The project will include EPAD trial delivery sites, and partners from the European Alzheimer's Disease Consortium (EADC), a network of over 50 memory clinics across Europe.

2.2. Research cohorts: all cohorts that collect data on aging and dementia would be eligible

Workplan

1) Select memory clinics for federated database
2) Support set-up local databases if needed
3) Connect 50 memory clinic database to federated database
4) Make different federated database interoperable
5) Run queries on amyloid prevalence and disease course in memory clinic data
6) Develop common portal for access data from research cohorts
7) (set up copy of DPUK platform in Europe-pending legal/Brexit issues)
8) Develop legal framework for data access (ELSI)

References (selection)

Lovestone et al, The European medical information framework: A novel ecosystem for sharing healthcare data across Europe; Learn Health Sys. 2019;e10214

Lisa Vermunt et al, European Prevention of Alzheimer's Dementia Registry: Recruitment and pre-screening approach for a longitudinal cohort and prevention trials; Alzheimer's & Dementia 14 (2018) 837-842

xxRef DPUK, HBP- MIF, personal health train

3.4.5 Neurodegeneration European Information Portal "NEUPORTAL"

NEUPORTAL – A common data discovery resource

Prepared by: Carlos Díaz

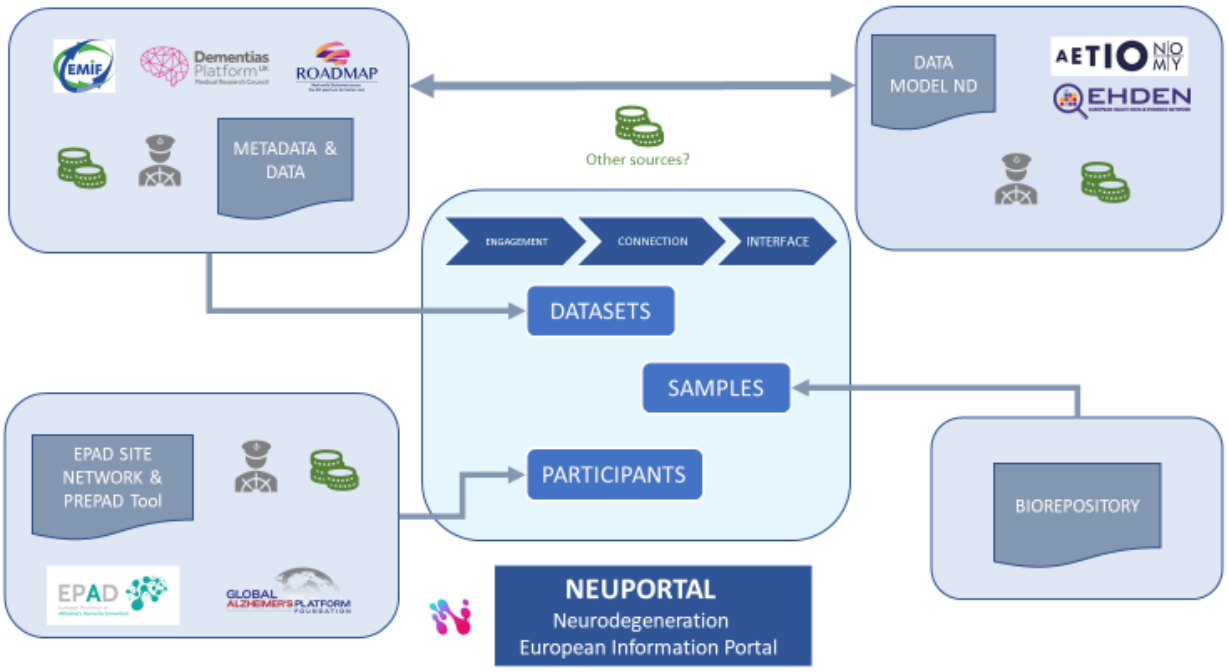


Figure 4. Neurodegeneration European Information Portal "NEUPORTAL".

Many IMI ND projects recruit research participants in order to generate data and samples. Data however are frequently not harmonised, the existence of samples only really known to project partners, and participants moved to other studies as appropriate. There is an impending need to have an integrated resource that allows to:

- Know which datasets are where, what they contain exactly and how data can be accessed. Some efforts have been carried out by **EMIF-AD**, Dementias Platform UK (**DPUK**) and **ROADMAP** to provide such 'catalogue', however all of these are separate.
- Have ways to harmonise the different data sets. A tool for this could be a common data model such as the OMOP CDM (www.ohdsi.org), which is promoted by the IMI project **EHDEN**. Similarly, the IMI ND project **AETIONOMY** has also been tackling taxonomy and data integration challenges, and its efforts could be leveraged.
- Know which samples are where, what they consist of exactly and how they can be used. There are many different biobanks but no single resource to allow searching across all of them.
- Many projects need to recruit patients for their studies. The **EPAD** project has created a tool (called PREPAD) to allow discovery of participants with certain characteristics across many European parent cohorts in an ethically safe manner. This tool could be leveraged to accelerate recruitment and engagement with appropriate local/regional/national cohorts or specific memory clinics, for example.

All things considered, a central resource that allows for searching and discovery of suitable data, samples or research participants across Europe could be an invaluable asset to accelerate research in IMI projects and beyond. This "NEUPORTAL" could be based on a federated data architecture so that no actual transfer of data is needed to a central database; it would simply establish connections with harmonised subsets of discovery variables at a local level, and offer a common user interface to enable queries and aggregated results – telling you where your data/samples of interest reside (and how you can access them), or which cohort is following up patients with the profile needed for your study.

4 Conclusion and next steps

The picture revealed by the integrated analysis carried out by NEURONET portrays a complex landscape in IMI ND research: there are nearly 200 institutions from 34 different countries involved in a total of fifteen consortia. Despite each of the projects has its own objectives, timelines, deliverables, milestones and results, NEURONET has been able to identify links and potential collaborations between these projects that could be exploited. The amount of information and data associated with these projects is vast and difficult to digest; therefore, NEURONET has focused on the main assets produced or developed by the projects, upon recommendation of the SCB. The result of this exercise is the asset map, which offers a global view of the productivity of the IMI ND portfolio, and that will be validated, then refined and updated when data from new projects becomes available. NEURONET has also examined the cross-project collaborations attempted so far, and elicit lessons learned. Finally, it has created a space with the SCB to discuss new potential synergies and collaborations, and completely novel ideas that could become future projects or initiatives.

Deliverable *D1.5 Integrated programme analysis v2* (due in month 24) will:

- Provide updated information on the IMI ND portfolio, including any new projects that join NEURONET.
- Provide an updated version of the asset map.
- Provide an updated collaboration network, highlighting synergies between IMI ND projects.
- Report on whether any of the detected synergies or new ideas reported in this deliverable have been actually implemented.

5 Annexes

5.1 Annex I. IMI ND projects participating in NEURONET

The fifteen IMI projects of the ND portfolio participating in NEURONET at the time of writing this deliverable are the following:

1. ADAPTED
2. AETIONOMY
3. AMYPAD
4. EMIF (focusing on EMIF-AD)
5. EPAD
6. EQIPD
7. IM2PACT
8. IMPRiND
9. MOPEAD
10. PD-MITOQUANT
11. PHAGO
12. PRISM
13. RADAR-AD
14. RADAR-CNS
15. ROADMAP

5.2 Annex II. Project dossier template

Project information

Project title:

Project website:

Project Leader/Co-ordinator:

Project summary (IMI):

Project dates:

Project budget (EUR):

IMI funding:

EFPIA funding:

Other contributions:

Total budget:

Project partners:

X academic partners, Y EFPIA partners, Z SMEs, X patient organization, Y regulatory agency, Z associated partner

Institution name	Type of Institution	Country

Project objectives:

Work packages and WP leads:

WP ID	WP name	WP lead
WP1		
WP2	etc	etc

A FULL LIST OF WP OBJECTIVES AND DELIVERABLES IS PROVIDED IN THE ANNEXES

Project scope - Research and data collection

Does the project involve clinical studies?	**Yes/No/Don't know (if yes, provide details)**
Type of study	
Disease being studied	
Disease stage targeted	
Member states in which participants are being recruited	
Prospective data collection in humans	

Project outputs/results

Is the project developing/has the project developed any of the following outputs/results?

Yes/No

If yes, please provide a brief description.

	Yes	**No**	**Description**
Large datasets			
Biomarkers			
Methodologies / Techniques / Assays			
Classifications / Taxonomies			
Tools			
Infrastructures			
Other new disease knowledge			
White papers, Guidelines, templates etc.			
Diagnostic / prognostic tools			
Organisational models			
Clinical cohorts			
Other			

Is the project participating in the Horizon 2020 Open Research Data pilot*?

Yes; No; Don't know

If yes, what data is being included, and what platforms/repositories are you using to host this data?

**EPAD, RADAR-AD, IM2PACT and PD-Mitoquant are from Call 11 onwards, which means they automatically participate.*

Project expertise

Has the project developed (or does it have plans to develop) expertise in any of the following areas?

Yes/No

If Yes, please provide a brief description, including whether any reports or guidelines on the topics have been produced (deliverables or other).

	Yes	No	Description
Data sharing and re-use			
Patient privacy, data protection and GDPR			
Interactions with regulatory bodies and HTAs			
Exploitation and sustainability of project results			
Communication and dissemination			
Patient engagement strategies			
Digital solutions and use of technology			

Collaboration

Has the project used the outputs/results generated by:

Another IMI project? Yes; No; Don't know. If yes, please provide details.

A non-IMI project/initiative? Yes; No; Don't know. If yes, please provide details.

Have any of the project outputs/results been shared for use by another (IMI or non-IMI) project?

Yes; No; Don't know

If yes, please provide details.

Beyond NEURONET, is the project involved in a collaboration or network with another IMI project (e.g. memorandum of understanding or collaboration agreement signed)?

Yes; No; Don't know

If yes, please provide details.

Have any <u>new</u> collaborations or networks been established between project partners as a result of their involvement in this project?

Yes; No; Don't know

If yes, please provide details.

Professional development

Has the project provided any professional development activities for researchers working on the project (e.g. training or mobility programmes)?

Yes; No; Don't know

If yes, please provide details.

Patient and public engagement

Are patient/healthcare professional/carer organisations involved in the project?

Yes; No; Don't know

If YES, are they involved as:

Project partners: (yes/no/don't know)

Advisory board members: **(**yes/no/don't know)

Working group members: (yes/no/don't know)

Please provide details on the scope of their involvement (e.g. responsible for ethics deliverables, advising on consent forms, involved in communication & dissemination etc).

Are there any specific patient or public outreach/engagement activities that have been carried out within the project?

Yes; No; Don't know

If yes, please provide details.

Needs and difficulties

Based on initial discussions with the projects, the following four topics were identified as being key areas of difficulty: Data sharing and accessibility; Working with regulators; Patient Confidentiality; and Sustainability. For these areas, please describe any issues your project has experienced and any

approaches you have taken to overcome these. Please indicate if they are unmet needs (i.e. issues have yet to be resolved).

The table is aimed to help guide your conversations with the projects (i.e. no need to have an entry for each of these areas).

	Issue, and (if relevant) approach used to resolve the issue
Data Sharing	
Interacting with data sources	
Data sharing agreements	
Data/metadata standards	
Harmonisation of data/metadata from different sources	
Data FAIRification	
Data sharing infrastructure or tools (e.g. catalogues, repositories)	
Biological sample sharing (blood, CSF etc.)	
Financial cost of data sharing	
Patient data, privacy and ethics	
Informed consent	
Institutional Review Board or Ethics Committee approval	
Issues related to GDPR & data privacy	
Participant recruitment issues (high screening failure rate, etc.)	
Communication of research results to lay audiences	

Sustainability	
Funding models post-IMI period	
IP rights and exploitation	
Procedures for patents, licenses and trademarks	
Regulatory/HTA interactions	
Scientific Advice Procedure	
Engagement with regulators and HTA agencies	
Other areas	
Recruitment and retention of skilled staff	
Career development support for ECRs employed	
Administrative/bureaucratic tasks (e.g. reporting, deliverable submission, etc.)	
Decision making and conflict resolution within the Consortium	
Legal issues	
Budget management	

The aim of NEURONET is to boost synergy and collaboration across the neurodegenerative disease portfolio of the IMI. Beyond the issues or unmet needs identified in the previous questions, how could NEURONET best support your project in achieving this goal?

5.3 Annex III. Collaborations survey

1. **Projects involved in the collaboration:**

2. **What was the intended collaboration about? Please describe.**

3. **Was it materialised, totally or partially?**
    - Yes, totally
    - Yes, partially
    - No

Comments/Notes: _____

4. **If it was, were the results fully satisfactory for both projects?**
    - Yes
    - No

Comments/Notes: _____

4.1. Did it require legal support (e.g. signature of MoU, collaboration agreement, etc.)?
    - Yes – please specify: _____
    - No

Comments/Notes: _____

5. **If it was not, what were the main reasons?**
    - Lack of time
    - No person actively following up
    - Technical obstacles
    - Financial obstacles
    - Legal obstacles
    - Other reasons - please specify: _____

Comments/Notes: _____

6. **Any other details or lessons learned that you want to share:**