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Impacts of public-private collaborative research on Alzheimer's disease: The case of the Innovative Medicines Initiative

Edited by
Elisabetta Vaudano, Jean Georges, Monica Ensini, Martin Hofmann-Apitius and Donald C. Lo

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Impacts of public-private collaborative research on Alzheimer's disease: The case of the Innovative Medicines Initiative

Topic editors

Elisabetta Vaudano — Innovative Health Initiative, Belgium
Jean Georges — Alzheimer Europe, Luxembourg
Monica Ensini — Health and Digital Executive Agency European Commission, Belgium
Martin Hofmann-Apitius — Fraunhofer Institute for Algorithms and Scientific Computing (FHG), Germany
Donald C. Lo — National Center for Advancing Translational Sciences (NIH), United States

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EDITED AND REVIEWED BY
Bruce Miller,
University of California, San Francisco,
United States

*CORRESPONDENCE
Elisabetta Vaudano
✉ elisabetta.vaudano@ihi.europa.eu

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Editorial: Impacts of public-private collaborative research on Alzheimer's disease: the case of the innovative medicines initiative

Elisabetta Vaudano[1]*, Jean Georges[2], Martin Hofmann-Apitius[3] and Donald Lo[4]

[1]The Innovative Health Initiative Joint Undertaking, Brussels, Belgium, [2]Alzheimer Europe, Luxembourg, Luxembourg, [3]Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Bonn, Germany, [4]EATRIS, Amsterdam, Netherlands

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Editorial on the Research Topic
Impacts of public-private collaborative research on Alzheimer's disease: the case of the innovative medicines initiative

The number of people living with dementia, mostly due to Alzheimer's disease (AD), has been recently estimated at more than 50 million globally (1), and this is only expected to rise further and substantially as the world's population ages. If we look at the entire AD continuum, global prevalence estimates increase to >400 million people, or ~22% of all people aged 50+ (2). While these statistics are staggering, most of those affected are in the earliest stages of the disease, and this suggests that there remains a real window of opportunity for tackling the AD challenge and introducing prevention and risk reduction strategies.

For people with mild cognitive impairment from AD and early AD dementia, the first disease-modifying therapies have been approved by the Food & Drug Administration (FDA) and in Japan (3, 4). However, only a fraction of patients will benefit from these first therapies due to the biological heterogeneity of the disease and the lack of readiness of healthcare systems. In addition, the modest effectiveness of these new treatments will need to be balanced against their side effects and the burden of current dosing regimens (e.g., infusions every 2–4 weeks) (5).

Despite these positive developments, much more needs to be done to de-risk the dementia area and transform scientific knowledge into concrete patient outcomes. "Silos" must be broken and communities set to work with a common agenda, across the public-private space, to co-create solutions. This will avoid a waste of resources on both the public and industry sides and foster collaboration instead of fragmentation of efforts. This approach of "radical collaboration" has been very successfully implemented by the public-private partnerships (PPPs) of the European Innovative Medicines Initiative (IMI) and its successor, the Innovative Health Initiative (IHI) (6).

This Research Topic volume provides a flavor of the achievements and learnings gained through the PPP projects in the IMI/IHI AD portfolio (7). The 11 papers cover a broad range of challenges and opportunities in AD, focusing on those critical for the development of new diagnostic approaches and treatments.

Difficulty in finding and accessing high-quality data and samples is hindering the validation of biomarkers for use in developing both diagnostics and treatments in AD. The EPND (Bose et al.) (8) collaborative platform uniquely enables the sharing, reuse, and large-scale analysis of the high-quality data and samples needed to accelerate biomarker validation, while maintaining robust protection for data subjects and giving data and research additional usability, beyond original studies.

While new biomarkers are emerging, amyloid detection with positron emission tomography (PET) remains the workhorse for characterizing the start and spread of AD in both trials and clinical practice. The AMYPAD project (9) significantly furthered our understanding of amyloid deposition in the brain and the optimal methodology to measure this process across tracers, highlighting the utility of amyloid PET for both initial diagnosis and prognosis, and enabling optimal therapy monitoring and/or patient management (Collij et al.) .

In clinical trials for AD and other neurodegenerative diseases, there is a critical need for novel outcome measurements of sufficient sensitivity, especially in the early stages of disease and for studying disease progression. In this context, digital endpoints could be game changers. Brem et al. share important learnings and findings from the RADAR-AD (10), MOBILIZE-D (11), and IDEA-FAST (12) projects on the value of remote technologies for assessing neurodegenerative diseases. They discuss the feasibility, acceptability, and usability of digital assessments, as well as the challenges, and regulatory learnings, emphasizing the importance of public/patient involvement and inter-project exchange as well as data and algorithm sharing.

Innovation in clinical trial design is a must for speeding up treatment development for AD, Saunders et al., and EPAD (13) pioneered the concept of platform trials, delivering key learnings and open assets. These include the EPAD longitudinal cohort study (LCS) data and biobank, and the trial network is now incorporated into the Global Alzheimer's Platform (GAP) for a truly global impact.

Fragmentation of data, results, and initiatives remains a major underlying issue in the AD field (and beyond) and is one of the key factors slowing down progress. The EHDEN (14) project is spearheading a new approach for the aggregated analyses of hundreds of millions of electronic healthcare records (EHRs) with speed, transparency, and privacy protection that can represent a true paradigm shift in the conduct of observational studies across many disease areas. Díaz et al. NEURONET (15) coordinated, harmonized, and integrated data and results from IMI AD projects, delivering important assets for the research community, like the knowledge base (16). Additionally, the NEURONET data-sharing Working Group (Bradshaw et al.) provided valuable examples of good practices and recommendations on how to overcome obstacles to data sharing, from organizational and technical issues to socio-technical hurdles. Provocatively, they consider whether we should think about data collaboration, rather than only data sharing.

Recent advances in diagnostics and the approval of new pharmaceutical treatments for AD herald the beginning of precision medicine in the AD field. Progress in implementing biomarkers, clinical trial design, and endpoints and in data sharing will further increase the offer of treatments. However, their implementation will challenge already over-burdened healthcare systems. The IHI project PROMINENT (17) is developing a digital platform and clinical support system that integrates diverse data and real-world evidence across each aspect of the care pathway, from diagnosis to treatment, for guiding treatment and assessing its benefits (Tate et al.). Uniquely, this will be achieved in a truly collaborative effort of dementia researchers, medical professionals, dementia patients, and their care partners with the developers of innovative health technologies.

PPPs funded under IMI represent ideal and powerful vehicles to integrate research efforts across the public and private sectors in the AD space, creating knowledge of high transferability, as demonstrated by the AETIONOMY outputs (18, 19) that have been further developed not only for AD (20) but also in the COVID-PHARMACOME (21). Analyzing the collaborative networks across IMI's AD projects, O'Rourke et al. and Hawksworth et al. highlight their impacts, suggest areas requiring improvement, and offer recommendations for future PPPs. Meanwhile, North et al. document how the IMI model has boosted multi-disciplinary collaboration across Europe (within industry, within academia, and across industry-academia) like never before. North et al. also note that the express goal of each project is to meet the needs of patients.

Public Involvement (PI), i.e., the active involvement of people with dementia in dementia research projects other than as research participants, is a key for advancing the AD field. Georges et al. highlight the critical role of patients as research partners, emphasizing current gaps and highlighting successful PI examples from IMI projects.

We hope that you will enjoy reading this Research Topic issue and will benefit from its messages and learnings.

Author contributions

EV: Conceptualization, Writing – original draft, Writing – review & editing. JG: Writing – review & editing. MH-A: Writing – review & editing. DL: Writing – review & editing.

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EDITED BY
Rufus Olusola Akinyemi,
University of Ibadan, Nigeria

REVIEWED BY
Daniele Urso,
King's College London,
United Kingdom
Kieran Breen,
St. Andrew's Healthcare,
United Kingdom

*CORRESPONDENCE
Angela Bradshaw
angela.bradshaw@alzheimer-europe.org

†These authors have contributed equally to this work

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The Innovative Medicines Initiative neurodegeneration portfolio: From individual projects to collaborative networks

Diana O'Rourke[1†], Nina Coll-Padrós[2†], Angela Bradshaw[3*†], Lewis Killin[2], Laurent Pradier[4], Jean Georges[3], Dalia M. Dawoud[5,6], Lennert Steukers[7] and Carlos Diaz[2] the Neuronet Consortium

[1]National Institute for Health and Care Excellence, Manchester, United Kingdom, [2]SYNAPSE Research Management Partners, Barcelona, Spain, [3]Alzheimer Europe, Luxembourg, Luxembourg, [4]Sanofi, Paris, France, [5]National Institute for Health and Care Excellence, London, United Kingdom, [6]Faculty of Pharmacy, Cairo University, Cairo, Egypt, [7]Janssen Pharmaceutica NV, Beerse, Belgium

The IMI public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) was launched in 2008 with an initial budget of €2 billion. Aiming to accelerate the development of innovative medicines for areas of unmet clinical need, the IMI has committed over €380 million to projects on neurodegenerative disorders (NDD), catalyzing public-private collaborations at scale and at all stages of the R&D pipeline. Because of this vast investment, research on neurodegenerative diseases has made enormous strides in recent decades. The challenge for the future however remains to utilize this newly found knowledge and generated assets to develop better tools and novel therapeutic strategies. Here, we report the results of an integrated programme analysis of the IMI NDD portfolio, performed by the Neuronet Coordination and Support Action. Neuronet was launched by the IMI in 2019 to boost synergies and collaboration between projects in the IMI NDD portfolio, to increase the impact and visibility of research, and to facilitate interactions with related initiatives worldwide. Our analysis assessed the characteristics, structure and assets of the project portfolio and identifies lessons from projects spanning preclinical research to applied clinical studies and beyond. Evaluation of project parameters and network analyses of project partners revealed a complex web of 236 partnering organizations, with EFPIA partners often acting as connecting nodes across projects, and with a great diversity of academic institutions. Organizations in the UK, Germany, France and the Netherlands were highly represented in the portfolio, which has a strong focus on clinical research in Alzheimer's and Parkinson's disease in particular. Based on surveys and unstructured interviews with NDD research leaders, we identified actions to enhance collaboration between project partners, by improving the structure and definition of in-kind contributions; reducing administrative burdens; and enhancing the exploitation of outcomes from research investments by EU

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taxpayers and EFPIA. These recommendations could help increase the efficiency and impact of future public-private partnerships on neurodegeneration.

KEYWORDS

neurodegeneration, collaboration, public-private partnership, research policy, IMI

Introduction

The Innovative Medicines Initiative (IMI) is a public-private partnership between the European Union (EU) and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). It was approved in December 2007 with a €2 billion budget, and subsequently renewed for the period 2014–2020 as IMI2, with a budget of up to €3.276 billion. The overarching mission of the IMI is "to improve health by accelerating the development of, and patient access to, innovative medicines, particularly where there is an unmet medical or social need." IMI aims to achieve its mission through the facilitation of engagement and collaboration between key stakeholders involved in healthcare research, such as universities, industry, small- and medium-sized enterprises (SMEs), patient organizations, and medicines regulators (1).

To address the key challenges facing the European healthcare systems, the pharmaceutical industry and regulatory agencies, IMI2 has focused its research across 12 priority disease areas, including neurodegenerative diseases (NDDs) for which there is a lack of available therapeutic interventions, despite high levels of research expenditure (2). In its Strategic Research Agenda (SRA), IMI2 identified several key areas of focus, including increased mechanistic understanding of NDDs, improved frameworks for risk factor screening, and innovative trials for disease prevention and treatment.

Guided by its Strategic Governance Group (SGG) on neurodegeneration, IMI2 has funded a diverse portfolio of projects in these focus areas. Projects such as PD-MitoQUANT, IMPRiND, PHAGO and ADAPTED address the molecular underpinnings of Parkinson's and Alzheimer's disease, while RADAR-CNS, RADAR-AD, IDEA-FAST and Mobilise-D are focused on digital assessment and endpoints across several NDDs. AMYPAD, a sister project to EPAD, is evaluating the role and relevance of amyloid imaging biomarkers across the dementia risk spectrum, while PD-MIND is trialing a repurposed, nicotinic agonist drug for Parkinson's disease. Together with EPAD, EMIF and AETIONOMY (IMI1 neurodegeneration projects that ended recently), these projects represent a breadth of research that covers the entire translational science spectrum, from preclinical research in cells and animal models to applied, clinical research involving human participants.

While initially planned as complementary concepts during the development of call topics and texts by the Strategic Governance Groups of the IMI, the diverse range of projects funded by the IMI bears the risk of excessive segmentation and lack of interaction between projects, limiting the impact of individual results and projects. To mitigate this risk, in March 2019 the NEURONET initiative was established to provide a platform for promoting collaboration, communication and synergies across the range of IMI funded neurodegenerative disease projects. This three-year Coordination and Support Action, which receives €1,199,125 in funding through IMI2, aims to maximize the impact of the portfolio as a whole by enhancing the visibility of project outputs and assets and creating active connections between projects and with other global research initiatives.

As both NEURONET and the IMI2 programme come to an end, it is a valuable opportunity to reflect on the lessons learnt and successes of the IMI NDD programme to inform future public-private partnership research programmes, including IMI's successor the Innovative Health Initiative (IHI, https://www.ihi.europa.eu/). In this article the NEURONET Consortium presents the results of an integrated analysis of the characteristics and structure of the project portfolio, provides an overview of assets generated by the projects, and reports on the lessons learned from past collaboration attempts between projects.

Methods

Identification of IMI NDD projects in scope

Firstly, we identified the IMI NDD projects that would be included within the scope of the analysis. All "neurodegenerative disease" or "Alzheimer's disease" related IMI projects were considered for inclusion in the portfolio. However, it was agreed to focus on active or upcoming projects, or projects that had finished within a year of the start date of NEURONET, in order to focus on the creation of synergies between present and future projects. Eighteen projects were identified and included in this

analysis. We undertook an integrated programme analysis of the scope and impact of the 18 projects that are currently part of the IMI NDD portfolio, based on publicly available information, project documentation, interviews and survey results. These include 15 IMI2 projects and three IMI1 projects that have recently ended (Table 1).

Data collection

We first identified a set of project parameters (Supplementary Figure 1) to be collected from the projects, including their scope and relative specialization, funding, participants, and outputs and assets. To collect this information, we developed a structured data collection form that was piloted with a subgroup of NEURONET partners for clarification and consistency. Firstly, we extracted information from publicly available sources, including the IMI website (https://www.imi.europa.eu), the CORDIS portal (https://cordis.europa.eu) and project websites. Where information was not available from these sources, we gathered information from the projects' Descriptions of Action/Work (DoA/DoW), newsletters, deliverables and other project reports.

Unstructured interviews were conducted with the leaders of 11 projects in the portfolio[1], to gain a more in-depth understanding of those projects and to understand the lessons learned from past cross-project collaborations. Following these interviews, a survey was sent to 8 IMI NDD projects (ADAPTED, AETIONOMY, AMYPAD, EMIF, EPAD, IMPRiND, PHAGO and the related EBiSC project) to map and evaluate 16 attempted cross-project collaborations. The projects were asked for 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 materialize the collaboration, and
4. whether there were any specific obstacles hindering the collaboration.

Finally, we undertook a content analysis of project presentations from the NEURONET Annual Event at the 2019 Alzheimer Europe Conference. All project information was then combined into a single document ("project dossier") which was validated by key representatives from each project to ensure completeness and accuracy. Understanding of project aims and status, as well as lessons learned and opportunities for collaboration, has been also continuously enhanced thanks to regular portfolio meetings gathering project leaders (under a "Scientific Coordination Board") and other project participants (under "Working Groups" devoted to four specific, common issues found on most projects: data sharing, ethics and privacy, HTA/regulatory interactions and sustainability, as well as a "Communications Experts's Group composed of project managers and communications officers).

1 AETIONOMY, AMYPAD, EMIF, EPAD, EQIPD, IM2PACT, MOPEAD, PHAGO, PRISM, RADAR-AD, ROADMAP.

IMI NDD portfolio analysis

To understand the structure and characteristics of the IMI NDD project portfolio, we conducted an integrated analysis of key metrics collected from the 18 IMI NDD projects, collected using the methods detailed in the previous section. Information was collated on every unique partner organization in the portfolio, including their organization type [Academic, EFPIA, Regulatory Agency, HTA body, patient/carer organization, SMEs, research funder, contract management organization (CMO), other] and the projects that they participate in. These data were used in network analyses (see below) and were analyzed in Microsoft Excel for the portfolio analysis.

The key information gathered about the IMI NDD portfolio has been summarized and collated through the publicly available NEURONET Knowledge Base (https://kb.imi-neuronet.org). The Knowledge Base was designed as an entry portal to the IMI NDD portfolio, providing a comprehensive overview of the breadth of IMI-funded NDD research, including detailed information about each project such as their objectives, deliverables and publications. The Knowledge Base also hosts interactive versions of the network analysis diagrams.

Network analyses

A network analysis was conducted to characterize the connections between partner organizations and projects across the portfolio. Network analyses were performed using *R 4.1.0* (3) and the *igraph* [v1.2.6; (4)] package t. Specifically, a project-by-participant incidence matrix was used to create bipartite network graphs that represent the extent to which projects or participants are connected to others (i.e. "degree"), the structural relationship between those projects or participants (i.e. "betweenness") and the strength of those connections (i.e., "weight"). In the case of the latter, this represents the number of projects that two participants collaborate on, or, conversely, the number of participants who all work on the same two projects.

Three network analyses were performed: (1) a network to show how partner organizations are connected to each other; (2) a partner network, with and without EFPIA partners; and (3) a project network. In the partner network, nodes represent each unique partner organization in the portfolio and the lines between them represent the number of projects that connect individual organizations. Nodes in the project network represent

TABLE 1 IMI neurodegenerative disease projects and calls.

Project	IMI call	Call topic description	Duration
EMIF	IMI1 CALL 4	A European medical information framework (EMIF) of patient-level data to support a wide range of medical research	January 2013–June 2018
AETIONOMY	IMI1 CALL 8	Developing an etiology-based taxonomy of human disease: Approaches to develop a new classification for neurodegenerative disorders with a focus on Alzheimer's disease and Parkinson's disease	January 2014–December 2018
EPAD	IMI1 CALL 11	European platform to facilitate proof of concept for prevention in Alzheimer's disease (EPOC-AD)	January 2015–October 2020
PRISM	IMI2 CALL 3	Linking clinical neuropsychiatry and quantitative neurobiology	April 2016–September 2019
RADAR-CNS	IMI2 CALL 3	Remote assessment of disease and relapse – CNS (part of the RADAR programme)	April 2016–March 2022
PHAGO	IMI2 CALL 5	Inflammation and ad: modulating microglia function – focussing on TREM2 and CD33	November 2016–April 2022
AMYPAD	IMI2 CALL 5	Understanding the role of amyloid imaging biomarkers in the current and future diagnosis and management of patients across the spectrum of cognitive impairment (from pre-dementia to dementia)	October 2016–September 2022
MOPEAD	IMI2 CALL 5	Evolving models of patient engagement and access for earlier identification of Alzheimer's disease: phased expansion study	October 2016–December 2019
ADAPTED	IMI2 CALL 5	From ApoE biology to validated Alzheimer's disease targets	October 2016–September 2020
ROADMAP	IMI2 CALL 6	Real world outcomes across the ad spectrum (ROADS) to better care (part of the BD4BO programme)	November 2016–October 2018
IMPRIND	IMI2 CALL 7	Identification of druggable targets modulating misfolded proteins in Alzheimer's and Parkinson's diseases	March 2017–February 2022
EQIPD	IMI2 CALL 9	Data quality in preclinical research and development	October 2017–September 2021
RADAR-AD	IMI2 CALL 12	Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease (RADAR-AD)	January 2019–June 2022
IM2PACT	IMI2 CALL 12	Discovery and characterization of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases	January 2019–December 2023
MOBILISE-D	IMI2 CALL 13	Linking digital assessment of mobility to clinical endpoints to support regulatory acceptance and clinical practice	April 2019–March 2024
PD-MITOQUANT	IMI2 CALL 13	Mitochondrial dysfunction in neurodegeneration	February 2019–July 2022
PD-MIND	IMI2 CALL 13	Pilot programme on a clinical compound bank for repurposing: neurodegenerative diseases	May 2019–April 2022
NEURONET	IMI2 CALL 13	Support and coordination action for the projects in the neurodegeneration area of the Innovative Medicines Initiative	March 2019–August 2022
IDEA-FAST	IMI2 CALL 15	Digital endpoints in neurodegenerative and immune-mediated diseases	November 2019–April 2025

individual IMI NDD projects, and the connections between them the number of partner organizations that participate in both projects.

To assess the relative importance of a partner organization within the network, two measures of centrality were calculated: the 'degree centrality' and "betweenness centrality" (5). The betweenness centrality represents the number of times a node is present in the shortest path between two nodes in the network. This provides an indication of the key organizations in the network in terms of their ability to facilitate dissemination and exchange of knowledge through their connections to different organizations. The degree centrality is the number of links that one organization has to all other organizations in the network, indicating the relative importance of an organization within that network.

Qualitative analyses

The results from the survey and transcripts of interviews with project leaders, as well as all other information captured through meetings, were analyzed qualitatively, focussing on

TABLE 2 IMI neurodegenerative disease project parameters.

Project	Duration (months)	Partner organizations (*N*)	Total cost	Disease area	Website	Logo
ADAPTED	48 months	13	€ 6,796,740	Alzheimer's disease	https://www.imi-adapted.eu	
AETIONOMY	60 months	16	€ 17,812,216	Alzheimer's Parkinson's Neurodegenerative diseases	https://www.aetionomy.eu	
AMYPAD	54 months	15	€ 27,329,288	Alzheimer's disease	https://amypad.eu	
EMIF	54 months	60	€ 55,784,311	Alzheimer's disease	http://www.emif.eu	
EPAD	57 months	39	€ 59,903,036	Alzheimer's disease	http://ep-ad.org/	
EQIPD	48 months	30	€ 9,360,692	Neurodegenerative diseases	https://quality-preclinical-data.eu	
IDEA-FAST	66 months	51	€ 40,922,059	Huntington's disease Parkinson's disease	https://ideafast.eu	
IM2PACT	60 months	27	€ 17,410,136	Neurodegenerative diseases	http://im2pact.org	
IMPRIND	60 months	18	€ 11,363,398	Alzheimer's disease Neurodegenerative diseases Parkinson's disease	https://www.imprind.org	
Mobilise-D	60 months	36	€ 49,361,564	Multiple sclerosis Parkinson's disease	https://www.mobilise-d.eu	
MOPEAD	39 months	15	€ 4,581,968	Alzheimer's disease	https://www.mopead.eu	
PD-MIND	36 months	10	€ 2,131,609	Parkinson's disease	https://www.pd-mind.org	
PD-mitoQUANT	42 months	14	€ 6,882,315	Parkinson's disease	https://www.pdmitoquant.eu/	
PHAGO	66 months	20	€ 18,088,176	Alzheimer's disease	https://www.phago.eu	
PRISM	42 months	23	€ 16,195,875	Alzheimer's disease	https://prism-project.eu	
RADAR-AD	54 months	16	€ 7,640,145	Alzheimer's disease	http://www.radar-ad.org	
RADAR-CNS	66 months	25	€ 25,712,110	Multiple sclerosis	https://www.radar-cns.org	
ROADMAP	24 months	26	€ 8,210,381	Alzheimer's disease	https://roadmap-alzheimer.org	

the key challenges and opportunities for improvement for project collaborations.

Results

Summary metrics of the IMI NDD portfolio

The IMI NDD portfolio represents a total investment of €385.5 million, with the majority of funding coming from the EU and EFPIA (Figure 1A). There is a mean funding per project of €21,415,889.94. The 18 projects in the portfolio target a range of NDDs, however, the predominant focus is on Alzheimer's disease, with a secondary focus on Parkinson's disease (Figure 1B). Most of the projects in the portfolio are dedicated to the study of 1 specific NDD ($N = 12$). However, six projects (AETIONOMY, EQiPD, IDEA-FAST, IM2PACT, IMPRiND, Mobilise-D) cover several NDDs or are not focused on a particular NDD and have more general objectives (Tables 1, 2).

There are 236 unique partner organizations participating in the 18 projects in the IMI NDD portfolio. The majority of these organizations are academic institutions ($N = 134$), with a further 52 SME organizations and 31 EFPIA partners (Figure 1C). The majority of organizations (63%, $N = 149$) participate in a single project, including 41 SMEs, representing 79% of all SMEs in the portfolio. There is an average of 25 partners (range 10–60) per project.

Partner organizations are based across 24 different countries. Organizations from the UK ($N = 48$), Germany ($N = 42$), France ($N = 22$) and the Netherlands ($N = 22$) are most frequently represented (Figure 1D).

Research focus and assets

From projects identifying new drug targets in Alzheimer's and Parkinson's disease, to the development of frameworks for access and assessment of real-world evidence, the IMI NDD portfolio covers a breadth of research and disease stages. Analysis of the 18 projects in the portfolio identified four projects that primarily focus on the identification and validation of novel targets through preclinical, mechanistic or *in vivo* research, including EQIPD, IM2PACT, IMPRIND and PD-Mitoquant. While IM2PACT, IMPRIND and PD-Mitoquant are characterizing specific disease mechanisms (blood-brain barrier dysfunction, protein aggregation and mitochondrial dysfunction, respectively), EQIPD has broader relevance across disease areas, establishing guidelines to strengthen the robustness, rigor and validity of research data. We identified three projects (ADAPTED, PHAGO, PRISM) involving translational research, spanning both preclinical and clinical stages of the drug development pipeline. For example, ADAPTED was focused on understanding the contribution of the apolipoprotein E (APOE) genetic risk factor to Alzheimer's disease, developing human cell models with disrupted APOE expression and investigating samples and data from patients with Alzheimer's disease.

We observed that the majority of IMI NDD projects were primarily focused on clinical research. Within these projects, PD-MIND is trialing a novel drug for the treatment of Parkinson's disease with mild cognitive impairment (MCI), while EMIF and EPAD have focused on developing large-scale cohort and electronic health record (EHR) studies on people at different stages of Alzheimer's development. Several projects are developing or testing news ways to detect and prognose NDDs, such as AMYPAD (amyloid imaging for Alzheimer's) and RADAR-AD, RADAR-CNS, IDEA-FAST and Mobilise-D (digital and/or gait biomarkers and endpoints). We observed that data assessment, access and sharing were a common focus across many clinical IMI NDD projects, with AETIONOMY organizing mechanistic knowledge on NDD, EMIF and EPAD developing methods for hosting and studying clinical study data, and ROADMAP creating a catalog and platform for real-world data access.

Since 2013, the 18 projects included in our analysis have developed a large number of assets, defined as tangible, accessible and re-useable project outputs that bring real value to the NDD research field. These assets are captured and depicted in the NEURONET Asset Map, a feature of the Knowledge Base that was developed following engagement with partners of the 18 IMI NDD projects. The Asset Map categorizes assets based on drug development pipeline stage (e.g., preclinical, clinical, real-world evidence) and asset type (e.g., datasets, cohorts, disease models, platforms and tools). Analyzing the 82 assets of the Asset Map, we observed that projects have developed a wide range of outputs, paralleling the breadth of the IMI NDD portfolio. As expected, given the clinical focus of IMI-funded NDD research, many of these assets are targeted at this stage of the drug development pipeline, including research cohorts (e.g., RADAR-CNS cohort of multiple sclerosis patients, EPAD longitudinal cohort study), patient samples and data (e.g., neuroimaging datasets from the AMYPAD studies, ADAPTED biosamples from people with different APOE genotypes) and tools for patient engagement, subject enrolment and clinical data analysis. The most well-populated area on the asset map, covering all stages of the drug development pipeline, was the category of "Tools, templates and guidelines," with eight IMI NDD projects generating assets that could help progress preclinical research, clinical research recruitment, and stakeholder engagement with regulators and HTA. Perhaps reflecting the challenges of NDD drug development, with few new treatments for NDD reaching the market in the last 20 years, we only identified three accessible, re-useable assets on real-world evidence or targeted at regulators.

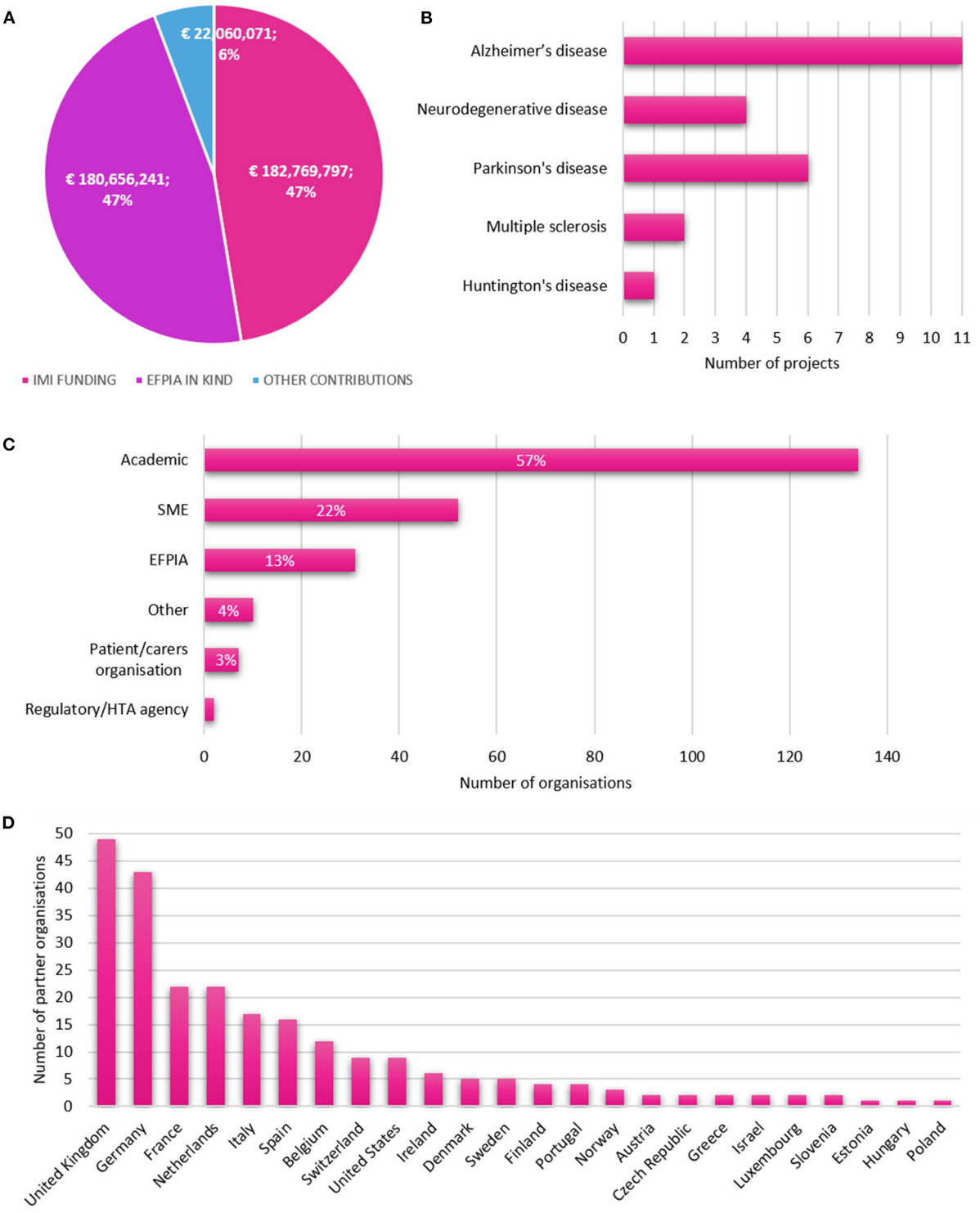

FIGURE 1
IMI neurodegenerative disease portfolio characteristics. A set of project parameters was collected for 18 projects in the IMI Neurodegenerative disease (NDD) portfolio from sources including EU databases, project websites and descriptions of work. **(A)** Total funding contributions for the IMI NDD portfolio, by source and amount. **(B)** Disease areas targeted by IMI NDD projects; number of projects. **(C)** Types of partner organisations in IMI NDD projects; number of organisations, by category. **(D)** Countries of partner organisations; by country.

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Partner network analysis

Figure 2A and Supplementary Figure 1 represents the network of all partner organizations across the IMI NDD portfolio. The results show the complexity of links across the network with a clear clustering of organizations at the center. The majority of organizations ($N = 149$) in the network are connected through participation in a single project, as indicated by the pink connections. There are a relatively small number of organizations that are the key nodes in the network, according to their betweenness centrality, as represented by the larger nodes in the visualization (Figure 2A and Table 3A). Of the top 20 organizations, 70% ($N = 14$) are EFPIA companies compared to just 5 academic institutions, in part due to the fact that there are many fewer EFPIA companies participating in IMI projects, compared to academic institutions, which make up 57% ($N = 134$) of the entire network. The majority (62%, $N = 83$) of academic organizations only participate in a single project. Janssen Pharmaceutica is the organization with the highest betweenness centrality in the network. This is partly the result of the large number of projects ($N = 13$) in which it participates and because it is also the biggest EFPIA contributor to the IMI NDD projects. None of the other organizations in the top 20 key nodes participate in more than nine projects.

Figure 2B and Table 3B show the results of the network analysis for partner organizations in the IMI NDD portfolio, when EFPIA organizations are excluded from the analysis. As with the overall network, there is a relatively small number of organizations that are key nodes in network, according to their betweenness centrality. Of the top 20 organizations, 80% ($N = 16$) are academic institutions. Erasmus Medical Center is the top non-EFPIA organization in the network, with the highest betweenness, centrality and joint highest project participation ($N = 7$) with Alzheimer Europe and Stichting VUMC.

When we assessed the degree centrality of organizations, we found that the minimum observed number of connections per organization across the whole network is 9, which means that every organization in the network is connected to at least nine other organizations. Janssen Pharmaceutica had the highest degree centrality ($N = 197$) which means that it is connected to 197 of 236 organizations in the IMI NDD portfolio (Table 3A). Excluding EFPIA organizations, the minimum observed number of connections per organization is 8. Erasmus Medical Center had the highest degree centrality ($N = 126$) which means that it is connected to 126 of 205 non-EFPIA organizations in the IMI NDD portfolio (Table 3B).

Figure 3 shows the connections between projects across the whole network, where projects are connected by sharing at least one organization. The project with the lowest number of connections is PD-MIND which is connected to nine other IMI projects in the portfolio. All other projects are connected to at least 14 other IMI projects, with five projects (EMIF, IDEA-FAST, PHAGO, PRISM and RADAR-CNS) connected to all other projects in the portfolio through at least one partner organization (Table 4A). For each project we analyzed the proportion of project partner organizations that it shares with all other projects in the portfolio (Table 4A). Overall, we found that there are a number of projects that share multiple organizations with others, notably EPAD, EMIF and ROADMAP, which all address clinical research and/or real-world evidence. In contrast, other projects share far fewer organizations with the rest of the project portfolio, such as PD MIND and MOPEAD. When EFPIA organizations were excluded from the analysis, we found that the percentage of shared partner organizations between projects was reduced, confirming earlier results regarding EFPIA organizations being the core organizations across the network. However, there are some examples of projects that share a

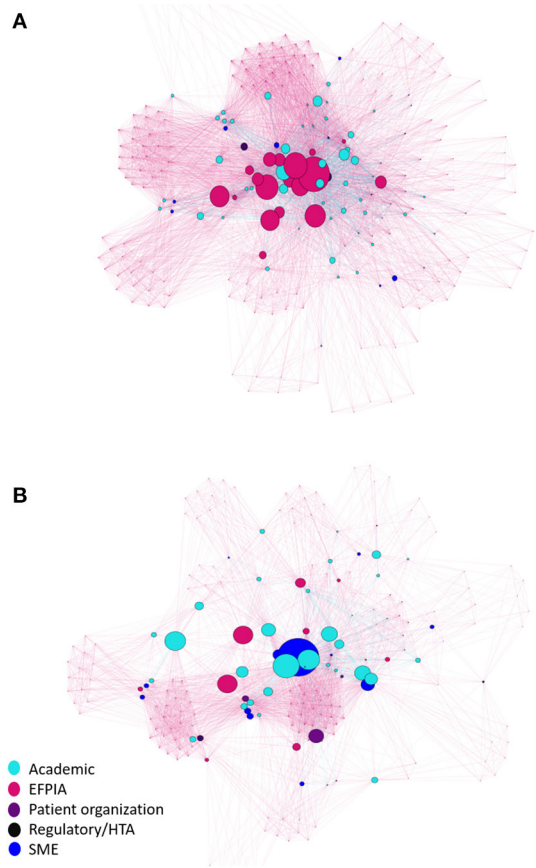

FIGURE 2
Network of unique partner organisations in the IMI NDD portfolio. **(A)** Network including EFPIA organisations. **(B)** Network excluding EFPIA organisations. Each organisation is represented by a single node, the size of which reflects how well-connected the organisation is with all the other organisations in the network (Betweenness Centrality). Lines connecting nodes are coloured according to the number of projects that connect individual organisations. Pink lines: participation in a single project. Blue lines: participation in 2 or more projects.

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TABLE 3A Top 20 key nodes in the network analysis of the IMI NDD portfolio: Including EFPIA partners.

Organization (Country)	Type	Projects (*N*)	Betweenness	Degree
Janssen Pharmaceutica (BE)	EFPIA	13	1,437	197
UCB Biopharma (BE)	EFPIA	7	1,068	164
Pfizer (UK)	EFPIA	7	1,022	177
Novartis (BE)	EFPIA	9	928	140
AstraZeneca (UK)	EFPIA	5	870	108
Sanofi Aventis (FR)	EFPIA	7	847	149
Eli Lilly (UK)	EFPIA	8	807	132
Erasmus Medical Center (NL)	Academic	7	679	148
Biogen (UK)	EFPIA	5	617	117
Merck Sharp Dohme (BE)	EFPIA	4	568	126
F Hoffmann La Roche (SUI)	EFPIA	7	515	153
Takeda (UK)	EFPIA	6	513	130
H Lundbeck (DK)	EFPIA	7	502	109
Abbvie (FR)	EFPIA	5	465	101
Stichting VUMC (NL)	Academic	7	458	130
Kings College London (UK)	Academic	5	417	101
University of Cambridge (UK)	Academic	5	389	132
Academisch Ziekenhuis Leiden (NL)	Academic	4	375	100
Alzheimer Europe (LU)	Patient/carer organization	7	366	113
Amgen (SUI)	EFPIA	3	365	111

TABLE 3B Top 20 key nodes in the network analysis of the IMI NDD portfolio: Excluding EFPIA partners.

Organization (Country)	Type	Projects (*N*)	Betweenness	Degree
Erasmus Medical Center (NL)	Academic	7	1,794	126
University of Cambridge (UK)	Academic	5	1,130	110
Stichting VUMC (NL)	Academic	7	946	109
Imperial College of Science, Technology and Medicine (UK)	Academic	3	891	75
Universitatsklinikum Erlangen (DE)	Academic	2	847	72
Academisch Ziekenhuis Leiden (NL)	Academic	4	843	82
University of Oxford (UK)	Academic	6	687	96
Alzheimer Europe (LU)	Patient/carer organization	7	683	92
Kings College London (UK)	Academic	5	639	81
Concentris Research Management (DE)	SME	3	598	75
Karolinska Institutet (SE)	Academic	6	579	86
VIB Center for Brain Disease Research (BE)	Academic	3	547	67
Parkinson's UK (UK)	Patient/carer organization	3	506	56
Charité Universitàtsmedizin Berlin (DE)	Academic	3	477	45
Stichting Katholieke Universiteit (NL)	Academic	5	428	59
University College London (UK)	Academic	4	393	71
University of Exeter (UK)	Academic	3	385	68
University of Sheffield (UK)	Academic	2	362	42
Mimetas (NL)	SME	3	360	38
Provincia Lombardo Veneta Ordineospedaliero di San Giovanni Di Dio Fatebenefratelli (IT)	Academic	2	330	66

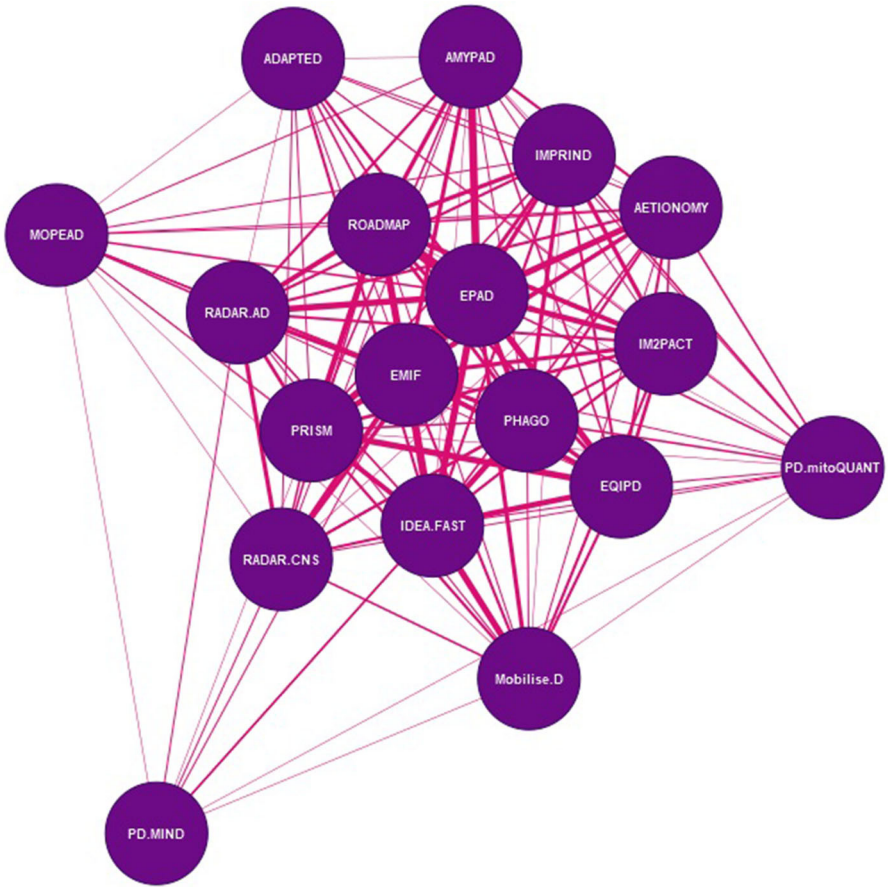

FIGURE 3
Network of shared organisations in IMI NDD projects. Each node in the network represents an IMI project. The lines between the nodes are weighted to show the number of organisations that participate in both projects – the wider the connector, the higher the number of shared organisations between projects.

comparably high proportion of non-EFPIA organizations, including AMYPAD and EPAD, and ROADMAP and EMIF (Table 4B).

Collaborations, challenges and opportunities

Overall, a response rate of 100% (16/16) was received for the survey of past collaborations. The results identified nine past collaboration attempts of which six were materialized (totally or partially) and three were unsuccessful. Overall, the projects reported that the main obstacle for collaboration was the need for collaboration agreements between projects or other legal requirements which led to lengthy delays in the sharing of data, often meaning that the data was shared too late for the collaborating projects' requirements.

Together, the responses from the survey and the multiple interviews held with project leaders across the whole portfolio identified 11 main themes (Figure 4) in relation to the challenges and opportunities for improvement across the three stages of an IMI project.

Before the call launch and topic development

Topic definition

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 gray zone between precompetitive and competitive space. For example, projects aiming to develop platforms for studies or clinical trials of drugs that rely on different industrial IP holders providing compounds to run studies under a single academic sponsor. In such cases, the operational set-up of the site network, study and trial platform (both on legal and financial grounds) within the IMI1 legal and

TABLE 4A Percentage of project partners shared between IMI NDD projects (including EFPIA).

Percentage of project partners shared with other IMI ND projects	ADAPTED	AETIONOMY	AMYPAD	EMIF	EPAD	EQIPD	IDEA-FAST	IM2PACT	IMPRIND	Mobilise-D	MOPEAD	PD-MIND	PD-mitoQUANT	PHAGO	PRISM	RADAR-AD	RADAR-CNS	ROADMAP	Total number of projects connected to
ADAPTED ($N = 13$ partners)		15%	15%	15%	31%	15%	31%	15%	15%	0%	15%	0%	8%	23%	15%	8%	15%	23%	15
AETIONOMY ($N = 16$ partners)	13%		19%	31%	56%	25%	19%	19%	6%	13%	13%	0%	13%	19%	19%	25%	6%	19%	16
AMYPAD ($N = 15$ partners)	13%	20%		40%	80%	20%	7%	13%	7%	0%	20%	0%	13%	13%	20%	27%	13%	40%	15
EMIF ($N = 60$ partners)	3%	8%	10%		27%	12%	18%	10%	8%	7%	5%	3%	3%	10%	13%	10%	10%	17%	17
EPAD ($N = 39$ partners)	10%	23%	31%	41%		23%	26%	21%	15%	15%	10%	0%	8%	21%	26%	23%	15%	36%	16
EQIPD ($N = 29$ partners)	7%	13%	10%	23%	30%		27%	17%	13%	17%	0%	0%	10%	20%	30%	7%	10%	17%	15
IDEA-FAST ($N = 51$ partners)	8%	6%	2%	22%	20%	16%		8%	8%	18%	4%	6%	4%	16%	14%	6%	6%	14%	17
IM2PACT ($N = 27$ partners)	7%	11%	7%	22%	30%	19%	15%		22%	15%	0%	0%	7%	11%	19%	15%	11%	26%	15
IMPRIND ($N = 18$ partners)	11%	6%	6%	28%	33%	22%	22%	33%		6%	11%	0%	17%	33%	17%	22%	11%	33%	16
Mobilise-D ($N = 36$ partners)	0%	6%	0%	11%	17%	14%	25%	11%	3%		3%	3%	3%	6%	11%	6%	8%	6%	15
MOPEAD ($N = 15$ partners)	13%	13%	20%	20%	27%	0%	13%	0%	13%	7%		7%	0%	13%	7%	20%	7%	13%	14
PD-MIND ($N = 10$ partners)	0%	0%	0%	20%	0%	0%	30%	0%	0%	10%	10%		10%	20%	10%	20%	20%	0%	9
PD-mitoQUANT ($N = 14$ partners)	7%	14%	14%	14%	21%	21%	14%	14%	21%	7%	0%	7%		21%	7%	0%	14%	7%	15
PHAGO ($N = 20$ partners)	15%	15%	10%	30%	40%	30%	40%	15%	30%	10%	10%	10%	15%		15%	20%	20%	25%	17
PRISM ($N = 23$ partners)	9%	13%	13%	35%	43%	39%	30%	22%	13%	17%	4%	4%	4%	13%		22%	13%	35%	17
RADAR-AD ($N = 16$ partners)	6%	25%	25%	38%	56%	13%	19%	25%	25%	13%	19%	13%	0%	25%	31%		38%	44%	16
RADAR-CNS ($N = 25$ partners)	8%	4%	8%	24%	24%	12%	12%	12%	8%	12%	4%	8%	8%	16%	12%	24%		12%	17
ROADMAP ($N = 26$ partners)	12%	12%	23%	38%	54%	19%	27%	27%	23%	8%	8%	0%	4%	19%	31%	27%	12%		16

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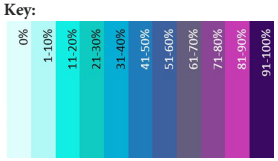

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TABLE 4B Percentage of project partners shared between IMI NDD projects (excluding EFPIA).

Percentage of project partners shared with other IMI ND projects	ADAPTED	AETIONOMY	AMYPAD	EMIF	EPAD	EQIPD	IDEA-FAST	IM2PACT	IMPRIND	Mobilise-D	MOPEAD	PD-MIND	PD-mitoQUANT	PHAGO	PRISM	RADAR-AD	RADAR-CNS	ROADMAP	Total number of projects connected-to
ADAPTED ($N = 10$ partners)		20%	10%	10%	20%	0%	10%	10%	0%	0%	20%	0%	10%	10%	10%	0%	0%	10%	10
AETIONOMY ($N = 12$ partners)	17%		25%	25%	42%	0%	8%	8%	0%	0%	17%	0%	8%	17%	8%	25%	0%	17%	12
AMYPAD ($N = 12$ partners)	8%	25%		42%	92%	17%	0%	8%	0%	0%	25%	0%	17%	8%	17%	25%	8%	33%	12
EMIF ($N = 50$ partners)	2%	6%	10%		18%	2%	14%	6%	6%	2%	6%	4%	2%	8%	8%	10%	6%	16%	17
EPAD ($N = 24$ partners)	8%	21%	46%	38%		8%	8%	13%	8%	0%	13%	0%	4%	8%	13%	21%	4%	25%	15
EQIPD ($N = 18$ partners)	0%	0%	11%	6%	11%		6%	6%	0%	6%	0%	0%	6%	6%	22%	0%	6%	11%	11
IDEA-FAST ($N = 40$ partners)	3%	3%	0%	18%	5%	3%		3%	3%	13%	0%	5%	3%	3%	5%	0%	0%	5%	13
IM2PACT ($N = 20$ partners)	5%	5%	5%	15%	15%	5%	5%		15%	5%	0%	0%	5%	0%	10%	10%	5%	20%	14
IMPRIND ($N = 11$ partners)	0%	0%	0%	27%	18%	0%	9%	27%		0%	9%	0%	18%	18%	0%	9%	0%	18%	9
Mobilise-D ($N = 24$ partners)	0%	0%	0%	4%	0%	4%	21%	4%	0%		0%	0%	0%	0%	4%	0%	8%	0%	6
MOPEAD ($N = 13$ partners)	15%	15%	23%	23%	23%	0%	0%	0%	8%	0%		0%	0%	0%	0%	15%	8%	8%	9
PD-MIND ($N = 9$ partners)	0%	0%	0%	22%	0%	0%	22%	0%	0%	0%	0%		11%	11%	11%	22%	22%	0%	7
PD-mitoQUANT ($N = 14$ partners)	9%	9%	18%	9%	9%	9%	9%	9%	18%	0%	0%	9%		18%	9%	0%	0%	0%	12
PHAGO ($N = 11$ partners)	9%	18%	9%	36%	18%	9%	9%	0%	18%	0%	0%	9%	18%		0%	18%	18%	9%	13
PRISM ($N = 16$ partners)	6%	6%	13%	25%	19%	25%	13%	13%	0%	6%	0%	6%	6%	0%		6%	13%	19%	14
RADAR-AD ($N = 12$ partners)	0%	25%	25%	42%	42%	0%	0%	17%	8%	0%	17%	17%	0%	17%	8%		42%	25%	12
RADAR-CNS ($N = 20$ partners)	0%	0%	5%	15%	5%	5%	0%	5%	0%	10%	5%	10%	0%	10%	10%	25%		0%	11
ROADMAP ($N = 17$ partners)	6%	12%	24%	47%	35%	12%	12%	24%	12%	0%	6%	0%	0%	6%	18%	18%	0%		13

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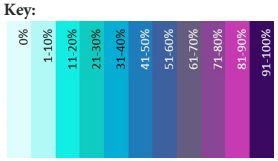

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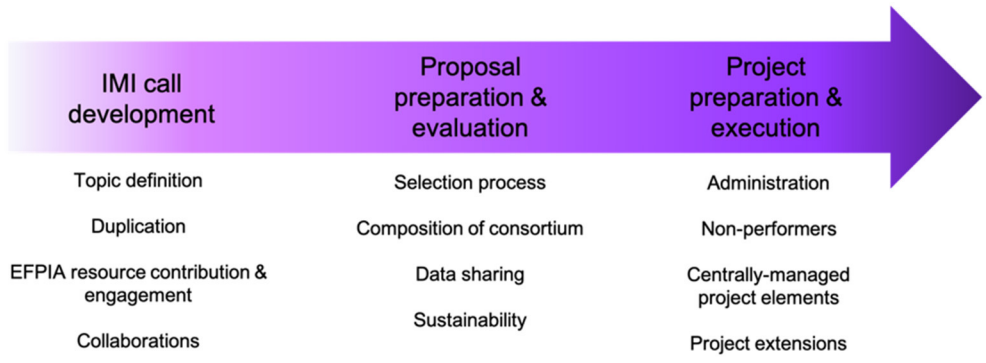

FIGURE 4
Challenges and opportunities for improvement across the IMI project lifespan.

financial framework can prove to be quite challenging and time-consuming, resulting in delays that could affect e.g., conformity to meet the timelines from IP holders.

Duplication

As indicated above, the 18 projects of the IMI NDD portfolio have developed a wide range of assets and outputs that could be of value to the NDD research community and other stakeholders. There is a need to improve the sharing of information about this wealth of assets, in order to de-risk investment being made in duplicative efforts, as well as to inform projects about the key lessons learned from the development of these assets. For example, for some IMI NDD projects, it would have been more useful to make use of existing cohorts, such as the EPAD longitudinal cohort, which formed the backbone of the AMYPAD clinical studies, instead of creating new ones.

EFPIA resource contribution and engagement

The intended resource contribution of some EFPIA partners in IMI projects does not always translate to active engagement, as priorities and personnel within organizations may change during the project duration. This can have an impact on the involvement of EFPIA or Associated partners and their actual resource contribution.

Collaborations – organically grown vs. imposed

Interdependencies with other calls/projects are often written in topic texts, as well as in short proposals. It is not always clear whether these collaborations are a critical dependency, or something that is just simply desirable. In the case of those that are critically dependent, separate Grant Agreements with distinct timelines, budget and objectives are typically difficult to reconcile. The intention to collaborate through 'letters of support' are often not realized due to a lack of assessment of feasibility and the resources needed to implement such a collaboration.

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

Selection process

The selection process for IMI projects involved two distinct stages. The first stage, during which an academic consortium was formed, with each partner assuming defined roles based on well-specified budgets, culminated in the selection of a single successful consortium, based on proposal ranking by external reviewers. EFPIA partners joined the proposal at the second stage, with consortia adapting, extending and optimizing the initial first-stage proposal to include their contributions. As a result of this two-stage process, collaboration between EPFIA and Academic partners is not always optimal and could be improved. In particular, as EFPIA partners are not involved in the selection of the winning application, they may end up in a collaboration with an academic partner (the selected applicant consortium) that is not always an optimal complement.

Stakeholders

Having large numbers of project partners increases the risk of a project becoming unwieldy, with large internal overheads (e.g. administrative) and a greater risk of absent or silent partners. This may impact overall project efficiencies and getting true value for money.

Sustainability

The ultimate impact of most IMI projects depends on its capacity to guarantee uptake of its results and to fully leverage the value of its assets beyond the funding period of the project.

However, most consortia struggle to develop credible plans for sustainability. Sustainability activities are challenging for several reasons, including: Consortia not being legal entities themselves; sustainability activities after the project period falling outside the Grant Agreement and therefore requiring a *de novo* commitment from interested parties; a disconnect within institutions between the principal investigators and decision-makers in terms of long-term commitment; and a lack of knowledge and experience within consortia about business planning, assessment and set up, leading to an inappropriate analysis of the value of assets and of the ways in which these could be sustained.

There is a trend to alleviate these challenges through the consideration of sustainability aspects at the beginning of projects, or even before they start. However, this does not necessarily increase buy-in or uptake by potential funders or customers, particularly because of the inherent risks of collaborative, distributed research efforts prevail until results are solid enough to gauge their exploitation potential, which typically occurs during the second half of any project.

Project preparation and execution

Administration

Administrative requirements within the IMI framework are generally considered as being quite cumbersome. Legal documents/procedures (e.g., Grant and Project/Consortium Agreements) are time-consuming to complete and can lead to the excessive use of templates and default conditions that are not adapted to the project's reality. During project execution, in order for two projects to share results, assets, confidential information and/or other solutions, all beneficiaries may need to approve and sign a dedicated collaboration agreement. This can be a very time-consuming process causing major delays and sometimes undermining timely collaboration.

Non-performers

Our surveys and interviews found that some project leaders felt that having an easier way out for non-performing partners would be beneficial in an IMI project. Coordinators or Leads do not always have enough leverage to remove non-performing partners, and are faced with challenges in reallocating budgets/tasks and formalizing the required amendments to grant agreements.

Data sharing

Data sharing between both public and private partners within the context of a PPP does not always materialize in practice. For example, partners are not always fairly acknowledged when sharing data with others. This acknowledgment 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.

Centrally managed project elements

Some project elements could be managed centrally (e.g., by IMI) through the provision of key tools, such as communications plans, technical solutions (e.g., website platforms) and project management tools. This would allow for a more efficient use of resources and would centralize project information and data, without the risk of information being lost when an individual project ends.

Project extensions

Whilst requests for additional time or resources at the end of the initial IMI project are common and enable consortia extra time, and in some cases extra resources to finalize the development of an asset or to make the asset sustainable, the possibility of, and process for allowing extensions would benefit from being more transparent.

Discussion

The IMI NDD portfolio represents a complex landscape of research projects implemented through public-private partnerships across multiple NDD areas, with a strong focus on Alzheimer's disease and a secondary focus on Parkinson's disease. The breadth of research being undertaken ranges from preclinical studies in cells and animals, translational work with samples and data from patients and participants, clinical studies including longitudinal cohort studies and clinical trials, and the development and testing of digital biomarkers.

Our findings show that the IMI NDD portfolio has 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 NDDs in general, and Alzheimer's disease in particular. For example, IMI projects such as EMIF and EPAD have developed platforms and infrastructures to speed up clinical development, also generating cohort datasets which have been widely used by researchers to advance the development of novel, non-invasive biomarkers for the diagnosis and monitoring of Alzheimer's disease from its very earliest stages (6, 7). The EQIPD Quality System, which includes a series of tools, guidance and requirements to support preclinical researchers ensure their work is robust and reliable, is being incorporated into the global Partnership for Assessment and Accreditation of Scientific Practice (PAASP) network (https://paasp.net). Together, the RADAR-CNS and RADAR-AD projects have developed and

refined the RADAR-Base system (https//radar-base.org), an open-source platform for remote assessment using wearables and mobile applications, which is now also being used by external groups for studies on remote monitoring of lung diseases (8). While research and innovation efforts such as these have opened new commercial possibilities based on new services and products, IMI efforts have been especially beneficial in terms of scientific progress and publishable results. It is also important to note that IMI NDD projects also provide intangible benefits, such as support for early career researcher training and development, as well as greater interaction and coordination across industry, academia and other sectors. Our analyses clearly show that the research, industry and societal sectors involved in IMI have benefited from the cooperation and knowledge sharing that take place in IMI projects. This has yielded a situation where collaboration across competing companies and researchers is seen as a natural thing and not as an exception.

Previous studies have highlighted challenges in assessing the performance and impact of PPPs in the life sciences (9). As shown by our analyses of the IMI NDD portfolio, PPP projects often have timelines of 4–6 years, aiming to impact lengthy drug development pipelines that can take decades to reach maturity. Moreover, the value of PPPs extends to parameters that are hard to measure quantitively, such as knowledge transfer, educational aspects and collaboration. Nevertheless, the number of PPPs launched per year has grown over time (from 8 in 2001–2003 to 54 in 2011–2013) (9) and analyses of research publications from IMI projects show that almost 60% of these are published in journals with a high impact factor (IF) (10–12). Editorials have highlighted how IMI projects are developing new regulatory tools and pathways to facilitate interactions with regulatory bodies, helping to identify and address obstacles to regulatory approval (13). These and other publications illustrate the value of the IMI model of research and development as a driver of innovation to address unmet clinical needs. Our findings provide further evidence to support this, highlighting the multiple benefits and positive impacts arising from IMI projects on NDD.

Across the IMI NDD portfolio there is a complex network of partner organizations, each with the potential to enable the exchange of new knowledge and tools within and between projects. We found that there is a relatively small number of organizations that are central to the IMI NDD portfolio, both in terms of the number of connections they have to all other organizations in the network and the connections they form between organizations. The majority of these key organizations participate in the largest projects in the portfolio and form the key links between different IMI projects. Unsurprisingly, EFPIA companies make up the largest percentage of these organizations, reflecting the intrinsic role that EFPIA have in the IMI model and the relatively small pool of EFPIA organizations from which participation can be drawn. Whilst academic organizations represent the largest group of stakeholders in the portfolio, they are also the most diverse: there are relatively few academic institutions that are involved in multiple projects, despite the portfolio representing the same overall field of research.

The key organizations in the network, particularly EFPIA companies, may have the greatest opportunities to create synergies and ensure the dissemination of knowledge, tools, methods and experience across the portfolio compared to other organizations whose involvement in multiple IMI projects is more sporadic. However, these organizations are frequently global entities with multiple departments and people involved across different projects thus making dissemination across the portfolio less likely.

On a project level, there is some clustering of groups of organizations who collaborate more frequently across multiple projects. These are generally projects that are focused on the study of Alzheimer's disease and are clinically driven, such as ROADMAP and EPAD, whilst other projects in the portfolio, such as PD MIND and MOPEAD, share comparably fewer organizations with other projects. For projects such as these, the lower number of connections to the rest of the network could potentially limit their ability to disseminate and leverage the new knowledge that is being generated within these projects and thus limit their potential impact.

NEURONET has attempted to address many of these challenges through a systems leadership type approach, promoting integration, knowledge transfer and cohesion across the portfolio, suggesting and supporting new collaborations, and facilitating the dissemination of project results both across and beyond the portfolio.

Along with these challenges, our analyses have identified a number of key lessons learnt from past collaborations. Firstly, 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 maneuver (e.g., 23a.1, "Beneficiaries…must take measures to implement the principles set out in points 1 and 2 of the Code of Practice"), the development of specific, but adaptable template documents for IMI projects in precompetitive and competitive spaces could be extremely valuable, whilst leaving 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.

To de-risk duplicative efforts in new IMI NDD projects, communication between IMI NDD projects could be improved from even the application stage, and greater connections could be created between projects and the IMI Strategic Governing Group (SGG), that was 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 toward sustainability, for example through conditional funding mechanisms that allow for extended grants renewable under the condition of tangible results being obtained.

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" partners). These rules could be implemented *via* Memoranda of Understanding (MoUs) between the steering committees of IMI projects and/or project partners (replacing traditional "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 collaboration is exactly expected of applicant consortia in that respect.

The quantity, value and impact of assets described above underlines the importance of ensuring timely and effective sustainability planning for IMI project outputs such as these. A first option could be to formalize the requirement for a "sustainability fund" to be set aside by a consortium for each new IMI project. 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. Ideally, the legal and practical terms for sharing of resources, data and know-how should be formalized from the start of a project (e.g., endorsing the Data Citation Principles, ensuring that data declaration of interests (DOIs) are appropriately used, providing specific guidance for biobanking and data storage, etc).

Our findings may prove useful for the forthcoming Innovative Health Initiative and other EU funding entities in shaping the next calls and framework programmes. Furthermore, NEURONET offers a unique role in providing an integrated view of IMI funded NDD research, facilitating synergies and collaboration, disseminating results and ensuring the sustainability of tangible assets beyond the duration of a project. In this role, NEURONET could bridge the gap between IMI and IHI, and provide a model of portfolio management that could be reproduced in other research areas.

In conclusion, our analysis reveals a complex landscape of IMI NDD projects covering the breadth of research and disease stages, with over 200 partner organizations from 24 different countries. Despite this complexity, our analysis identified multiple connections between organizations and projects. Whilst our analysis has not sought to understand whether these connections have led to the dissemination of information between projects, it does highlight the potential role of key organizations to facilitate the exchange of new knowledge and promote the uptake of tools and assets developed by individual IMI projects. Our findings also underline the value of systems leadership approaches in identifying and addressing complex challenges for research on neurodegenerative diseases. Since NEURONET was established in 2019, it has focused on boosting the visibility and impact of projects and identifying and supporting new cross-project synergies and collaborations. By analyzing the structure of the IMI NDD portfolio and previous collaboration attempts, NEURONET has been able to identify links and potential new synergies and collaborations, as well as providing recommendations that could help increase the efficiency and impact of future public-private partnerships on neurodegeneration.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DO'R, NC-P, and AB performed data collection, content analysis, and drafted the manuscript. LK and DO'R performed network analyses and developed manuscript figures. LS and CD conducted interviews. JG coordinated the Alzheimer Europe conference at which project presentations were delivered. LP, JG, DD, LS, and CD coordinated the project. All authors provided critical comments on the manuscript draft and approved the final version of the manuscript.

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Conflict of interest

Authors NC-P, LK, and CD were employed by SYNAPSE Research Management Partners. Author LP was employed by Sanofi. Author LS was employed by Janssen Pharmaceutica NV.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.994301/full#supplementary-material

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EDITED BY
Ming-Chyi PAI,
National Cheng Kung University, Taiwan

REVIEWED BY
Terence J. Quinn,
University of Glasgow, United Kingdom
Antonio Guaita,
Fondazione Golgi Cenci, Italy

*CORRESPONDENCE
Dianne Gove
dianne.gove@alzheimer-europe.org

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Keeping track of and recognizing the value of Public Involvement work in dementia research

Jean Georges, Ana Diaz-Ponce, Daphne Lamirel, Soraya Moradi-Bachiller and Dianne Gove*

Alzheimer Europe, Luxembourg, Luxembourg

The Public Involvement (PI) of people with dementia is slowly but progressively moving from a "nice to have" to a "must have" element of good-quality dementia research. Research funders and ethics committees increasingly ask for evidence of the planning of such involvement. The actual conduct and outcome of PI are, however, unfortunately typically under or inadequately reported. In this article, we provide an overview of what PI is and why it is important to dementia research and Alzheimer Europe's approach to PI. We draw on our recent experience of compiling a set of examples of PI in different European projects in publicly available sources. This highlighted the difficulty of finding information about PI activities and the almost total lack of details of such activities in formal reports, official records, and/or public project websites. In this article, we emphasize gaps and call for more stringent conditions for the inclusion and reporting of PI work in the context of the approval and funding of dementia research projects. We call for the establishment of obligatory reporting on the nature, specific challenges, and impact of PI in dementia research in formal reports (e.g., to funders), in public project websites, and in peer-reviewed articles. Such reporting should cover several key factors such as who was involved, how they were involved, and what impact PI had on the research process.

KEYWORDS

dementia, Public Involvement, research, public-private partnership, neurodegeneration

What is Public Involvement and why is it important to dementia research?

Public Involvement (PI) in the field of dementia research is about the active involvement of people with dementia in research projects other than as research participants. It may also involve people who are at risk of developing dementia, members of the general public, informal (unpaid) carers, and people who use, or have used, health and social care services concerning dementia. PI can take many different forms but typically involves members of these groups working together with researchers and sharing their perspectives, experiences, and needs with regard

to the research topic, design, and conduct of the study. This differs from Public Engagement, which can be defined as raising awareness, stimulating interest, and disseminating information and knowledge to the general public (including patients) about research studies and topics. However, these two terms have developed independently in different countries and contexts. Many different terms are used such as Public Involvement (PI), Public Engagement (PE), Patient and Public Involvement (PPI), Patient, Carer and Public Involvement (PCPI), and Patient and Public Involvement and Engagement (PPIE). The lack of clarity and consistency about the terminology contributes toward confusion about the concept itself and hampers efforts to promote it as an essential part of good-quality dementia research.

Drawing on Ives et al. (1) and Gradinger et al. (2), the two main objectives of PI work in dementia research can be summarized as follows:

1. to give people with dementia a voice in research that is relevant to their lives and well-being (linked to democratic decision-making, public accountability, legitimization, and transparency, as well as the right to voice),
2. to improve the research process and outcomes, affecting the quality, relevance, and/or utility of research (both from a research and user perspective), and to provide knowledge that might otherwise be missing (e.g., highlighting issues and asking questions about things that researchers have perhaps not considered, often drawing on personal experience within a non-medical or technical frame of reference (3).

The involvement of people with dementia throughout the whole process of research (starting with the identification of the topic through to the dissemination of the results to lay audiences) helps researchers to develop methods and tools that are best suited to participants' needs (potentially improving recruitment, retention, and compliance) and ensuring that research is also meaningful in the sense of addressing worthwhile topics for people with dementia and society as a whole.

In this article, we describe our approach to PI and briefly reflect on a recent experience of identifying examples of PI in European projects in the field of neurodegenerative research, based on publicly available information. We emphasize gaps and call for more stringent conditions for the inclusion and reporting of PI work in the context of the approval and funding of dementia research projects.

What is AE's approach to Public Involvement?

AE has always been keen to promote the involvement of people with dementia in its work and, more specifically, in dementia research. The involvement of people with dementia started several years ago in a more ad hoc manner, but has been consolidated and expanded over the years: This was done through the setting up of the European Working Group of People with Dementia (EWGPWD) in 2012 and, more recently, the development of some project-linked Advisory Boards also involving people at risk of developing dementia.

Over the years, the organization has adopted an inclusive person-centered approach to PI in research. Several aspects of this approach have been described in different academic papers including a Position Paper on Public Involvement in dementia research (written in collaboration with members of the international network of psychosocial researchers INTERDEM and people with dementia from the EWGPWD) and a report on inclusive research (4). With regard to terminology surrounding PI, whilst we used the term PPI in our earlier work, we replaced this with the term PI following discussions with people with dementia at Alzheimer Europe's annual conference in 2020. This was in response to objections from members of national dementia working groups, as well as from members of the EWGPWD, to being labeled and positioned as patients outside of their specific interpersonal doctor-patient relationships.

Relevant elements of this approach include:

- Ensuring that the PI activities are carefully planned and are timely, meaningful, and correspond to individual interests, wishes, and abilities.
- Thinking in terms of diversity (instead of representation), which involves listening to the perspectives and learning from the lived experience of very different people with dementia.
- Providing the necessary support for the people involved to be able to meaningfully and confidently participate in the PI activities, including, for example, providing accessible information in advance of the meeting about the topic to be addressed and facilitating the meeting in a manner that promotes the meaningful participation of everyone involved.
- Building and maintaining mutually respectful relationships between people with dementia and researchers, which also includes acknowledging the work of the people with dementia involved and providing feedback about the way their input has (or has not) been used and its impact on the research.

This approach is, however, not set in stone and continues to change and evolve. AE has been responsible for the PI activities of several European-funded research projects, many of which have been supported by the Innovative Medicines Initiative (IMI), which is a public-private partnership (PPP) between the European Union (European Commission) and the European pharmaceutical industry (EFPIA, the European Federation of Pharmaceutical Industries and Associations). AE has been a

full partner in several IMI-funded projects, including among others the "Real world Outcomes across the Alzheimer's Disease spectrum for better care: Multi-modal data Access Platform (ROADMAP)" and the "Remote Assessment of Disease and Relapse—Alzheimer's Disease" (RADAR-AD) projects. In the ROADMAP project, which was conducted between 2016 and 2018, we involved people with dementia in a one-off activity that had a significant impact on the project as it was about the conceptualization of the progression and staging of dementia, their views on what constitutes a meaningful delay of the disease, and their feedback on a European survey for people with dementia and carers.

More recently, in RADAR-AD, a project-specific Patient Advisory Board was set up and has been providing feedback from the beginning of the project to all work packages involved. This work has shown the benefits and challenges of bringing together people affected by dementia, researchers, and representatives from the pharmaceutical industry in the context of research. For example, working collaboratively in this way with several stakeholders and different companies may be easier for people affected by dementia than working with one single company (e.g., in terms of trust, timing, confidentiality issues, etc.). Details of the PI activities carried out within these projects have been published elsewhere (5–7).

What are the gaps with regard to PI in dementia research?

AE is not the only organization working in this way in Europe. In many, but not yet all, countries, PI in dementia research has been gradually growing over the last decade. Some European funding programmes, such as the Joint Programme for Neurodegenerative Diseases (JPND) and the Innovative Medicines Initiative (IMI), have, in recent years, strongly promoted and supported PI activities in research. A scoping review in 2020 (8) suggested that the number of published studies reporting PI activities was increasing, with PI taking place at different stages of the research process and with different methods being applied. A gap analysis carried out by the IMI-funded "Patients active in research and dialogues for an improved generation of medicines" (PARADIGM) project also identified several PI activities involving different groups of patients in the process of developing drugs and treatments.

However, the evaluation and reporting of the impact of PI still represent an important gap (8). The PARADIGM gap analysis work came to similar conclusions and highlighted the lack of publicly available information about the PI activities carried out in this context. When reporting exists, it is often fragmented and lacking the necessary details to make it possible for others to fully understand what was done, with whom, when, how, the outcomes—both positive and negative, the learning experiences, and the resulting value of the activity itself (PARADIGM tool "Guidance for Reporting and Dissemination of Patient Engagement Activities").

Similarly, in their well-known GRIPP (Guidance for Reporting Involvement of Patients and the Public) guidelines, aimed at improving the quality and consistency of PI work and reporting, Staniszewska et al. (9) criticized the quality of reporting within scientific and peer-reviewed articles. They described reporting on PI as often being inconsistent and thus limiting the possibilities to learn from these research studies, and emphasized the importance of reporting what members of the public consider important to report.

In 2021, as part of activities carried out under an operating grant by the EU health programme, AE set out to identify 20 different examples of PI activities and methods used within the scope of European research projects in the field of neurodegeneration. As a first stage, we searched four key repositories/databases of European research into neurodegenerative disorders, namely CORDIS Community Research and Development Information Service, the JPND Research Database, IMI Project factsheets, and the Active and Assisted Living (AAL) programme website. After this, when necessary, we contacted researchers involved in the projects who were responsible for the PI work (when details were available) to ask for information. Finally, we hand-searched project websites for further information.

The first challenge was to identify projects that were planning or conducting PI activities and who was in charge of such activities. The databases and research platforms that we looked at contained a wealth of information but did not have specific search categories for PI work or any other information that could indicate that PI activities had been planned or conducted. The fact that different terminology is used to refer to PI, as stated earlier, maybe another relevant factor hindering the visibility and "searchability" of PI activities in this context. Some research funding bodies, for example, use the term PPI whereas others use the term PE (but to refer to what would be considered as PI under certain other classifications).

A second challenge was that there was very little information, if any, in the public domain about the nature of the PI work undertaken and of specific challenges linked to conducting PI with this population. It is possible that some projects had reported on the PI work in more detail but such reports may have been internal or were simply not readily available. Information on PI work was even more difficult to obtain if the project had already finished or the person responsible for the PI work had moved to a different position.

The PI work that we were able to identify varied considerably in terms of its approach, scale, impact on the project, the involvement of research partners, and how it had been reported.

It was very difficult to capture differences or come to conclusions in relation to the models and methods used given the scarcity of the information available in the public domain. A couple of projects published peer-reviewed articles about some of the PI activities that had been conducted. Apart from this, the most common place where PI work was made public was the project website. In most of the IMI projects that we looked at, the project website had a dedicated section for PI or information for patients or the general public. However, the work carried out was not always described in sufficient detail, and, in particular, the information about how the PI input had been used and its impact on the project were even less likely to be in the public domain. This is an important gap, which makes it difficult to help ensure that the input provided by people living with dementia is used in a meaningful way (which has ethical, financial, and scientific implications). It is also important that people involved in the PI activities receive information about how their input was used (or why not) and what the impact of this was for the project.

What are we calling for?

We very much welcome the commitment of European funding organizations to PI work in the field of dementia. We firmly believe that this is hugely beneficial to dementia research and it respects the right of people with dementia to have a voice in matters affecting their lives. The mapping exercise that we conducted in 2021 demonstrates the importance of ensuring that PI work is not only properly conducted but also properly documented.

There are often concerns about whether PI work is meaningful or a mere box-ticking exercise to obtain funding or ethics approval. To ensure that PI work truly contributes toward good research and that it is meaningful and well-conducted, it must be reported thoroughly and accurately. It cannot be a "black box" activity (e.g., "we conducted PI work"). National and European dementia research funders must insist not only on projects doing PI work but also on the deliverables and publicly available information about what was done. Amongst other things, further visibility of this work could be an inspiration for other organizations willing to conduct PI and could help to better understand the impact and benefits of PI in research projects.

We, therefore, recommend that:

- organisations' funding research should require at least one public deliverable for PI work and encourage researchers to publish details of the PI work on project websites or other places where the information is publicly accessible.
- academic publishers should require researchers to provide precise details of the nature, specific challenges, and impact of PI work in their manuscripts submitted for publication, and if PI was not carried out then to explain why this was the case.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

DG and AD-P conducted the mapping review. JG, DG, and AD-P drafted the article. JG, DG, AD-P, DL, and SM-B provided critical comments on the manuscript draft and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Elisabetta Vaudano,
Innovative Health Initiative, Belgium

REVIEWED BY
Li Xiaofeng,
Chongqing Medical University, China

*CORRESPONDENCE
Carlos Díaz
cdiaz@synapse-managers.com

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Avoiding fragmentation: The potential of synergistic efforts across the IMI portfolio

Carlos Díaz[1]*, Lewis Killin[1] and Nigel Hughes[2]

[1]Synapse Research Management Partners SL, Madrid, Spain, [2]Observational Health Data Analytics/Epidemiology, Janssen Research and Development, Beerse, Belgium

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Introduction

There is a growing consensus in the scientific community that the harmonization and federation of data sources is a key enabler for the generation of actionable real-world evidence, which is essential to support timely decision-making. Healthcare systems, research communities, industry and, increasingly, citizens themselves generate data on a continuous basis. However, the wide range of methods used to capture, format, structure, and ultimately analyze such data limits the potential for data use and reuse. These obstacles are especially important when trying to solve research and clinical questions different from those that originally triggered data collection. Fostering transparent and efficient use of these data is essential for improving disease understanding and the development of much-needed novel therapies and interventions that can benefit the increasing number of patients affected by various degenerative, chronic, and debilitating neurological conditions worldwide.

A fragmented and complex landscape of initiatives

Many previous efforts have focused on centralized data collection and processing, often within the context of single initiatives. These bespoke exercises, while beneficial, were frequently limited to the original research question, a local/regional/national focus, and/or time and funding considerations. Because of their custom nature, reusing collected datasets, data standardization pipelines, and derived tools is often too costly or technically difficult. New projects and studies usually resort to starting from scratch with their data collection and management strategies, which is not only inefficient but also causes delays and consumes valuable resources unnecessarily. In the research landscape, syndromes such as "reinventing the wheel" and "not invented here" are frequently visible.

In neurodegeneration (ND), for example, a plethora of specific cohort studies have been created stemming from individual memory clinics and clinical centers. These coexist with networks and global initiatives (e.g., the World Economic Forum's Davos

Alzheimer's Collaborative),[1] with different degrees of interaction among them. Most cohort studies collect broadly similar information, but they differ greatly in size, population, protocols, data formats, etc. The landscape is so varied and complex that specific efforts have been made to simply catalog existing cohorts and provide adequate metadata, such as in the Innovative Medicines Initiative (IMI) European Medical Information Network—(EMIF)[2] project. Understanding what is available and under what conditions, as well as the potential for reuse, can be a daunting task.

Some current efforts go one step further, providing platforms for exploration, interrogation and, in some cases, aggregation or integration, as well as direct access to datasets, increasingly under federated models that respect the autonomy of contributing centers and alleviate concerns about ethical and legal issues associated with data protection. Examples include the Global Alzheimer's Association Interrogation Network (GAAIN),[3] the EBRAINS Research Infrastructure,[4] the Alzheimer's Disease Data Initiative (ADDI),[5] and the recently launched, IMI-funded European Platform for Neurodegenerative Diseases (EPND).[6] Most of these platforms offer several layers of access, allowing users to dig down from pure metadata browsing to actually performing analytics to varying degrees. Developing an enticing, ethically sound value proposition for researchers and data generators is critical for the ultimate success of these initiatives.

Challenges and possible ways forward

Merely listing some of the current initiatives above demonstrates that fragmentation remains a major underlying issue in the ND field, and is likely one of the factors undermining the radical progress demanded by society for decades. The existence of a variety of solutions is not the problem – each is a valuable effort on its own – instead, the issue is that each new initiative is designed, developed, promoted, and attempted to be sustained in a practically isolated way. Ambition, innovation, outreach, buy-in from stakeholders, and true collaboration are all naturally limited beyond the confined space created by the specific funding flows supporting each endeavor.

Furthermore, as espoused by programmes such as IMI, public-private partnerships (PPPs) that include, but also support, multiple stakeholders in the public sector, e.g., research and enhancing clinical care, and the private sector, for research and development, have become an increasingly important model. In disease areas such as ND, PPPs can be an ideal framework to respond to this need due to the complexity of these diseases, the difficult nature of diagnostic and therapeutic development, and the required resources.

Switching from a maze of datasets and cohorts to a maze of platforms does not solve the current challenges in ND if the scientific richness and data generously contributed by citizens are constrained to one of the thousands of time-limited, insufficiently funded initiatives. Indeed, and given the scientific system structure and inertia, it does not seem that any given "definitive" solution will be able to resolve fragmentation on its own. Instead, it may be that more attention is needed toward key underlying issues such as: (1) data standardization and interoperability according to open standards in a transparent, agnostic, and flexible way; (2) programme management activities that are fully devoted to integrating individual projects and maximally exploiting synergies between them; and (3) system leadership approaches that promote open, non-judgemental spaces for peer-to-peer discussion and creativity across the range of stakeholder groups, enabling broad consensus on priority research questions to be tackled. The realization within research and clinical communities of the need for data harmonization has never been clearer than through the ongoing European Health Data and Evidence Network (EHDEN)[7] project, an IMI-funded initiative that in the past 4 years has managed to mobilize over 250 healthcare and research institutions across Europe interested in mapping their data to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. The use of an open common data model and derived analysis tools facilitates aggregated analyses of hundreds of millions of electronic healthcare records (EHRs) with speed, transparency, and privacy protection that can represent a true paradigm shift in the conduct of observational studies. By approaching standardization from a "research-question-agnostic" perspective, EHDEN is tackling a key challenge that hampers data use, and facilitating data being findable, accessible, interoperable, and reusable (FAIR). The impact of such innovative approaches can be seen also in the regulatory space, e.g., the recently launched DARWIN EU®[8] initiative of the EMA.

Specifically, in the ND field, IMI has also been at the forefront of international data harmonization and integration efforts with regard to research cohorts, with flagship projects such as the aforementioned EMIF, the European Prevention of Alzheimer's Disease Consortium (EPAD),[9] the Amyloid

1 www.davosalzheimerscollaborative.org
2 www.emif.eu
3 www.gaain.org
4 www.ebrains.eu
5 www.alzheimersdata.org
6 www.epnd.org
7 www.ehden.eu
8 www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu
9 www.ep-ad.org

Imaging to Prevent Alzheimer's Disease project (AMYPAD),[10] and the recently launched EPND. But importantly, this has been complemented at a higher, cross-project level, by the Efficiently Networking European Neurodegeneration Research (NEURONET)[11] action, which has successfully built bridges across the IMI ND portfolio, creating a space where more than 20 distinct ND research projects could meet, discuss synergies, and generate new ideas. A key strength of NEURONET has been to support and communicate about the field neutrally and to remedy initiative fragmentation without constructing another new scientific hegemony. To that end, NEURONET has produced outputs that have represented the assets and experiences of its constituent studies as a transparent and one-stop resource. These are best represented by its Knowledge Base[12] and its series of guidance deliverables, which outline cross-project experts' views and experiences on topics such as data sharing, data privacy, HTA and payer strategy, impact analysis, communication, and sustainability activities. The Knowledge Base in particular presents an accessible consolidation of resources that would otherwise be kept separate on an individual project or stakeholder channels. In addition, it enables the creation of tools of common interest that would not be in scope for any specific project. For example, the Regulatory and HTA Decision Tool signposts to different agencies, organizations, and case studies relevant to the assessment of new interventions, and the Asset Map graphically represents the usable outputs generated by any of the projects, ranging from disease models and ontologies to cohorts, datasets, and more. Importantly, this material is both applicable to the immediate IMI environment and to researchers who work outside of it. The privileged position of NEURONET as a neutral actor has also allowed it to organize meetings for "out-of-the-box" thinking, in an attempt to boost creative reflection around some of the most pressing research needs, without the limitations imposed by ordinary fora.

With its main role as a facilitator, NEURONET was well-positioned to establish the NEURO Cohort initiative. Here, it proposed a way of uniting 40 research and clinical sites across Europe, all interested in collecting a minimal data set about people living with or at risk of ND on a continuous basis in order to facilitate feasibility assessment and the establishment of future research projects. Critically, the design of the minimal dataset was done in collaboration with the sites to respect their autonomy whilst also reflecting their most commonly collected variables, which were also of interest to the community. Creating NEURO Cohort as an agreed baseline for common activity—with minimal overhead—has provided a foundation for further potential research at scale.

The "grassroots" approach of NEURONET, in which all projects and sites are equally important and participate on the same level in decision-making, can be seen as an initial template for the above-mentioned systems leadership philosophy, which can allow the gathering of stakeholders with differing interests – with none of them dictating the agenda – around a common objective.

Conclusion

The acceleration of these coordination, harmonization, and integration efforts in recent years offers a unique opportunity to multiply and elevate concerted action to the next level, overcoming the inherent limitations of time-boxed and fixed-budget projects. This could also imply the creation of multi-stakeholder, sustainable observational spaces that go beyond data silos of specific types (e.g., EHRs, cohort data, patient-reported outcomes, and digital device data) or typical of certain research communities (e.g., clinical, regulatory, research cohort, and trial studies) to cut across them as well, at scale. A multi-project "Research Programme on Neuroscience" has recently been proposed that could link mapped EHR data from EHDEN (which captures medical history, drug use, co-morbidities, etc. of a large number of individuals) with the research cohort data from NEURONET (which capture deep phenotyping and biomarkers relevant to specific diseases and conditions, for a limited number of individuals). If successful, the data space resulting from synergies across two seemingly unrelated initiatives could become a unique resource attracting a variety of researchers, sponsors, and stakeholders, radically enhancing our global capacity for generating the necessary real-world evidence that can make a difference in addressing the ND diseases that affect millions.

For the past 15 years, IMI has been spearheading the creation of public–private consortia in Europe, involving hundreds of academic, healthcare, industrial, regulatory, and patient advocacy groups. It is important that the power of such a research ecosystem is not diminished by fragmentation and limitations resulting from project silos, and that appropriate action is taken to focus on key common challenges of global relevance, both within and outside the field of ND. This may necessitate new perspectives that promote programme management and integration as a priority. ND diseases represent a therapeutic area that clearly requires a collaborative research approach supported by considerable, relevant, and representative data, and this probably necessitates ambitious frameworks such as those developed by IMI's public–private partnerships. These, however, may need to be

10 www.amypad.eu

11 www.imi-neuronet.org

12 https://kb.imi-neuronet.org

interconnected by design, as part of deeply integrated research programmes capable of mobilizing the capacity and resources required to provide faster and more efficient progress in the field.

Author contributions

CD, LK, and NH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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EDITED BY
Elisabetta Vaudano,
Innovative Health Initiative, Belgium

REVIEWED BY
Annamaria Vezzani,
Mario Negri Institute for Pharmacological Research (IRCCS), Italy

*CORRESPONDENCE
Craig W. Ritchie
Craig.Ritchie@ed.ac.uk

†These authors have contributed equally to this work and share first authorship

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The European Prevention of Alzheimer's Dementia Programme: An Innovative Medicines Initiative-funded partnership to facilitate secondary prevention of Alzheimer's disease dementia

Stina Saunders[1†], Sarah Gregory[1†], Matthew H. S. Clement[2], Cindy Birck[3], Serge van der Geyten[4] and Craig W. Ritchie[1,5*] on behalf of the EPAD Consortium

[1]Edinburgh Dementia Prevention, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom, [2]Alzheimer's Disease Data Initiative, Kirkland, WA, United States, [3]Alzheimer Europe, Luxembourg, Luxembourg, [4]Janssen Research and Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium, [5]Brain Health Scotland, Edinburgh, United Kingdom

Introduction: Tens of millions of people worldwide will develop Alzheimer's disease (AD), and only by intervening early in the preclinical disease can we make a fundamental difference to the rates of late-stage disease where clinical symptoms and societal burden manifest. However, collectively utilizing data, samples, and knowledge amassed by large-scale projects such as the Innovative Medicines Initiative (IMI)-funded European Prevention of Alzheimer's Dementia (EPAD) program will enable the research community to learn, adapt, and implement change.

Method: In the current article, we define and discuss the substantial assets of the EPAD project for the scientific community, patient population, and industry, describe the EPAD structure with a focus on how the public and private sector interacted and collaborated within the project, reflect how IMI specifically supported the achievements of the above, and conclude with a view for future.

Results: The EPAD project was a €64-million investment to facilitate secondary prevention of AD dementia research. The project recruited over 2,000 research participants into the EPAD longitudinal cohort study (LCS) and included over 400 researchers from 39 partners. The EPAD LCS data and biobank are freely available and easily accessible *via* the Alzheimer's Disease Data Initiative's (ADDI) AD Workbench platform and the University of Edinburgh's Sample Access Committee. The trial delivery network established within the EPAD program is being incorporated into the truly global offering from the Global Alzheimer's Platform (GAP) for trial delivery, and the almost 100 early-career researchers who were part of the EPAD Academy will take forward their experience and learning from EPAD to the next stage of their careers.

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Discussion: Through GAP, IMI-Neuronet, and follow-on funding from the Alzheimer's Association for the data and sample access systems, the EPAD assets will be maintained and, as and when sponsors seek a new platform trial to be established, the learnings from EPAD will ensure that this can be developed to be even more successful than this first pan-European attempt.

KEYWORDS

Alzheimer's disease, Longitudinal Cohort Study, public-private partnership, Innovative Medicines Initiative, secondary prevention

Introduction

Early detection of Alzheimer's disease (AD) pathology offers an opportunity for intervention, either to delay symptom onset or to stop the disease development entirely. Due to the long silent period in the AD pathology where the disease starts developing more than 20 years before traditional symptoms of dementia manifest (1, 2), identifying individuals at risk of dementia in pre-dementia stages is a major aim of many disease-modifying therapies currently developed for AD. However, because of the stage of illness that patients present with in current *memory clinics*, clinical trials commonly recruit individuals who are in the more advanced stages of the disease and there is a dearth of knowledge in the longitudinal modeling of AD trajectories in the preclinical period of disease to inform trial design. Moreover, recruitment rates for AD research remain low, resulting in drug studies commonly missing recruitment targets (3). To this end, the European Prevention of Alzheimer's Dementia (EPAD) program was established in 2015, funded by the European Union's Innovative Medicines Initiative (IMI), and is now succeeded by the Innovative Health Initiative.

EPAD aimed to assist in the development of interventions for the secondary prevention of AD. The program set out to develop a clinical trial platform that could test multiple interventions concurrently in a multitude of sites across Europe. Individuals recruited by these sites were highly phenotyped and formed a readiness cohort referred to as the EPAD Longitudinal Cohort Study (LCS). The first participant consented in May 2016, and until the study closure in March 2020, over 2,000 research participants eligible for secondary-prevention studies were recruited into the EPAD LCS, generating several million data points and over 1 million aliquots of cerebrospinal fluid (CSF), plasma, serum, saliva, and urine (4). Due to the longitudinal nature of the study, participants completed a varying number of visits which are detailed in the results section.

EPAD stemmed from a need to develop new pharmacological agents for AD where there had been a significant lack of progress over 15 years at the time. Individuals recruited into the EPAD LCS were aimed to fill the continuum of low to high risk of developing AD but not have dementia. Although the original focus of the EPAD proposal had been on preclinical AD (evidence of AD pathology with no manifest symptoms), the funded EPAD project expanded recruitment to include people with prodromal AD (evidence of AD and manifest symptoms, although insufficient to satisfy criteria for dementia). There were several reasons for why a platform trial design was chosen for EPAD. A platform trial enabled (1) a single operational environment, (2) a single master protocol (including sharing placebo data), (3) a site network and community that conducted all three elements of research participant engagement (register, cohort, and trial), and, therefore, (4) a single sponsor to oversee the whole program under a single governance framework.

In the current article, we summarize the key findings of the EPAD study to date, detail the data access policy, and define the substantial residual assets of the EPAD project for the scientific community, patient population, and industry. Additionally, we describe the EPAD structure with a focus on how the public and private sectors interacted and collaborated within the project, reflect how IMI specifically supported the achievements of the above outputs, and conclude with a view for future.

Methods

The EPAD program was the winning response to a call put out by IMI to undertake deep phenotyping of individuals at risk of AD to determine their eligibility for a secondary-prevention Proof of Concept (PoC) trial. It was recognized that deep phenotyping would reduce screen failures in PoC (drug trials) as knowing amyloid status, cognitive function, medical comorbidities, and *Apolipoprotein E* (*APOE*) status before invitation to the PoC trial would enable approaching individuals who are already deemed eligible per the PoC study protocol. IMI was uniquely positioned to fund such an innovative platform trial in AD as it brings together the pharmaceutical industry [under the European Federation of the Pharmaceutical Industry and Associations (EFPIA)], academia, the third sector, and small and medium enterprises (SMEs).

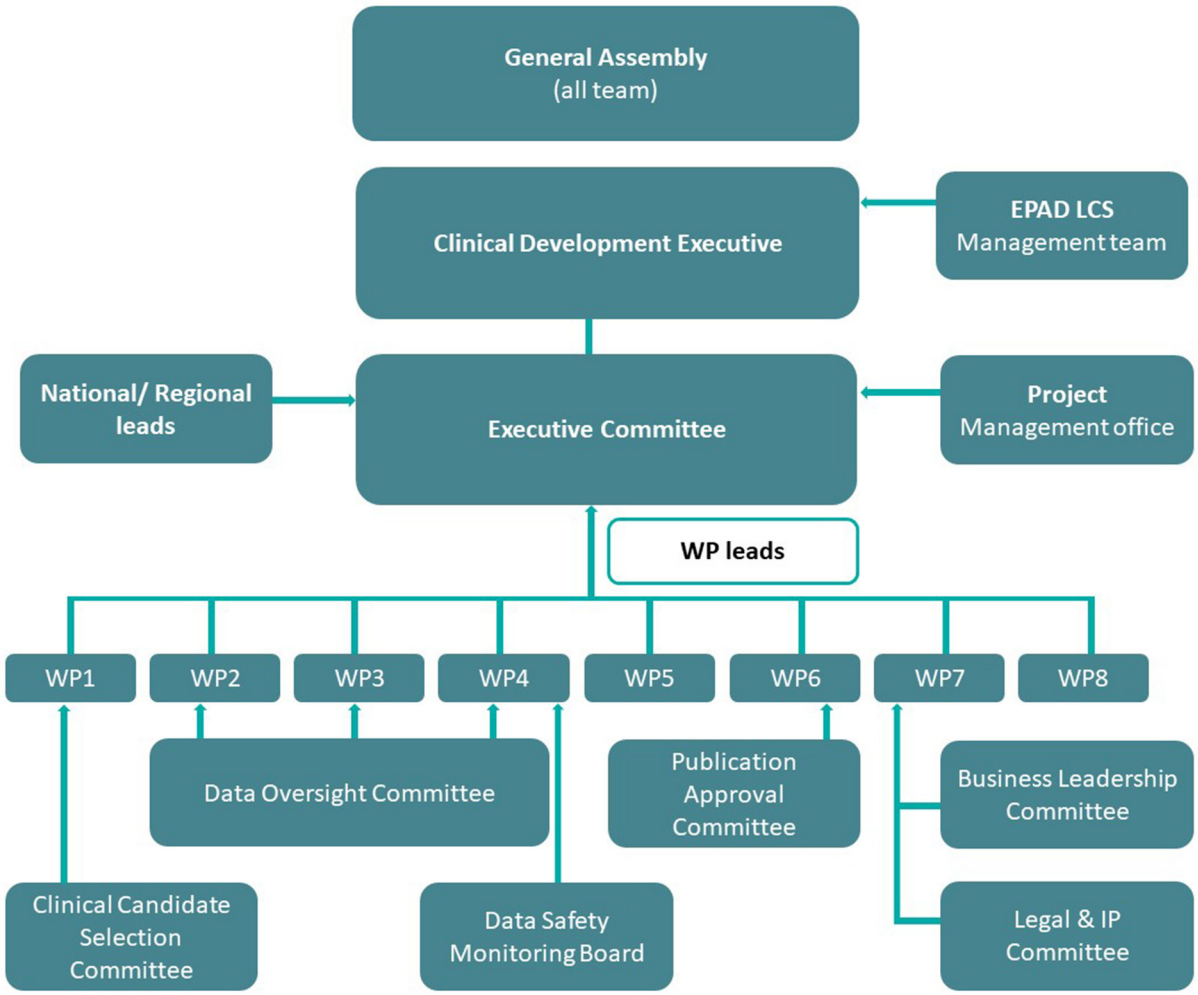

FIGURE 1
EPAD governance structure. Work Package 1: Scientific Challenges; Work Package 2: Statistical/Methodology Engine Room; Work Package 3: Parent Cohorts and EPAD Register; Work Package 4: EPAD Cohort and EPAD Trials; Work Package 5: Project Management; Work Package 6: Dissemination; Work Package 7: Business Model and Sustainability; Work Package 8: Ethical, Legal and Social Implications.

Private-public partnership

EPAD had a budget of €64 million, involved 39 partners which operated across 29 sites in 10 countries in Europe, and (at its peak of activity) had 410 people from Europe and the USA receiving direct salary costs from the grant. As a public-private partnership, the EPAD coordination was shared by partners from academia and EFPIA. The private-public partnership was achieved through all governance entities and work packages being jointly led by an EFPIA and an academic lead.

Study management

EPAD was managed by the executive committee which met monthly and had a balanced representation from EFPIA, academia, and the project management office. From an operational perspective, EPAD was divided into eight work packages (WPs; Figure 1) with representatives again from industry and academia (5). These work packages were complimented by transversal working groups and committees that dealt with specific needs at various stages of the program's development. Data support was provided by numerous partners, that is, IXICO (neuroimaging partner), Aridhia (data-management partner), and IQVIA (clinical research organization). Moreover, from the outset, it was recognized that the value of the data collected in the EPAD LCS (and PoC trial) would be at a breadth and scale to help facilitate conceptual advance in the understanding of disease models in the early phases of neurodegeneration. The EPAD data, therefore, had to be both open access and of the highest quality.

TABLE 1 Baseline characteristics of 1,843 non-screen failed participants in the EPAD LCS (8).

Variable		Mean (SD)	Frequency (%)	Number currently unknown
Gender	Female		1,035 (56.6%)	
	Male		793 (43.4%)	
Age, years		65.7 (7.41)		
Age group	Under 75 years old		1,612 (88.2%)	
	75 years old and above		216 (11.8%)	
	Years of formal education*	14.4 (3.70)		
Education	Up to secondary		722 (39.5%)	
	Beyond secondary to ordinary first degree		451 (24.7%)	
	Postgraduate studies		655 (35.8%)	
Family history of AD?	No		657 (35.9%)	
	Yes		1,171 (64.1%)	
APOE ε4 genotype	No *APOE ε4* alleles		1,077 (58.9%)	
	One *APOE ε4* allele		618 (33.8%)	57
	Two *APOE ε4* alleles		76 (4.2%)	

*Years of education is country-specific.

Structure

The EPAD LCS was set up to collect longitudinal data for disease modeling purposes (6) and also to act as a readiness cohort for PoC trials. Although the observational LCS was successfully undertaken throughout Europe, the IMI funding period ended without the PoC trials starting. The objective of the PoC trial was to develop a platform and master protocol for a perpetual, Bayesian adaptive trial for the secondary prevention of AD dementia. To create readiness for a trial to start, EPAD built and certified trial delivery centers (TDCs) across Europe which undertook the cohort study and were approved and highly qualified to conduct PoC trials thereafter.

Participant involvement

Finally, EPAD also recognized from the outset that all clinical research projects benefit from the insights of people with lived experience, either as research participants and/or those affected by the disease. At a national level, the research participants were coordinated into national panels, who would discuss their experience of the LCS and help design communication materials. These national panels would also be asked to provide formal feedback on protocol amendments. By 2019, four national panels had been established, in Spain, the Netherlands, England, and Scotland, and each panel sent representation to the annual EPAD general assembly (7).

Results

Open access data: The EPAD LCS dataset

The most substantial output from the IMI period of EPAD was the EPAD LCS, recruiting 2,096 research participants of whom 1,828 were available for analysis (Table 1). The EPAD LCS dataset is unique, whereby 37% of the sample were amyloid positive at the point of enrollment to the study (CSF Aβ <1,000 pg/ml using the Roche Diagnostic Elecsys® System) (8). This resulted in $n = 358$ deeply phenotyped participants who fill the criteria for preclinical AD. As the LCS finished in Spring 2020, a small proportion of the early recruits completed 3 years of follow-up and four study visits (baseline, month 6, month 12, month 24, and month 36) (Table 2).

All data, images, and samples from the EPAD LCS have been released as V.IMI (V = version) and are now freely available to all researchers globally *via* the Alzheimer's Disease Data Initiative's (ADDI) online platform, the AD Workbench (https://www.alzheimersdata.org/ad-workbench). The AD Workbench was publicly launched in November 2020 after a successful pilot that was supported by a coalition of organizations and industry partners interested in improving Alzheimer's and related dementia data sharing (https://www.alzheimersdata.org/about-addi). The EPAD dataset was the first full dataset to be made available on the AD Workbench and is the most highly requested dataset having received over 200 data access requests to date.

The EPAD LCS created a huge biobank of more than 100,000 samples (CSF, blood, saliva, and urine), all stored in a single location at the Roslin Institute within the University

TABLE 2 Number of completed research participant visits and availability of key assessment data at each visit (8).

	Visit 1 (baseline)	Visit 2 (6 months)	Visit 3 (1 year)	Visit 4 (2 years)	Visit 5 (3 years)
N	2,096	1,571	1,190	397	90
Break-down of number of samples per visit					
Blood samples (*APOE*[a])	2,007	0	0	0	0
MRIs[b]	1,927	0	601	249	6
Lumbar punctures (includes "retest" [c])	1,806	0	350	204	8
RBANS[d] tests	2,014	1,561	1,180	396	90
CDR[e] tests	2,024	1,556	1,181	394	90

[a]Blood sample to measure *APOE* is only collected at baseline visit as per protocol.
[b]MRI scan is not performed at 6-month visit as per protocol.
[c]Lumbar puncture is not performed at 6-month visit as per protocol.
[d]Repeatable Battery for the Assessment of Neuropsychological Status.
[e]Clinical Dementia Rating Scale (blind rater).

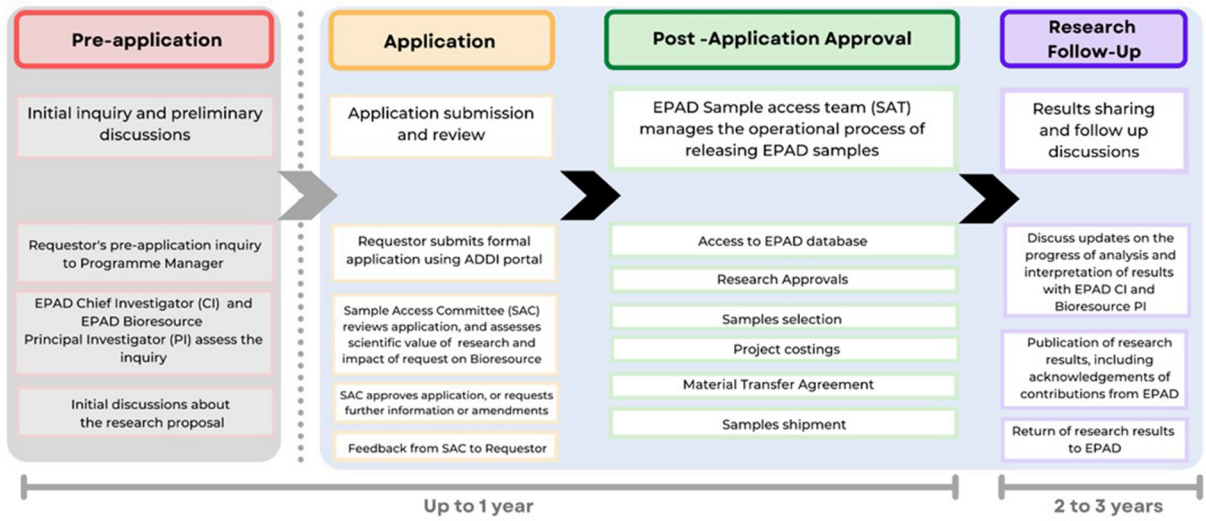

FIGURE 2
Requestor's journey to access EPAD samples and corresponding data.

of Edinburgh under optimal conditions. EPAD works on the principle that samples should be used and not stored indefinitely for (potential) future use and also that access should not be prohibited by costly access requirements. In essence, access should only be affected by the quality of the scientific question and the willingness to share derived data back into the main EPAD database. Data access applications are processed within several business days of the request and image requests are processed in 4 weeks. For sample access, researchers are encouraged to make informal inquiries about the scope of their research and to discuss the range of samples EPAD can offer. Sample access is governed by the rules of the Sample Access Committee that were designed with reference to the terms of the IMI-EPAD project agreement. The sample access process is illustrated in Figure 2 and can be started at https://ep-ad.org/samples-access/.

Description of dataset and study methodology

As the EPAD project progressed, four datasets were made freely available ensuring the use of the data for the AD research community worldwide:

1. EPAD LCS V500.0, which includes data from the first 500 people to enter the cohort;

2. EPAD LCS V1500.0, which includes data from the first 1,500 people to enter the cohort;
3. EPAD LCS V500.1, which includes updated data from the first 500 participants, including 1-year follow-up data; and
4. EPAD LCS Version.IMI (V.IMI), which includes the final longitudinal data with cognitive, clinical, biomarker, and neuroimaging and lifestyle risk factor datasets from the over 2,000 participants of the EPAD LCS.

Each dataset was registered to a DOI for unique and specific identification of the dataset in publications and reference materials. To learn what data and associated metadata are available in the EPAD data release, visit the EPAD website (https://ep-ad.org/).

For a detailed overview of the study methodology and outcomes, refer to the V500.0 baseline data release article (9). The V500.0 is also the dataset used in many of the analyses described in the following section summarizing key findings to date.

To access all the data collected and processed during the IMI period of EPAD, please request the latest and final EPAD dataset (V.IMI) on the AD Workbench.

Summary of key findings to date

At the time of writing this article, there are 42 EPAD-associated articles, spanning a broad range of topics; 17 results articles, nine review articles, seven methods articles, six results articles funded or associated with EPAD but not using EPAD LCS data, two editorials, and one article on data access. The articles have included 204 authors, across 94 institutions in 16 different countries. The 17 results articles include 115 individual authors from 63 institutions in 14 countries. Except for one article, all authors are from Europe or the USA. Authors were affiliated with academic institutions, charity organizations, SMEs, and pharmaceutical companies, demonstrating the public-private partnership continued from the set up and running of the project through to dissemination. Table 3 gives an overview of the results articles and findings; all articles are also listed on the EPAD website (www.ep-ad.org).

Biomarkers

Nine published articles have reported on biomarkers, imaging, and cognition. The Amyloid/Tau/Neurodegeneration (ATN) framework has been used by two articles to define participants by biomarker status. Through this framework, 57.1% of the EPAD LCS cohort included by Ingala et al. (10) were A-T-N-, 32.5% were on the AD-continuum, and 10.4% suspected non-Alzheimer's pathology. The authors found that both age and cerebrovascular burden progressed with biomarker positivity. Additionally, phosphorylated tau was associated with cognitive dysfunction in individuals without dementia, and memory and language domains were affected in the earliest stages of neurodegeneration across the cohort (10).

Calvin et al. (20) found significant differences by age, *APOE ε4*, family history, body mass index, mini-mental state examination, and white matter lesion (WML) volume across the ATN groups. Prediction of AD pathology improved by adding these components to a ROC curve; however, there was no additional value in including established dementia composite risk scores (20).

A further study considering disease modeling applied a two-stage approach utilizing longitudinal cognitive and clinical outcomes, biomarkers (baseline and longitudinal), and risk factor data. The two-stage approach demonstrated clinical and biological utilities in trajectory stratification and was able to identify subgroups of interest in the dataset (15).

AD biomarkers, specifically cerebrospinal fluid (CSF) Aβ1-42, have also been investigated about multimorbidity in the EPAD cohort. When including the number of conditions as a continuous variable representing multimorbidity, each additional condition was associated with a decreased likelihood of amyloid positivity and higher CSF Aβ concentrations, suggesting that the established association between multimorbidity and dementia may be due to a pathway other than amyloid (11).

An analysis of sex differences with regard to *APOE ε4* carrier status found a significant interaction of sex, *APOE ε4,* and Aβ, with male participants showing a stronger association between *APOE ε4* and Aβ on pTau compared to female participants. In this same study, female *APOE ε4* carriers, but not male, with high levels of CSF Aβ had significantly elevated pTau compared to non-carriers, suggesting that accumulation of pTau may be independent of amyloid for women (18).

Both cross-sectional and longitudinal analyses of the EPAD dataset found associations between self-reported measures of sleep and AD biomarkers. Sleep disturbance was associated with lower CSF Aβ concentrations at both baseline and longitudinal follow-up, poor sleep quality was associated with higher CSF tTau at baseline and short sleep duration was associated with higher CSF pTau and tTau (14).

Analysis of cognitive results has also given rise to interesting findings. One study investigating the concept of cognitive dispersion found that it was associated with both age and education, but not with AD pathology, in the EPAD cohort (12). A second study investigating associations between Aβ, tau, and specific cognitive tests identified biomarker-specific profiles of cognitive impairment. A primarily hippocampal task was associated with higher levels of tau, while a frontal executive task was associated with higher levels of Aβ (13).

Focusing on neuroimaging, Lorenzini et al. (21) investigated associations among amyloid, age, and vascular risk with white matter hyperintensities (WMH). The analysis found a two-component pattern, whereby the first component identified a

TABLE 3 Overview of results papers originating from analysis of EPAD data or EPAD participants.

Publication title	Theme	Summary of main findings
Application of the ATN classification scheme in a population without dementia: Findings from the EPAD cohort (10)	Biomarkers	• Used the ATN framework to define participants by biomarker status • 57.1% of participant were A-T-N- • 32.5% of participants were on the AD continuum • 10.4% of participant were suspected non-Alzheimer's pathology • Age and cerebrovascular burden increased with biomarker positivity • Cognitive dysfunction appeared with phosphorylated tau positivity (T+)
Associations between multimorbidity and cerebrospinal fluid amyloid: a cross-sectional analysis of the European Prevention of Alzheimer's Dementia (EPAD) V500.0 cohort (11)	Biomarkers	• Analyzed for associations between multimorbidity and cerebrospinal fluid (CSF) amyloid • Each additional condition was associated with a decreased likelihood of amyloid positivity (when using <1000pg/ml as cut off) • Each additional condition was associated with an increase in CSF amyloid of 54.2 pg/ml (95% CI: 9.9–98.5) • Having two or more conditions was inversely associated with amyloid positivity compared to one or no conditions
Cognitive Dispersion is not associated with cerebrospinal fluid biomarkers of Alzheimer's disease: results from the European Prevention of Alzheimer's Dementia (EPAD) v500.0 cohort (12)	Cognition and biomarkers	• Analyzed for associations between cognitive dispersion and CSF biomarkers • Found no significant associations between cognitive dispersions and any of the CSF analytes or categorical amyloid positivity • Greater cognitive dispersion seen in participants who were older and those who had less education
Cognitive functions as predictors of Alzheimer's disease biomarker status in the European Prevention of Alzheimer's Dementia cohort (13)	Cognition and biomarkers	• Analyzed for predictive value of cognitive functions for Alzheimer's disease biomarker status • Tau was significantly associated with an episodic verbal memory task • Amyloid beta was significantly associated with a central executive task
Cross-sectional associations between sleep quality reports and core Alzheimer's disease biomarkers in cognitively unimpaired adults from the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS) (14)	Sleep and biomarkers	• Analyzed for associations (cross-sectionally and longitudinally) between self-reported sleep and CSF AD biomarkers • Cross-sectional analysis found that poor sleep quality was associated with higher CSF tTau, shorter sleep duration was associated with higher CSF pTau and tTau • Greater sleep disturbance was associated with lower CSF Aβ both cross-sectionally and longitudinally
Disease modeling of cognitive outcomes and biomarkers in the European Prevention of Alzheimer's Dementia longitudinal cohort (15)	Disease modeling	• Developed a two-stage approach for modeling of longitudinal cognitive and clinical outcomes • Demonstrated clinical and biological utility in incorporating multiple factors to modeling trajectory, subgroup identification and predictive power
European Prevention of Alzheimer's Dementia Registry: Recruitment and prescreening approach for a longitudinal cohort and prevention trials (16)	Recruitment methods	• Analysis of feasibility of recruitment approach employed in EPAD LCS • Demonstrated success of using a virtual registry to preselect participants for AD studies
Involving research participants in a pan-European research initiative: the EPAD participant panel experience (17)	Participant involvement	• Analysis of the impact of the participant involvement panels • Panel members provided important and useful feedback on study documentation • Panel members involved with design of new study materials • Panel members represented the project at national and international meetings

(Continued)

TABLE 3 (Continued)

Publication title	Theme	Summary of main findings
Interactions between apolipoprotein E, sex, and amyloid-beta on cerebrospinal fluid p-tau levels in the European prevention of Alzheimer's dementia longitudinal cohort study (EPAD LCS) (18)	Biomarkers	• Analyzed for associations between CSF amyloid and p-Tau by sex and *APOE ε4* carrier status • There was a significant interaction between sex, *APOE ε4* and amyloid-beta on pTau • This interaction appeared to be significant in male but not female participants • In female participants, those who were *APOE ε4* carriers with higher CSF amyloid had significantly elevated pTau levels.
Lived time and the affordances of clinical research participation (19)	Participant involvement	• Analysis of interviews with study participants to understand their experiences of involvement • Taking part in research gave a role, an opportunity to keep busy and stay useful • Incidental benefit of receiving a full health check up, an 'MOT' • Future research participant in clinical trials largely approach through an altruistic lens
Prediction of Alzheimer's disease biomarker status defined by the "ATN framework" among cognitively healthy individuals: results from the EPAD longitudinal cohort study (20)	Biomarkers	• Used the ATN framework to define participants by biomarker status • Key variables differed between ATN biomarker groups: age, *APOE ε4*, family history, body mass index, mini mental state examination score and white matter lesions • Prediction of AD pathology improved by adding these key variables to model • Addition of established risk composite scores did not improve predictive power
Prescreening for European Prevention of Alzheimer's Dementia (EPAD) trial-ready cohort: impact of AD risk factors and recruitment settings (6)	Recruitment methods	• Analysis of the impact of risk factors and recruitment settings on prescreening • Participation in the EPAD LCS was associated with lower age, higher education, male sex and family history of dementia • Amyloid positivity was associated with higher age and *APOE ε4* allele carrier status • Results were similar across all prescreen settings (clinical cohort, research in-person cohort, research online cohort, population based cohort)
Regional associations of white matter hyperintensities and early cortical amyloid pathology (21)	Imaging	• Component analysis of white matter hyperintensity (WMH) patterns • Component 1: fronto-pariteal WMH pattern association with amyloid in the medial orbitofrontal-precuneus, vascular risk and age; associated with lower global cognitive performance • Component 2: poster WMH pattern associated with amyloid in the precuneus-cuneus, less related to age and vascular risk; associated with lower memory scores
The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study: Baseline Data Release V500.0 (9)	Baseline data release	• Description of the first 500 participants baselined into the EPAD LCS • Mean age of cohort 66.4 (6.7) years, 47.8% male • Participants represented a spectrum of normal aging (CDR=0, Amyloid -), preclinical AD (CDR=0, Amyloid +), prodromal AD (CDR=0.5, Amyloid +), and non-AD related cognitive change (CDR=0.5, Amyloid-)
The influence of diversity on the measurement of functional impairment: An international validation of the Amsterdam IADL Questionnaire in eight countries (22)	Functional assessment validation	• Cross-cultural validation of the functional assessment questionnaire • Limited bias evident for age, gender, education, and culture in the measurement of functional impairment

(Continued)

TABLE 3 (Continued)

Publication title	Theme	Summary of main findings
"Ready for What" Timing and Speculation in Alzheimer's Disease Drug Development (23)	Conceptualization of readiness	• Analysis of interviews with EPAD associated staff on meaning of readiness • Discussion of importance of temporal specificity regarding the concept of readiness in preclinical research • Trial readiness is a challenging concept to grasp within a field with a highly speculate drug development pipeline
Self-reported diabetes is associated with allocentric spatial processing in the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (17)	Cognition	• Analysis of associations between self-reported diabetes and allocentric spatial processing test performance • Significantly poorer performance on the Four Mountain Test for those with diabetes compared to those without, with a global pattern of cognitive impairment • Poorer performance on the Four Mountains Test and attention index of the Repeatable Battery for the Assessment of Neuropsychological Status was specific to diabetes, compared to obesity and hypertension
Assessing and disclosing test results for "mild cognitive impairment": the perspective of old age psychiatrists in Scotland (24)	Associated results paper	• Analysis of clinicians interviews on the topic of MCI diagnostic disclosure • Lack of specific and sensitivity assessment measures for identifying etiology of MCI available in clinical practice • Direct impact on management on individuals with MCI

frontoparietal WMH pattern which was associated with amyloid (in the medial orbitofrontal precuneus), vascular risk, and age, and, in turn, was associated with lower performance in all cognitive domains; and the second component with a posterior WMH pattern associated primarily with precuneus-cuneus amyloid and poorer performance in tasks of memory (21).

Furthermore, the IMI-funded Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) study was a sister project to the EPAD study and focused entirely on amyloid as one of the hallmark biomarkers in the AD process. The study was designed as two distinct projects: the Prognostic Natural History Study (PNHS) which performed amyloid-PET in the EPAD LCS cohort as well as later on other similar cohorts to investigate the added value of amyloid imaging in early detection of AD (25) and the Diagnostic and Patient Management Study (DPMS) aimed to assess the clinical impact and cost-effectiveness of amyloid-PET in memory clinic patients (26). The close collaboration with the AMYPAD project illustrates how data from EPAD benefits AD projects more broadly.

These articles on biomarker discoveries highlight the deep phenotyping available in the EPAD LCS and demonstrate some important emerging findings, particularly around the effects on cognition of tau in participants without dementia and the need to expand beyond amyloid when considering the multifactorial risk factors for AD.

Cognition

One article led by Gregory et al. (27) tested for associations between cardiovascular health and cognitive test performance, finding associations between having diabetes and performing significantly more poorly on the Four Mountains Test (FMT), a test of allocentric processing. This was on the background of a global cognitive impairment seen for those participants with self-reported diabetes, as measured using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Analysis of associations between cognitive test performance and both obesity and hypertension found patterns of impairment, however, neither was as global as diabetes, and only the FMT was specific to those with diabetes, suggesting that this may be an important task to identify early cognitive impairment in a high risk for future dementia group (27).

Participant involvement

Two articles presented data on participant involvement, one from analysis of reasons why participants joined a cohort and platform trial, and the second focused on panel achievements. Analysis of interviews with older adults in a clinical trial platform found that participants spoke about being involved in research giving them a role, keeping busy, staying useful, as well as receiving the incidental benefit of getting a full health checkup, while there was mainly an altruistic motivation when

considering possible future clinical trial participation (19). The findings suggest that participants may not expect to personally benefit from future clinical trials but wish to contribute toward drug development in AD, thus making them part of a future in which preventative medicine could 1 day help them, or people like them. The participant panel structure within EPAD was found to have a wide impact on the overall project, with examples of benefits including feedback on documentation, support on the design of novel recruitment materials, and representation of EPAD at national and international meetings (17). These articles evidence the important role participants played, both as data and sample donors, and active stakeholders in the EPAD project, lending credence to the value of this dataset to the wider AD community.

Recruitment methods

Given the novel recruitment methods used in the EPAD project, two results articles exclusively reported on this. The first reviewed the set up and utility of the virtual registry and found that such a system can be used for the preselection of participants for AD studies (16). The second article reviewed participation rates and found that compared to those who declined participation, those enrolling in the EPAD LCS were younger, more educated, more likely to be male, and have a family history of dementia (6). This evidence can inform future cohort and trial recruitment strategies and is also useful to set the context for who the participants included in the EPAD LCS are.

Other

Other articles include a conceptualization of what "readiness" means (23) and cross-cultural validation of the Amsterdam Instrumental Activities of Daily Living (IADL) (22). Articles funded by EPAD have explored topics, such as clinicians' experience of MCI disclosure, with evidence demonstrating a lack of specific and sensitive assessment methods for identifying the etiology of MCI in clinical practice, which may impact the management of individuals with MCI (24).

The broad scope of articles affiliated with EPAD shows the multi-disciplinary approach that was taken in the work package set up, with continuing diverse academic collaborations as a key legacy of this project.

EPAD early career researcher support

Supporting early career researchers (ECRs) was a core principle from the outset of EPAD and was primarily achieved through the establishment of the EPAD Academy, and also through supporting Ph.D. research. The Academy, which was open for all ECRs affiliated with the EPAD project, aimed to identify and support junior researchers' needs for career advancement through specific activities, such as contributions to scientific publications, participation in conferences, and development of guidelines and follow-on studies. The academy activities, involving nearly 100 ECRs, included a webinar series, workshops at the General Assembly, and hosting of ECRs at partner organizations. Ultimately, the academy helped to nurture the next generation of AD researchers and thought leaders by creating and facilitating opportunities for junior researchers' career advancement, with many of the EPAD Academy members leading and co-authoring the publications arising from EPAD. This ECR support has continued through the IMI-funded Neuronet's annual events held for ECRs working within the IMI neurodegenerative disease portfolio. The EPAD leadership recognizes that continuing the networking opportunities are critical to our next generation of scientists.

EPAD impact on the patient community

EPAD has left a tangible clinical legacy with there being no doubt that the community of clinicians, academics, and research participants underpinned the European "Brain Health" direction. This movement began with considering how best to prepare for future needs with the potential arrival of disease-modifying therapies (28, 29). Rapidly, these discussions have started to translate to new clinical care pathways, with the exemplary models of Brain Health Scotland (30) and the Davos Alzheimer's Collaborative (DAC) Health Care Readiness Flagship (31). The European Taskforce for Brain Health Services has released a series of manuals detailing the set up (32–37) with many recommendations reflecting the EPAD protocol.

EPAD impact on the pharmaceutical industry and SMEs

Although the PoC did not open to recruitment, EPAD nevertheless had an important impact on the AD pharmaceutical industry. First, the cohort continues to exist at local sites, with most participants having consented to re-contact and with local follow-up studies underway at some sites. This allows accessing a well-phenotyped pool of trial-ready participants, to de-risk clinical programs, as well as a network of highly trained sites keen to engage in preclinical AD clinical research studies. The set up of EPAD also optimized adaptive design methodologies through modeling and simulation efforts, as well as recruitment tactics and patient outreach. The process of establishing EPAD also developed a deep understanding of both public and private organizations of the European Union ecosystem, affording networking opportunities across the consortium and informal

interactions with authorities and regulators, as well as key opinion leader organizations. This community building was an integral part of the public-private partnership. The community that was built within EPAD between all types of partners led to a breakdown of the traditional silos of academic and healthcare vs. industry. In particular, participant panel groups were afforded opportunities to meet staff employed in the private sector, allowing both parties to learn more about the research environment from novel perspectives. While not run, the PoC drug-ready platform infrastructure exists and could be re-opened or replicated to benefit from the existing protocol, legal framework, vendor agreements, and regulatory acceptability work. The ongoing opportunity to access data, and importantly biological samples, continues to be important to the pharmaceutical industry and many SMEs to inform ongoing clinical development programs. Several SMEs also benefitted from their involvement, winning additional contracts for future aligned work.

More difficult to capture is the community that was built within EPAD between all types of partners, breaking down the traditional silos of academic and healthcare vs. industry.

Discussion

The EPAD project received €64 million in financial investment, recruited over 2,000 research participants into the LCS, and involved more than 400 researchers across 39 partner organizations. The ongoing EPAD LCS data and biobank access are key outcomes of this work, with both freely available and easily accessible *via* ADDI's AD Workbench platform and the Sample Access Committee. A growing number of EPAD-associated publications demonstrates the unique value of this cohort, with results to date suggesting many interesting future research avenues to explore. It is expected that in the coming years, data analysis from numerous research groups will yield many important observations to be published and therein influence our collective knowledge of many biological and clinical aspects of AD. Moreover, further follow-up of research participants who were in the EPAD LCS will continue at both local and national levels under separate protocols and data can be linked back to the IMI data as well as across the new follow-up projects through designed-in data interoperability using, for example, ADDI's AD Workbench. Other legacies of EPAD include benefits to ECR careers, the trained and experienced established site network, and lasting impacts to industry partners.

Securing ongoing funding for EPAD was seriously hampered by the 2020/21 COVID-19 pandemic which curtailed the ability to set up new clinical trials or continue to follow-up with EPAD research participants. Platform trials helped defeat COVID-19; from 2021 onward, they will also be key to defeating one of the greater challenges of our time which is AD. The framework established for the EPAD PoC will undoubtedly be a critical learning opportunity for these future platform trials (38), alongside learnings from ongoing platform trials developed within the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) (39).

There were many clear strengths of EPAD. First, the data collected were of the highest quality. Although the cohort itself was not a drug study, as data collected from the LCS would potentially be used as run-in data in a future clinical trial, the LCS data were collected in accordance with Good Clinical Practice (GCP) and Clinical Data Interchange Standards Consortium (C-DISC) standards/guidelines. This is unusual for an observational study and involved high levels of quality control checks, meaning the data are robust and reliable. Being able to trust in the validity of data collected by someone else is of the utmost importance to researchers accessing datasets. The EPAD LCS also forms the largest collection of imaging and CSF data in preclinical AD globally, offering both cross-sectional baseline data and longitudinal follow-up. With some centers already working on local follow-up studies, this longitudinal information collection is ongoing and will provide important opportunities to answer some of our key research questions in the field of AD. The centering of participants' involvement was also seen as key to EPAD from its initiation and has been identified both internally and externally as a strength of EPAD. The panel involvement from multiple centers and countries allowed the project to collect data that were not only meaningful to academic and industry partners but also those living with the greatest risk of future AD. Delivering research that is important to those facing the greatest burden of this disease must be at the heart of what we in the AD research community do. There was also, despite challenges, the achievement of redirecting science and operational elements to build this novel approach to tackling AD through secondary prevention. The community within EPAD was largely responsible for this, through engaging actively in supporting the approach to fostering junior talent through the EPAD academy.

There were also several limitations to EPAD. The main challenge in the EPAD LCS was enrolling individuals in a cohort who were also eligible for clinical trial opportunities. This was particularly keenly noticed for individuals with MCI, who were understandably eager to join drug trials rather than a cohort. This resulted in some of the participants with MCI dropping out of the LCS prematurely. In addition, the cohort should be acknowledged as underrepresenting certain parts of the European population with an overrepresentation of white and highly educated participants. Although this is true of most cohort studies in this area, future cohorts should endeavor to build more inclusive recruitment mechanisms. Local follow-up studies are working to redress this balance, with the EPAD Scotland study as an example where new participants without tertiary education are being recruited

to better reflect the general Scottish population. Despite the positive engagement in challenging the status quo, it remained difficult to secure the willingness of numerous third-party organiztions or departments within partner organizations to innovate in legal, research governance, and institutional cultural change. More specific to the PoC, although intervention owners were enthusiastic about using a platform trial to run PoC studies in AD, they were ultimately reluctant to hand over the sponsorship for a critical asset to a university. This, in combination with the difficulties in agreeing on the common legal framework that was usable and acceptable across stakeholders were the main contributors to the PoC trials not starting, and needs to be addressed in future efforts in this area.

To conclude the EPAD project, it has been a great example of what public and private partnerships can achieve and IMI funding was critical to this. ADDI, GAP, IMI-Neuronet, and follow-on funding from the Alzheimer's Association for the data and sample access systems ensure that the EPAD assets will be maintained and, as and when sponsors seek a new platform trial to be established, the learnings from EPAD will ensure that this can be developed to be even more successful than this first pan-European attempt.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by NHS Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS and SGr: conceptualization, writing—original draft, and writing—reviewing and editing. MC and CB: writing—reviewing and editing. SGe and CR: conceptualization and writing-reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author MC was employed by Alzheimer's Disease Data Initiative. Author CB was employed by Alzheimer Europe. Author SGe was employed by Janssen Research and Development, a Division of Janssen Pharmaceutica NV. Author CR was employed by Brain Health Scotland.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Elisabetta Vaudano,
Innovative Health Initiative, Belgium

REVIEWED BY
Matteo Pardini,
University of Genoa, Italy
Dana Hilt,
Frequency Therapeutics, United States

*CORRESPONDENCE
Pieter Jelle Visser
PJ.visser@maastrichtuniversity.nl

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Data and sample sharing as an enabler for large-scale biomarker research and development: The EPND perspective

Niranjan Bose[1,2], Anthony J. Brookes[3], Phil Scordis[4] and Pieter Jelle Visser[5,6,7]* on behalf of the EPND Consortium

[1]Health and Life Sciences, Gates Ventures, Kirkland, WA, United States, [2]Department of Health Metrics Sciences, University of Washington, Seattle, WA, United States, [3]Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom, [4]UCB Biopharma UK, Slough, United Kingdom, [5]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands, [6]Alzheimer Center Limburg, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands, [7]Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden

Biomarker discovery, development, and validation are reliant on large-scale analyses of high-quality samples and data. Currently, significant quantities of data and samples have been generated by European studies on Alzheimer's disease (AD) and other neurodegenerative diseases (NDD), representing a valuable resource for developing biomarkers to support early detection of disease, treatment monitoring, and patient stratification. However, discovery of, access to, and sharing of data and samples from AD and NDD research are hindered both by silos that limit collaboration, and by the array of complex requirements for secure, legal, and ethical sharing. In this Perspective article, we examine key challenges currently hampering large-scale biomarker research, and outline how the European Platform for Neurodegenerative Diseases (EPND) plans to address them. The first such challenge is a fragmented landscape filled with technical barriers that make it difficult to discover and access high-quality samples and data in one location. A second challenge is related to the complex array of legal and ethical requirements that must be navigated by researchers when sharing data and samples, to ensure compliance with data protection regulations and research ethics. Another challenge is the lack of broad-scale collaboration and opportunities to facilitate partnerships between data and sample contributors and researchers, in addition to a lack of regulatory engagement early in the research process to enable validation of potential biomarkers. A further challenge facing projects is the need to remain sustainable beyond initial funding periods, ensuring data and samples are shared and reused, thereby driving further research and innovation. In addressing these challenges, EPND will enable an environment of faster and more disruptive research on diagnostics and disease-modifying therapies for Alzheimer's disease and other neurodegenerative diseases.

KEYWORDS

neurodegenerative disease, Alzheimer's disease, data-sharing, sample-sharing, platforms, biomarker research, cohort

Introduction to EPND

Nearly 55 million people around the world live with dementia, with Alzheimer's dementia making up 60 to 70 percent of global cases (1). The second most prevalent neurodegenerative disorder, Parkinson's disease (PD), has impacted more than 8.5 million people globally, and disability and death due to PD is "increasing faster than for any other neurological disorder." (2). These numbers are only expected to worsen over time, with the Institute for Health Metrics and Evaluation (IHME) forecasting the number of people with dementia will almost triple in the next decades, from 57 million in 2019 to over 152 million cases by 2050 (3). Although they represent the leading causes of disability and dependency globally (1, 2), there exists a high unmet need for effective diagnostics and disease-modifying therapies for neurogenerative diseases. The progression and severity of these diseases vary widely between patients, due in part to the complex underlying pathophysiological mechanisms. Improved and validated diagnostic tests using imaging or fluid-based biomarkers, such as positron emission tomography (PET), cerebrospinal fluid (CSF) and blood tests to detect proteins such as beta-amyloid, tau and alpha-synuclein, could help support early detection of disease, assessment of treatment efficacy, and more accurately stratify patients (4). However, great challenges hinder progress: biomarker discovery, development, and regulatory validation are reliant on large-scale analyses of high-quality data and samples, and currently, discovery of, access to, and sharing of these valuable resources is hindered by varied information 'silos' that limit collaboration. In addition, there exists an array of complex requirements for secure, legal, and ethical sharing that has impeded much-needed progress in AD and other neurodegenerative disease (NDD) research.

The European Platform for Neurodegenerative Diseases (EPND) project aims to address some of these specific barriers and deliver a scalable and sustainable platform for sample and data sharing that will integrate existing data and sample discovery tools. The project, a public-private partnership that started in late 2021, is a collaboration between the Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). EPND involves 29 organizations across Europe, the United States, and Israel that are united under a common goal: to change the way NDD research is utilized and accessed to accelerate impact.

EPND will be a platform for data and sample discovery, access, and analysis. It will gather a global community of scientists to advance research for the identification and regulatory validation of biomarkers, and in doing so, facilitate the accelerated development of diagnostics and treatment of AD and other NDDs.

EPND: Opportunities to accelerate neurodegenerative disease biomarker and therapeutic research

Harmonizing a fragmented landscape and addressing technical barriers

Currently, there is insufficient visibility of and access to high-quality, longitudinal, and well-characterized data and samples for AD and NDD research (5). Hundreds of cohorts across Europe, and more globally, hold significant amounts of data and samples that have been collected to answer specific questions related to AD and NDD research. But often, these datasets and samples are stored in different public institutions and/or in pharmaceutical companies, which tend to make them siloed, and/or not visible or accessible to external researchers. Another reason discovery can be difficult is the fragmentation of the technical tools, as they tend to cover a few aspects of discovery specific to the cohorts they are built for.

EPND aims to overcome these silos by building connections to existing platforms and leveraging and building on existing tools. Through MONTRA (6), for example, an application for data publishing and discovery, EPND can connect to existing catalogs like EMIF-AD, which includes 48 AD- and dementia-related cohorts representing over 85,000 patients (7). Through new and existing application programming interfaces (APIs), including Café Variome (8), EPND will enable data discovery. On the sample side, technologies, such as the MOLGENIS software (9) and the ELIXIR platform will support EPND's connection to sample catalogs and potentially biobanks via a federated approach. Facilitating discoverability of these resources by the larger research community can enable further analyses, as well as the surfacing of additional insights after the original study/trial leads have reported on initial findings.

EPND will also leverage an existing data platform developed by the Alzheimer's Disease Data Initiative (ADDI). The AD Workbench, one of EPND's critical pieces of infrastructure, will allow the platform to connect to an existing global network of data scientists and datasets. This connection will further promote collaboration and the generation of additional resources for a community of researchers from various neurodegenerative disciplines and research areas, and in doing so, advance and broaden their fields.

To meet the various technical and governance requirements of participating cohorts, EPND will offer a range of options by which cohorts can make their data and samples discoverable. A federated option can be offered to cohorts that must keep all patient-level data (including data about samples) local on premise or behind a firewall. A distributed configuration can enable cohorts to make their data temporarily available for analysis by permissioned users of the EPND platform, but the data and data about samples will be hosted within a

secure local environment. A centralized option will also allow data to be temporarily available for analysis on the EPND platform, but the data (including data about samples) would be hosted in a secure public cloud environment. Methods to enable discovery, filtering, and querying of the various levels of data residing within these environments are currently being developed and refined to ensure privacy and security. Standard operating procedures for EPND use, as well as training, will clarify expectations for all users to ensure data and sample quality is kept high and regulatory frameworks are not violated. Researchers will be able to submit access requests for data and samples through the EPND platform. While options for the delivery of data to a researcher will depend on the technical and governance requirements of the cohorts, the EPND platform will provide secure, private, cloud-based workspaces where researchers can perform their analyses, save their work, and collaborate with others that have been granted permissioned access. In some cases, cohorts may be able to allow researchers to receive a copy of the data to be downloaded for local analysis. When the governance requirements will not allow researchers direct access to patient-level data, the EPND platform can support federated access to enable remote analyses via containerized scripts that are sent to the remotely hosted data and subsequently return the results.

Though existing technologies and infrastructures will be leveraged to establish the platform, any new tools and capabilities developed will be made open source, so the broader research community can benefit.

Safeguarding legal and ethical sharing of sensitive data and samples

Keeping up to date with frequently changing regulations can be resource-intensive, and ensuring adherence to legal and ethical frameworks can be a hindrance to the exchange of valuable data and samples. Navigating these complex requirements for safe, legal, and ethical sharing can add a heavy burden to individual researchers/institutions. This dichotomy means that both researchers and legal requirements "have been challenged by the need to balance the twin aims of making data accessible to researchers while at the same time protecting the privacy of study participants and patients." (10).

Assuming datasets and samples can be accessed, there will still be legal and ethical hurdles to be crossed, from understanding participant consent, to complying with data privacy requirements, to understanding changing country-specific requirements. In particular, researchers cite the GDPR as a particular obstacle to the secondary use of samples and/or data due to its lack of clarity on pseudonymization, controllership, derogations, and research exemptions.

EPND will develop a set of ethical, legal, and regulatory principles in the form of White Papers to guide platform design and the responsible discovery and sharing of data and samples. Over time, these principles will form the backbone of governance and data protection frameworks that facilitate research via EPND and reduce the burden of compliance for participating cohorts and users, all while ensuring the highest ethical standards are maintained across the platform. This guidance will aim to address the challenges and common principles associated with sharing human samples and associated data, while supporting compliance with GDPR by clearly identifying roles and responsibilities between cohort contributors, controllers, processors, and users of data. In addition, the project will consider the requirements regarding the quality of data and the principles related to sharing and access to data and samples when seeking biomarker qualification or drug approval from regulatory authorities. These White Papers, guidelines, and frameworks should facilitate and potentially streamline collaborations among users. Importantly, EPND will use its public-private expertise to co-create this guidance with input of patients and their caregivers, to build trust, awareness, and understanding within the community that represents the ultimate beneficiaries of AD and NDD research and innovation.

In addition to developing White Papers, guidance, and frameworks, EPND will also have dedicated resources to assist cohorts with understanding their ethical-legal readiness to share data and samples. Being able to help cohorts navigate these ethical and legal requirements is expected to further support contributions to the EPND platform.

Enabling and driving broad-scale collaboration

Currently, few many-to-many or cross-disciplinary opportunities for cooperation across partners are leveraged, with the research ecosystem favoring simpler frameworks. This leads to siloing of datasets, with limited collaboration or reuse of data and samples. Consequently, the underutilization of these data and/or samples represents a significant missed opportunity for research.

EPND will promote and facilitate collaborations by connecting contributors of data and samples with users in the global community. By sharing their data and samples, scientists will advance their individual research while contributing to shared goals. Data and sample re-use could facilitate the development of more accurate disease progression models; identify novel risk factors and molecular drivers of disease; provide natural history studies for clinical trial arms; train artificial intelligence-based risk prediction algorithms; support the validation of biomarkers in diverse populations; and more

(11). During proposal development, over 60 NDD cohorts across Europe acknowledged their willingness to collaborate with the EPND project. Being able to facilitate connections among these cohorts and others will be key to starting and maintaining the EPND community. Also, as noted above, the AD Workbench will offer access to a global network of interoperable datasets and will also enable collaboration with a broader community of users who may contribute ancillary or relevant data to the platform. Additionally, connecting to the AD Workbench will allow users access to secure cloud-based workspaces, with shared analytical tools, where they can work with other researchers and/or curate, harmonize, and analyze data. ADDI's AD Connect, a user-community resource that includes forum and knowledgebase features, is one potential option to promote and facilitate conversations and sharing of questions, knowledge, and lessons learned among EPND users and the broader global network of AD Workbench users.

Another key component to increasing collaboration is to increase the visibility and discoverability of cohorts, which otherwise would not have the opportunity to be part of a larger network. This increased visibility and discoverability will promote information and data and sample exchange among researchers. EPND could be best positioned to make a large number of cohort datasets discoverable and interoperable for future research, as heterogeneity in cohort datasets, linked to the use of different data models, sampling methods, and recruitment criteria, compounds these issues and further impedes the use of data and samples for large-scale research (12). Entry into EPND's catalog – in datasets or completed case studies – will require minimal effort on the part of contributors, making it easy for researchers to add value to the community, and ensuring they have opportunities to participate in studies before they are published.

Ensuring sustainability after project completion

When projects and studies end, collected data and samples can become difficult to access by the scientific community. As such, public-private partnership projects are often challenged to consider what it would take to maintain and operate assets after initial funding periods have lapsed (13).

EPND will allow scientists to reuse data and samples for future projects, not only for original conclusions to be examined, verified, or occasionally corrected, but to facilitate the testing of new hypotheses. This extends the value of the original research investment (14), not only because it increases data validity, but because in promoting and facilitating reuse, greater value is extracted from original research, all while helping avoid unnecessary repetition of studies. As an example of extending the useful life of existing datasets, EPND plans to have mutually supported relationships with other IMI projects, such as EMIF, where the data will be made accessible and findable for the broader research community. Furthermore, as the EPND becomes a part of a global network with ADDI, there will be access to datasets from the EPAD project, including their Longitudinal Cohort Study (15). EPND will extend the useful life of the data collected by these projects, allowing researchers to access data and samples in one cohesive space, so they can build on each other in a useful fashion. The partnership with ADDI will also allow EPND to leverage the AD Workbench as an ongoing resource for the EPND user community without incurring additional expenses.

EPND will also establish an infrastructure that will be continuously refined through a series of case studies that utilize data and samples, including case studies on fluid

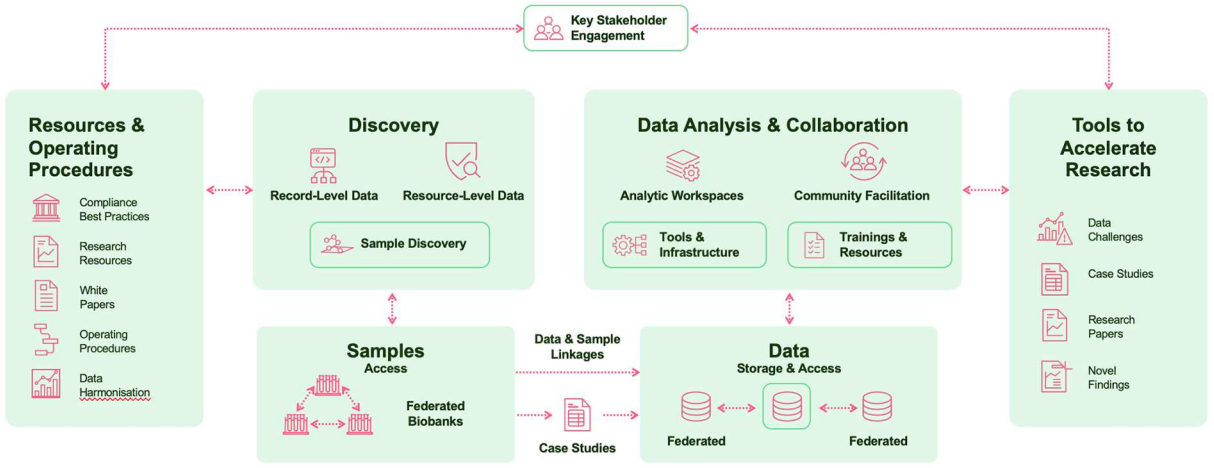

FIGURE 1
EPND programme overview.

biomarkers, clinical data, prospective longitudinal data, and digital biomarker data. These case studies will test the functionality and features of the platform, while simultaneously being able to adjust processes and platform elements to ensure the infrastructure is durable and can be self-sustaining. Learnings from case studies will include an understanding of operational and governance components required to select, permission, share, and process data and samples. Novel findings and new data generated from case studies will be made available on EPND, ensuring these resources can continue to be used for future research. EPND will also strive for regulatory validation of any potential biomarkers to enhance the utility of EPND and its overall goal to accelerate development of diagnostics and treatment of AD and other neurodegenerative diseases. Finally, there will be benchmarking exercises to compare EPND's offerings to other initiatives and platforms, and outreach to potential users to better understand how to attract and incentivize use of the platform.

The ambition: Validate research that speeds up the fight against neurodegenerative diseases

The ultimate goal of EPND is to accelerate research into the discovery and validation of biomarkers to support development of diagnostics and disease-modifying therapies for Alzheimer's disease and other neurodegenerative diseases.

The universal platform will enable the sharing, reuse and large-scale analysis of high-quality data and samples to accelerate biomarker discovery, development, and validation, while maintaining robust protection for the fundamental rights of data subjects. It will promote collaboration, harmonize a fragmented landscape, and ensure the highest legal and ethical standards are met, all while giving data and research additional usability, beyond original studies (Figure 1).

By creating a virtuous cycle of discovery, access, and re-use of data and samples to facilitate new research, as part of a sustainable process and infrastructure facilitating collaboration across a global community of users, EPND will be a scalable, sustainable solution to support more disruptive research on biomarkers and disease-modifying therapies for Alzheimer's disease and other neurodegenerative diseases in Europe, while opening a pathway to become a model scaled beyond Europe – and beyond AD and NDD themselves.

Author contributions

NB, AB, PS, and PV jointly conceived and led the work, providing critical comments on manuscript drafts, and approving the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

NB was employed by the company Gates Ventures. PS was employed by the company UCB Biopharma UK.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Alberto Serrano-Pozo,
Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Eric McDade,
Washington University in St. Louis, United States
Scott McGinnis,
Brigham and Women's Hospital and Harvard Medical School, United States

*CORRESPONDENCE
Lyduine E. Collij
✉ l.collij@amsterdamumc.nl

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The amyloid imaging for the prevention of Alzheimer's disease consortium: A European collaboration with global impact

Lyduine E. Collij[1,2]*, Gill Farrar[3], David Valléz García[1,2], Ilona Bader[1,2], Mahnaz Shekari[4], Luigi Lorenzini[1,2], Hugh Pemberton[5], Daniele Altomare[6], Sandra Pla[7], Mery Loor[7], Pawel Markiewicz[5], Maqsood Yaqub[1], Christopher Buckley[3], Giovanni B. Frisoni[6], Agneta Nordberg[8], Pierre Payoux[9], Andrew Stephens[10], Rossella Gismondi[10], Pieter Jelle Visser[1], Lisa Ford[11], Mark Schmidt[11], Cindy Birck[12], Jean Georges[11], Anja Mett[3], Zuzana Walker[5], Mercé Boada[13,14], Alexander Drzezga[15], Rik Vandenberghe[16], Bernard Hanseeuw[17], Frank Jessen[15], Michael Schöll[18], Craig Ritchie[19], Isadora Lopes Alves[20], Juan Domingo Gispert[1] and Frederik Barkhof[1,2,5] on behalf of the AMYPAD consortium

[1]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, location VUmc, Amsterdam, Netherlands, [2]Amsterdam Neuroscience, Brain Imaging, Amsterdam, Netherlands, [3]GE Healthcare, Amersham, United Kingdom, [4]Barcelona Beta Brain Research Center, Barcelona, Spain, [5]Centre for Medical Image Computing, and Queen Square Institute of Neurology, UCL, London, United Kingdom, [6]Laboratory of Neuroimaging of Aging (LANVIE), Université de Genève, Geneva, Switzerland, [7]Synapse Research Management Partners, Barcelona, Spain, [8]Department of Neurobiology, Care Sciences and Society, Center of Alzheimer Research, Karolinska Institutet, Stockholm, Sweden, [9]Department of Nuclear Medicine, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [10]Life Molecular Imaging GmbH, Berlin, Baden-Württemberg, Germany, [11]Janssen Pharmaceutica NV, Beerse, Belgium, [12]Alzheimer Europe, Luxembourg, Luxembourg, [13]Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya, Barcelona, Spain, [14]Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain, [15]Department of Psychiatry, University Hospital of Cologne, Cologne, North Rhine-Westphalia, Germany, [16]Faculty of Medicine, University Hospitals Leuven, Leuven, Brussels, Belgium, [17]Institute of Neuroscience (IONS), Université Catholique de Louvain, Brussels, Belgium, [18]Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden, [19]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, Scotland, United Kingdom, [20]Brain Research Center, Amsterdam, Netherlands

Background: Amyloid-β (Aβ) accumulation is considered the earliest pathological change in Alzheimer's disease (AD). The Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) consortium is a collaborative European framework across European Federation of Pharmaceutical Industries Associations (EFPIA), academic, and 'Small and Medium-sized enterprises' (SME) partners aiming to provide evidence on the clinical utility and cost-effectiveness of Positron Emission Tomography (PET) imaging in diagnostic work-up of AD and to support clinical trial design by developing optimal quantitative methodology in an early AD population.

The AMYPAD studies: In the Diagnostic and Patient Management Study (DPMS), 844 participants from eight centres across three clinical subgroups (245 subjective cognitive decline, 342 mild cognitive impairment, and 258 dementia) were included. The Prognostic and Natural History Study (PNHS)

recruited pre-dementia subjects across 11 European parent cohorts (PCs). Approximately 1600 unique subjects with historical and prospective data were collected within this study. PET acquisition with [^{18}F]flutemetamol or [^{18}F]florbetaben radiotracers was performed and quantified using the Centiloid (CL) method.

Results: AMYPAD has significantly contributed to the AD field by furthering our understanding of amyloid deposition in the brain and the optimal methodology to measure this process. Main contributions so far include the validation of the dual-time window acquisition protocol to derive the fully quantitative non-displaceable binding potential (BP_{ND}), assess the value of this metric in the context of clinical trials, improve PET-sensitivity to emerging Aβ burden and utilize its available regional information, establish the quantitative accuracy of the Centiloid method across tracers and support implementation of quantitative amyloid-PET measures in the clinical routine.

Future steps: The AMYPAD consortium has succeeded in recruiting and following a large number of prospective subjects and setting up a collaborative framework to integrate data across European PCs. Efforts are currently ongoing in collaboration with ARIDHIA and ADDI to harmonize, integrate, and curate all available clinical data from the PNHS PCs, which will become openly accessible to the wider scientific community.

KEYWORDS

amyloid, positron emission tomography (PET), consortium, Alzheimer's disease, diagnosis, prognosis

1. The scientific landscape of Alzheimer's disease

Dementia is a major cause of disability, dependency, and mortality in the elderly population. It is estimated that by the year 2050, up to 150 million individuals will be affected by this condition (1). Care of these patients comes with considerable societal and economic impact, stressing the importance of optimal diagnostics and the availability of disease-modifying therapies. The main cause of dementia is Alzheimer's disease (AD), which is a neurodegenerative disorder that progressively impairs cognitive functioning (primarily memory and executive functioning). One of the first observable changes in the AD brain is the accumulation of the amyloid-β (Aβ) protein, which can be detected *in vivo* by positron emission tomography using radiolabeled tracers. Currently, three fluorine-18 radiotracers have been approved for clinical use by the European Medicine Agency (EMA) and by other competent authorities worldwide; [^{18}F]flutemetamol/Vizamyl^{TM} (FMM) (2) by GE Healthcare, [^{18}F]florbetaben/Neuraceq^{TM} (FBB) (3) by Life Molecular Imaging, and [^{18}F]florbetapir/Amyvid^{TM} (FBP) (4) by Eli Lilly. The detection of amyloid pathology supports a clinical diagnosis of AD and provides useful information on its clinical progression (5). After some years of clinical use of the amyloid PET tracers, the appropriate use criteria (AUC) were drafted (5, 6) and today amyloid-PET imaging is more frequently used in a clinical setting. However, reimbursement of the technique is lagging due to the lack of definitive evidence supporting its clinical utility and cost-effectiveness in the diagnostic workup.

In the clinical trial setting, the role of amyloid-PET has increased significantly over the past decade. Initial trials did not require biomarker confirmation at study entry, and amyloid-PET was therefore rarely used as an inclusion criteria, resulting in a high fraction of enrolled subjects being amyloid-negative (6, 7). As the field advances, biomarker confirmation for trial inclusion has become the standard and nowadays amyloid-PET is generally used as a quantitative measure of amyloid burden for both trial enrollment and to assess target engagement. As both ongoing and future trials are moving from an interventional to a preventive approach, the role of amyloid-PET imaging in clinical trial design is again changing. Also, the arrival of plasma biomarkers, which are being actively developed at present, will most likely have an important role in future clinical and research settings (8) and already have a prominent role in screening participants for trial enrollment (9), challenging the use of amyloid-PET imaging. Nonetheless, the technique holds the advantage of being the only validated measure against

neuropathology as the gold standard (10), in contrast to fluid biomarkers, PET provides regional information and a measure of the extent of Aβ pathology (11), and is able to support disease monitoring efforts (12).

2. The innovative medicines initiative 'AMYPAD' study

It is within this context, that the Innovative Medicines Initiative (IMI) funded the 'Amyloid Imaging to Prevent Alzheimer's Disease' (AMYPAD) study. Since its original kick-off in October 2016, the AMYPAD consortium is a unique collaboration of a wide range of partners, including nine academic institutes, three industry/ European Federation of Pharmaceutical Industries Associations (EFPIA) (GE Healthcare [GEHC], Life Molecular Imaging [LMI] and Janssen Pharmaceuticals), 2 'Small and Medium-sized enterprises' (SME's) (IXICO and SYNAPSE), and 1 patient organization (Alzheimer Europe) (www.amypad.eu). With the funding formally ended in at the end of September 2022, AMYPAD has formed new collaborations with ARIDHIA and Alzheimer's disease Data Initiative (ADDI) to maintain, curate, and provide access to the large database of biomarkers collected from nearly 2400 subjects who have been included in the study at large. In this paper, we want to highlight the important collaborations necessary to make AMYPAD a successful project, reach not only the scientific community but also engage society at large, and illustrate how these endeavors ensured the value of the consortium during and after the funding period.

3. The AMYPAD studies

The AMYPAD consortium is led by Professor Frederik Barkhof from the Amsterdam UMC, location VUmc, and Dr. Gill Farrar from GE Healthcare. AMYPAD aimed to optimize the use of amyloid-PET in both clinical and research settings. Also, collaborators had a strong desire to develop a robust analytical methodology to ensure that measures of the amyloid burden by PET are both accurate and consistent across different centres and multiple tracers. To these ends, two trials were set-up: the *Diagnostic and Patient Management study (DPMS)* including a memory clinic population; and the *Prognostic and Natural History Study (PNHS)*, focused on a pre-dementia and mainly pre-clinical population.

3.1. Diagnostic and patient management study (DPMS)

AMYPAD DPMS aimed to assess the clinical impact and cost-effectiveness of amyloid-PET in memory clinic patients. One of the AMYPAD DPMS main strengths is its randomized controlled study design. Participants were allocated to three study arms: ARM1, amyloid-PET performed early in the diagnostic workup (within 1 month); ARM2, late in the diagnostic workup (after 8 ± 2 months); or ARM3, if and when the managing physician chose to scan the subject. This allowed comparing a diagnostic pathway that includes amyloid-PET (ARM1) with one without amyloid-PET (ARM2). The study recruitment was finalized in October 2020 and a total of 840 participants with variable cognitive stages (244 with subjective cognitive decline plus [SCD+], 341 with mild cognitive impairment [MCI], and 255 with dementia) were enrolled from eight memory clinics, resulting in the largest European study implementing amyloid-PET in clinical practice. The main outcome was the difference between ARM1 and ARM2 in the proportion of participants receiving an etiological diagnosis with very high diagnostic confidence after 3 months. As a secondary outcome, we are assessing the cost-effectiveness of amyloid-PET by using longitudinal health-related outcomes and information on the participants' use of healthcare resources. Please refer to Frisoni et al. (13) and (14) for a detailed description of the study rationale and baseline features of the final recruited patient population, respectively.

3.2 The prognostic natural history study (PNHS)

Originally, the PNHS was closely associated with its sister project 'European Prevention of Alzheimer's dementia' (EPAD), aiming to perform amyloid-PET in this well-phenotyped cohort to investigate the added value of this imaging technique in assessing a participant's risk to develop cognitive decline due to AD. However, to facilitate timely recruitment into the study, other cohorts with similar aims and readily collected data across Europe were invited to participate as parent cohorts (PCs). In return, AMYPAD PNHS provided the newly collaborating PCs with the opportunity to perform amyloid-PET imaging. Effectively, this framework boosted the recruitment for PNHS and resulted in the availability of longitudinal data in a significant proportion of participants in several studies across Europe. To date, 17 centres have contributed to the PNHS across 11 PCs [EPAD (15), EMIF-AD 60++ (16) and 90+, ALFA+ (17), FACEHBI (18), FPACK (19), UCL-2010-412, Microbiota, AMYPAD DPMS [*via* the VUmc] (13), DELCODE (20), and H70 (21)], with several additional PCs expressing interest in joining forces after the IMI-funding period. By the end of the study in June 2022, 1,192 prospective baseline and 227 follow-up scans had been performed. An additional 1,300 PET scans were also made available through collaborations with the PCs, bringing the final total available scans for PNHS analysis to over 2,700 PET images across 1,624 participants. Please see Lopes

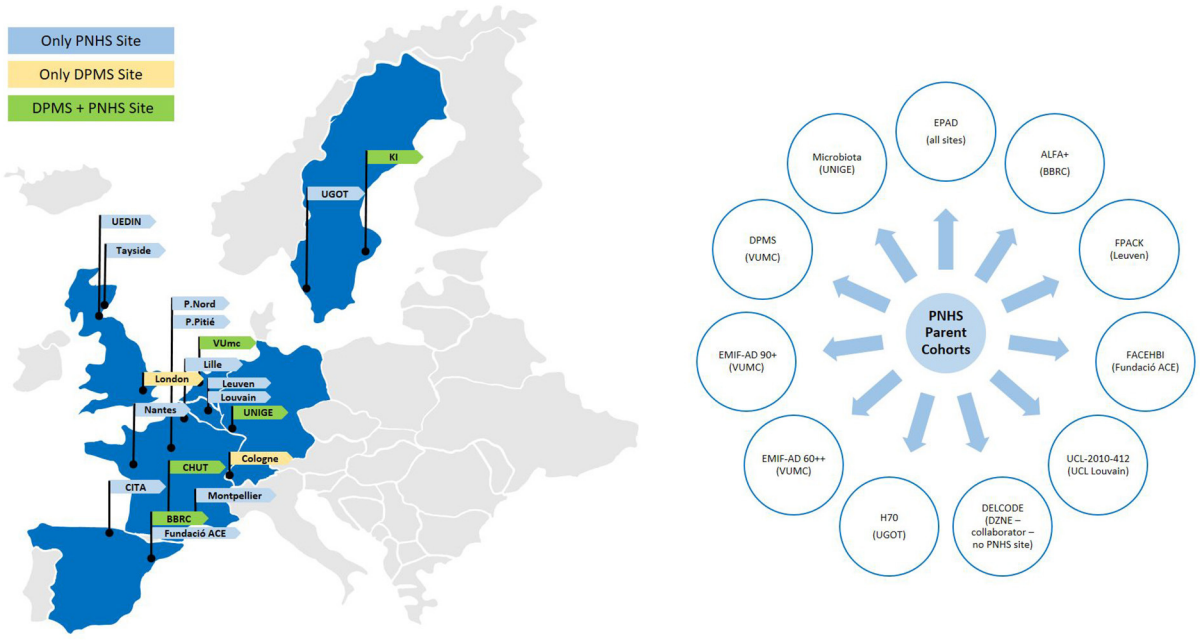

FIGURE 1
Network of study cohorts and sites that contribute to the AMYPAD consortium. Sites affiliated with the DPMS study are shown in yellow, sites affiliated with the PNHS are shown in blue, and sites affiliated with both trials are shown in green. *EPAD*: European Prevention of Alzheimer's Dementia; *ALFA+* for Alzheimer and Families; *FPACK* Flemish Prevent AD Cohort-KU; *FACEBHI* Fundació ACE Healthy Brain Initiative; *UCL-2010-412* University College Louvain 2010-412 study; *DELCODE* Longitudinale Studie zu Kognitiven Beeinträchtigungen und Demenz; *H70* Gothenburg H70 Birth cohort study; *EMIF-AD 60++ and 90+* Medicine Initiative European Medical Information Framework for AD Twin60++ and 90+ study from the Alzheimercenter Amsterdam; *DPMS* Diagnostic and Patient Management Study from AMYPAD.

Alves et al. (22) for an overview of the study design and scientific aims of the PNHS. An overview of AMYPAD affiliated sites can be found in Figure 1.

4. The value of EFPIA partnerships

4.1. Availability of PET radiotracers

Beyond the academic collaborations, a key partnership within AMYPAD was the support of our EFPIA partners through the supply of the EMA-approved [^{18}F]flutemetamol (FMM) and [^{18}F]florbetaben (FBB) PET radiotracers by GE Healthcare (GE) and Life Molecular Imaging (LMI), respectively. Both GE and LMI maintain distribution networks in Europe to provide respective tracers to investigators; imaging sites in the AMYPAD consortium were chosen so that there was a relatively equal distribution of manufacturing availability of the two PET tracers between the AMYPAD study centres. The short shelf life of these F-18 radiolabeled tracers (~8–10 h) limits the geographic distribution of the products and therefore careful logistical planning between manufacturing sites, nuclear medicine departments, and referring physicians was required to optimize the utility of each batch produced. A working party was specifically set up for the duration of clinical scanning to pay careful attention to the consistent delivery of both tracers to facilitate including the maximum numbers of subjects for both DPMS and PNHS.

As per standard guidelines, 185MBq (FMM) or 300MBq (FBB) of tracer were injected intravenously and 20-min scans were acquired 9- min post-injection. All PNHS images were centrally collected by IXICO and processed using their in-house LEAP pipeline (23), providing global and regional Centiloid (CL) values. For the DPMS, amyloid-PET scans were processed and analyzed using AMYPYPE, a modified Cortex ID (24) PET-only pipeline, which provides global CL units as well as regional z-scores compared to a reference population. For 515 PNHS participants, dynamic amyloid-PET scans were performed with the so-called coffee-break protocol (25), which allows for full quantitation (i.e., BP_{ND}) and additionally provides a measure of relative flow (i.e., R_1), in addition to CL values. In addition, 318 of these participants had, at least, one longitudinal dynamic amyloid-PET scan. Dynamic amyloid-PET was performed longitudinally in a sub-set of DPMS ($n = 45$), bringing the total number of collected 'coffee-break' scans over 900 and making AMYPAD a unique resource to study in what scenarios dynamic amyloid PET imaging could be advantageous over standard acquisition and quantification.

4.2. Regulatory interactions

One of the fundamental premises of IMI partnerships is to ensure that the technology that is widely used in research can also optimally be used for routine clinical workup. Both PET tracers used in the AMYPAD consortium (FMM and FBB) were previously approved by the EMA through pivotal phase III registration studies wherein a high correlation was verified between visual inspection of the images, as either negative or positive, for neuritic amyloid and the *post-mortem* measures of amyloid burden. However, further studies relating to the value of the amyloid-PET agent to improve diagnostic thinking were suggested by EMA, and hence the DPMS was designed also to investigate this component. In fact, dialogue with both EMA and Health Technology Assessment instances (HTAs) was first conducted in 2016, with a goal to incorporate EMA's input into the study design *via* formal Scientific Advice, as well as initiating dialogue with HTA bodies. A second Scientific advice was conducted in 2019, providing further input, particularly in the area of quantitative methodology for measuring amyloid load using PET. Specifically, focus was given to EMA's view on the opportunity for quantitative metrics, such as the Centiloid measure, to assist with both subject selection and therapy monitoring, as well as for prediction of cognitive progression and measuring small early changes over time. During this period, quantitation was added to the Summary of Product Characteristics (SmPCs) of both tracers used in AMYPAD, as a result of data packages presented to EMA showing the value of quantitation as an adjunct to the visual read of a adjunctive diagnostic scan.

AMYPAD aims to continue discussions with various regulators, such as EMA and FDA, even beyond its IMI period, to facilitate a wider appreciation of both the robustness and value of quantitative methodology to measure amyloid PET burden.

4.3. Interacting with other IMI partners and external collaborators

AMYPAD had a close working relationship with EPAD (https://ep-ad.org/) in that a large number of the initial PNHS participants were recruited from the Longitudinal Cohort Study (LCS). EPAD has also developed data access models that AMYPAD benefited from (see section 8 below). Additionally, AMYPAD has been an active member of coordination and support action (CSA) NEURONET (https://www.imi-neuronet.org/), which was created to set up an efficient platform to boost synergy and collaboration across IMI's wider neurodegenerative disorders (ND) portfolio. Here, members of AMYPAD were represented on the NEURONET Scientific Coordination Board, the Working Group on sustainability and the NEURO Cohort Task Force. Furthermore, AMYPAD's cohorts, datasets and algorithms were signposted in the NEURONET Asset Map. This in turn was held on the NEURONET Knowledge Base, which also signposts and reports further information about the AMYPAD project, including its deliverables, partners and publications (https://kb.imi-neuronet.org/). Other close relationships have developed with other global consortiums. Collaborations with IDEAS, ALFA, AIBL and ADNI are ongoing, whilst data sharing with additional cohorts such as OASIS, EMIF-AD, ABIDE, and ADC yielded the highly cited work on the pooled multi-tracer amyloid staging model (26) (see section 6.1).

5. Amyloid burden in Centiloid units for DPMS and PNHS

The goals of AMYPAD rely on the assumption that amyloid burden can be accurately quantified irrespective of the radiotracer that was used for the acquisition of the PET scans. In this regard, the Centiloid (CL) method has been proposed as an absolute scale to quantify amyloid burden, allowing the pooling and comparison of data across tracers and quantification pipelines. This scale assigns a CL value of 0 to the lack of amyloid burden (similar to what would be observed in a young control group), and a CL value of 100 to the typical amyloid load of mild-moderate AD patients.

To verify the assumption that CL values are comparable across the two tracers used in AMYPAD, we have conducted a Gaussian Mixture Modeling (GMM) exercise on the distribution of CL values in the DPMS and the PNHS. GMM is a data-driven statistical technique capable of estimating the parameters of a finite number of Gaussian distributions that underlie the observed distribution of values. GMM has been widely used to model global estimates of amyloid burden as measured by PET (27). It is well-established in the literature that the distributions of amyloid load values, when recruiting memory clinic patients, show a bimodal distribution with one Gaussian modeling the distribution of 'negative' scans and another one that of the 'positive' ones (28, 29). Such a bimodal distribution fits well with the clinical use of the amyloid tracers that are typically rated visually as positive or negative, but it is not suitable to describe the distribution observed in cognitively unimpaired individuals at high risk of AD, which is dominated by a Gaussian centred around zero CL that is skewed toward higher values (27). Such a distribution violates the assumption of the GMM that the data points follow a finite number of Gaussian distributions. In addition, GMM presents other limitations such as sensitivity to the initialization parameters, and the lack of spread estimates (i.e., the 95% confidence interval [95%CI]) of the estimated parameters (relative proportion, mean and standard deviation).

To overcome such limitations and robustly model the distribution of CL values also in this early population, we have introduced several methodological innovations to the modeling.

First, to circumvent the dependency of initial estimates and the lack of spread estimates of the Gaussian parameters, we have implemented a bootstrapped version of the GMM. This method performs a GMM with random initial parameters in 100,000 bootstrap samples from the original distribution. Bootstrapping is a technique that randomly resamples a given distribution with replacements for a high number of times. By doing so, it mimics the sampling of the recruited population in the study and is, therefore, capable of providing generalizable estimates. Using this method, we can also obtain spread estimates to the Gaussian parameters and, due to the random initialization at each of the bootstrap samples, we compensate for the dependency of the GMM to the initial parameters

Finally, to overcome the limitation of some of the distributions not resulting from a finite number of "pure" Gaussian distributions, a non-Gaussian distribution has been added to the GMM to model the intermediate CL values. The distribution of these intermediate CL values is modeled using a dedicated function that is linked to the means and standard deviations of the positive and negative Gaussians and only the relative proportion of intermediate values is estimated by the GMM. This strategy is based on previous work on the modeling partial volume voxels of magnetic resonance scans (30). Using this procedure, we modeled the distribution of the CL values in the DPMS study, also stratifying it by tracer (Figure 2A).

Of note, our version of the GMM estimated a negative Gaussian with a mean of 0.42 CL, close to zero as expected, with 95% CI below 2 CL [−0.94, 1.90]. The mean of the positive Gaussian was 92.52 CL, slightly below the value of 100 CL expected for a group of typical mild-moderate AD patients. Since the DPMS included amyloid-positive participants at earlier AD clinical stages (SCD+, MCI) such a lower CL value was also expected. Moreover, when stratifying by tracer, the 95%CI of all parameters overlapped between the two tracers, thus confirming that the CL scale provides comparable estimates of amyloid burden across the two tracers in the DPMS.

Regarding the PNHS, the developed GMM method could also adapt to the expected distribution that was dominated by a negative Gaussian skewed toward lower values. In this case, it can be observed that the relative proportion of the distribution of intermediate values is higher (20%) than that of the positive one (7%). In this case, the 95%CI of the mean value of the negative Gaussian also included the zero, as expected (Figure 2B).

6. Pan-European scientific collaborations

In addition to scientific data generated from both the DPMS and PNHS, AMYPAD researchers have significantly contributed to the AD field by furthering our understanding of amyloid deposition in the brain and the optimal methodology to measure this process. Several key papers have been published using either locally readily available datasets, open-access sources, or the academic collaborations established under the AMYPAD umbrella.

From a methodological perspective, the consortium has validated the implementation of the coffee-break or dual-time acquisition protocol for both the FMM and FBB radiotracers (25). This acquisition protocol results in fully quantitative data (i.e., BP_{ND}) and additionally provides a surrogate measure of cerebral blood flow (i.e., R_1) while allowing for interleaved scanning, which translates to efficient scanner use and reduced participant burden (9). Subsequently, we investigated the value of fully quantitative measures in the context of clinical trials, showing that sample sizes in AD secondary prevention trials can be reduced by the acquisition of dynamic PET scans and/or by restricting inclusion to subjects with intermediate amyloid burden or *APOE*-ε4 carriers. Moreover, using a targeted early composite leads to reductions in sample size requirements in primary prevention trials (31).

The concept of an early composite is the focus of a second major line of research within the AMYPAD consortium, namely the value of regional rather than global amyloid-PET investigations to improve disease tracking, risk profiling, and prediction of cognitive decline over time. A major collaboration was the development of a multi-tracer staging model, which included over 3,000 amyloid-PET scans from six cohorts, including historical data of several PCs aligned with the PNHS (26). Taking these findings, we performed preliminary analyses in predicting changes in cognitive functioning in a preclinical population of the OASIS-3 open-access dataset. We showed that regional and longitudinal amyloid-PET improved the prediction of cognitive decline in specific domains (mean follow-up period was 4.0 ± 1.9 years) (32). This is considered the groundwork for the primary end-point of the PNHS trial.

The third line of research has been to optimize the use of amyloid-PET in the clinical setting. Firstly, from a regional perspective, implementing the results of the previously mentioned quantitative studies in our approach to performing visual assessments. We showed in a collaborative paper between VUmc and BBRC that visual assessment of amyloid-PET images can identify early amyloid accumulation and grade the extent of deposition. This approach goes beyond the use of a binary global measure, currently implemented in the clinical routine. Moreover, our results were confirmed by *post-mortem* data from the Phase III Flutemetamol trial, kindly provided by GEHC (33).

Our most recent focus is on the implementation of (Centiloid) quantification into the clinical routine, to not only support visual assessment of challenging cases, but also prepare the field for a potential necessity which could arise from the possible approval of disease-modifying therapies in the near future. To this end, academic and EFPIA partners collaborated

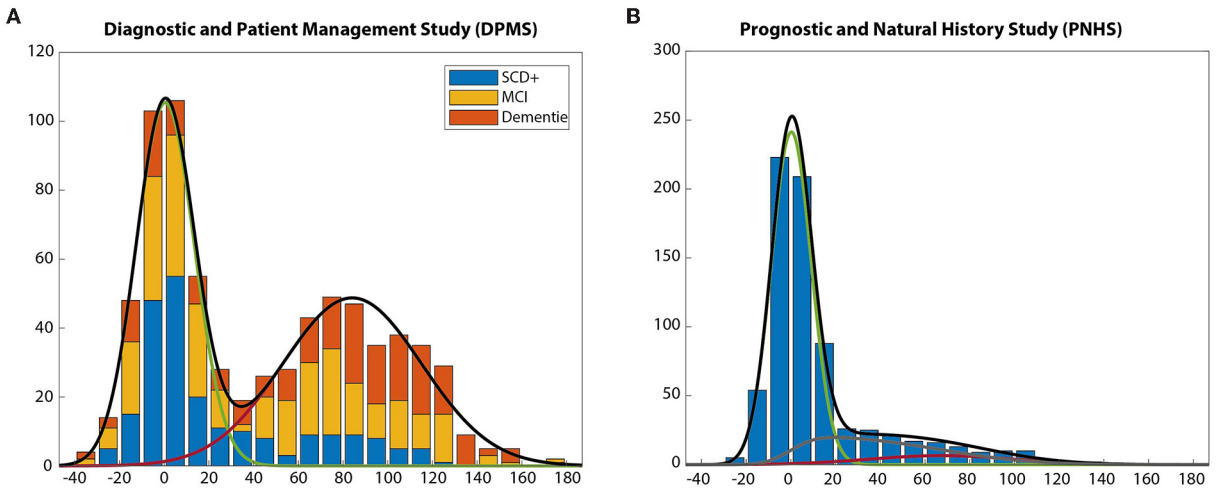

FIGURE 2
Centiloid distributions across DPMS and populations. **(A)** Centiloid distribution across patient populations, reflecting a bi-modal distribution. **(B)** Centiloid distribution across per-dementia subjects, mostly cognitively unimpaired, skewed toward lower amyloid burden.

on a comprehensive review regarding possible quantification approaches for the clinical setting (34) as well as engaging with regulatory bodies to share the in-depth knowledge that AMYPAD has gained using these methods during the course of the project. In this context, the AMYPAD team has investigated the robustness of the Centiloid quantification method (35), its feasibility in detecting early Aβ pathology (36), and its ability to detect changes over time. This work has been collated into a Biomarker Qualification Opinion document, which has been submitted to the EMA at the end of September 2022.

7. AMYPAD success beyond the trials: SYNAPSE and Alzheimer Europe

Management, communication, and dissemination were a core part of the AMYPAD project to ensure that activities and results have been communicated and shared with internal and external stakeholders in a clear, consistent, and effective manner. To combine an adequate use of resources and a successful outreach, Synapse Research Management Partners (SYNAPSE) and Alzheimer Europe work in close collaboration with all project partners.

Firstly, a Project Management Office was set up to follow up on project activities and to monitor compliance with the work plan, planned resources and schedule according to IMI2 JU rules. SYNAPSE, a firm specialized in the high-quality management of complex research and development projects in the biomedical sector, led the management activities of the project including areas such as financial management (e.g., monitoring budget and resource consumption), legal (e.g., amendments or subcontracting of study centers), risk management, and deliverable quality control procedures. The day-to-day management was crucial for the completion of the deliverables and the achievement of project milestones, and the establishment of the project governance facilitated the collaboration with other related initiatives (including EPAD, NEURONET, European Platform for Neurodegenerative Diseases [EPND], and ADDI).

Secondly, a communication plan for the AMYPAD project, led by Alzheimer Europe, was developed at an early stage of the project. In this plan, a consistent communication strategy was defined, to provide continuous up-to-date information about the project and disseminate its results among different stakeholders, but also to liaise and establish synergies with neighboring initiatives. This strategy was adopted throughout the project execution and targeted a variety of key audiences, including among others the patient community, regulators, payers, policymakers, and the wider scientific community. Specific attention was paid to reaching out to the dementia community. Alzheimer Europe used its extensive network of 37 member associations from 33 countries and its communication tools (e.g., website, social media, newsletter, Dementia in Europe magazine, annual conference) to relay information on the AMYPAD project. This represented a major opportunity to target Alzheimer's associations/patient groups affiliated with Alzheimer Europe. In addition, AMYPAD communication objectives were met thanks to tailored strategies and the use of cross-channel communication. AMYPAD communication tools such as the project's website (https://amypad.eu/) and the active

presence on social media channels such as Twitter maximized the outreach by creating continuous visibility of the project and engagement with stakeholders in the discussion on the different topic areas covered by the project.

8. Toward open source

8.1. Imaging harmonization

8.1.1. PET harmonization

It is well established that the Centiloid scale, used in the two trials in AMYPAD, is robust to differences in image resolution and quality (35). Given such a robust behavior, it could have been argued that there was no need to harmonize the differences in image resolution and quality inherent to multi-center PET studies. However, this may not hold true when estimating regional amyloid burden, as opposed to global ones. In this regard, one of the goals of AMYPAD is to better understand the information provided by regional patterns of amyloid deposition, on top of global estimates as the CL scale. As an example of such added value, we recently described three distinct spatial-temporal trajectories of amyloid accumulation (37) and proposed a visual staging method based on the regional pattern of positivity of the PET scans (33). Since AMYPAD will serve to assess the clinical value of the regional information of PET scans, an image harmonization standard operational procedure (SOP) has been developed in collaboration with EARL (https://earl.eanm.org/), the initiative of the European Association of Nuclear Medicine (EANM), to harmonize quantification in nuclear medicine imaging. This SOP is based on the acquisition of Hoffman phantom scans in the AMYPAD imaging network to account for inter-scanner differences and provide several indicators of image quality (Figure 3) (38).

8.1.2. Advanced MRI harmonization

In addition, most PNHS PCs had available historical advanced magnetic resonance imaging (MRI). These include resting-state functional MRI (rs-fMRI), diffusion-weighted imaging (DWI) and arterial spin labeling (ASL). The PNHS team has, therefore, aligned efforts with the 'EPAD imaging core' to process all collected scans using a harmonized pipeline as described in Lorenzini et al. (39). To promote accessibility and replicability, standard image-derived phenotypes (IDPs) will be computed from MRI sequences and shared as spreadsheets. IDPs are image-specific summary statistics that provide a quantitative way to investigate structural and functional brain characteristics. For rs-fMRI, a group-level independent component analysis (ICA) will be performed on 4 mm MNI-registered bold time series, using FSL Melodic (40) to identify canonical resting-state networks (RSN). A dual regression approach will then be used to compute the mean time series and functional connectivity strength of each RSN. Similarly, bold time series will be summarized within atlases region of interest. Functional connectivity matrices in atlas space and graph properties will be derived. For DWI, pre-processed data will first be fed into the FSL Brain Extraction Toolbox (BET) (41) and then into FSL DTIFIT, to fit the diffusion tensor model to the data and produce diffusion tensor imaging (DTI) scalars maps (fractional anisotropy (FA), and mean (MD), axial (AD) and radial (RD) diffusivity). On these data, the Tract-based spatial statistics (TBSS) pipeline will be used to compute global and regional FA features from the JHU ICBM-DTI-81 atlas (42). For ASL, mean cerebral blood flow (CBF) and spatial coefficient-of-variation will be computed as described in Mutsaerts et al. (43). These processing steps have been integrated in an in-house workflow to perform semi-automatic QC of MRI data. This set of QC functionalities was written as an extension to ExploreASL (43) called ExploreQC (39). The semi-automated QC procedure was based on two steps: feature estimation and visualization. Image quality features were computed from five image feature domains: motion, noise, inhomogeneity, asymmetry, and descriptives. The visualization module consists of an interactive dashboard with violin and scatter plots for observing variation between and within sites, respectively. Individual scans can be visually inspected by selecting their data points on the scatter plots, allowing to visualize the scans themselves together with the QC features (Figure 4). The toolbox in freely available online (https://github.com/luislorenzini/ExploreQC).

Overview of the quality control workflow. QC features are computed in the feature estimation module and cover 5 image features domains. Feature distributions can then be interactively inspected between-sites (5A) and within-sites (5B). Single-subject scans can be opened by clicking on the scatterplots (5C). Adapted from Lorenzini et al. (39).

8.2. Clinical data harmonization

Different strategies were used for the harmonization of the clinical data in the AMYPAD trials, mostly determined by the design of each study. The prospective nature of the DPMS allowed for the implementation of harmonized strategies already from the beginning of the project, which were executed during the whole data collections. However, the PNHS dataset is composed by the combination of prospective and historical data from multiple sources, these limited the capacity to define harmonize methods during data collection, as most data was already obtained, and required a more thoroughly process of harmonization across the different data sources.

The AMYPAD DPMS clinical dataset includes baseline and follow-up variables concerning sociodemographic, clinical, and cognitive features of 840 memory clinic patients. These data were prospectively collected locally by the teams of the 8

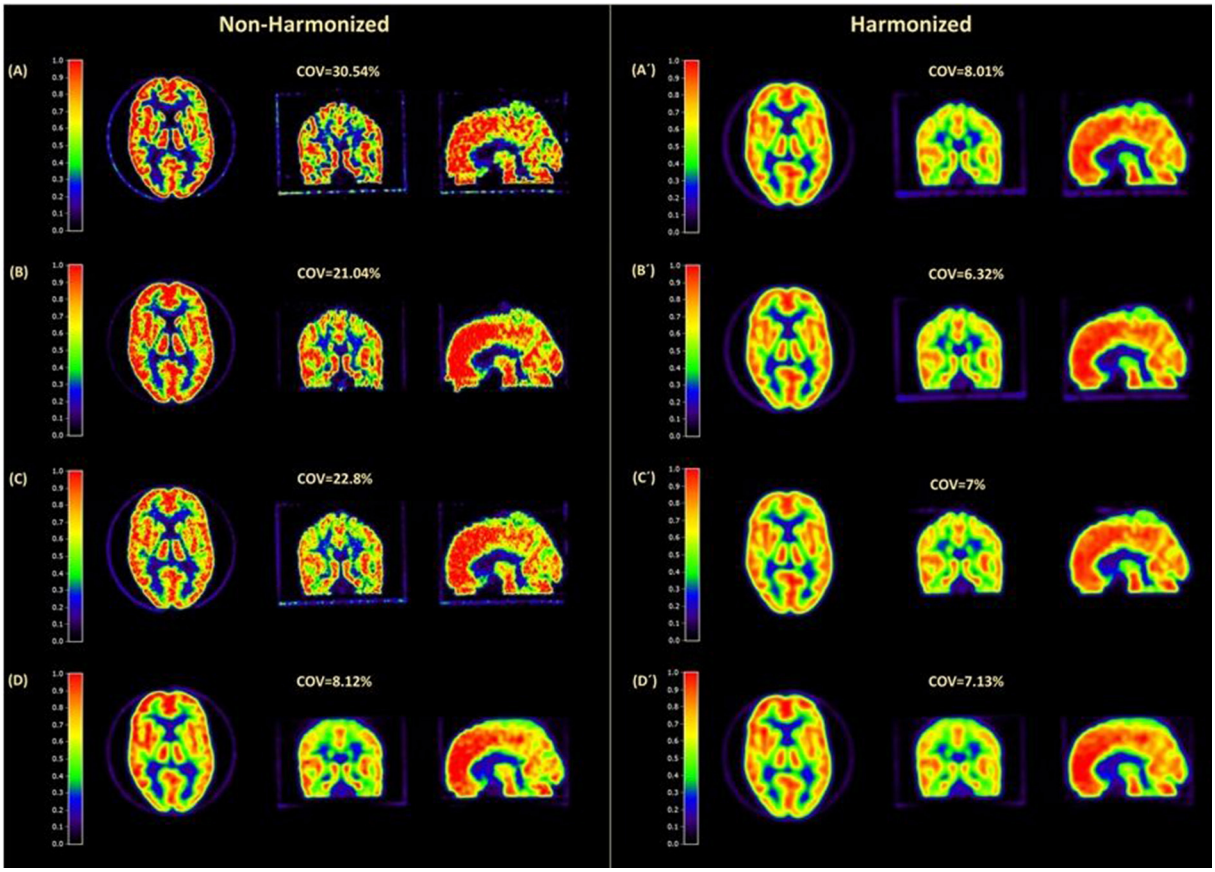

FIGURE 3
Visual illustration of amyloid PET harmonization results. Example images of the Hoffman phantom were acquired on four different scanners before **(left panel)** and after **(right panel)** harmonization. Coefficient of variance (COV%), which is an indication of image noise, is shown for each scan. Before harmonization, the COV% difference was more than 22, while after harmonization this ranged only ∼1.

AMYPAD DPMS recruiting memory clinics using electronic case report forms (developed by IXICO) and, therefore, following harmonized procedures defined in advance during the early phases of the study. Then, after data collection, the AMYPAD DPMS dataset had a final quality-checked by the sponsor team (University of Geneva).

Meanwhile, the AMYPAD PNHS clinical dataset is a combination of prospective and historical data from 17 European sites. Due to the variety of sources and data formats present across the Parent Cohorts, the data curation process in PNHS deals with multiple challenges. Among these obstacles, the most notables are the use of different data models, measurements, and cognitive questionnaires. Therefore, it was decided to perform a comprehensive process of data curation based on the work of the Data Curation Network (https://datacurationnetwork.org) which developed a standardized set of CURATED steps (Check, Understand, Request, Augment, Transform, Evaluate, and Document).

This process resulted in the largest European dataset phenotyping longitudinally individuals at risk of AD-related progression, which currently consists of ∼3,350 subjects, ∼1,600 of those with a baseline amyloid PET and about 940 of them having at least one follow-up PET acquisition. The dataset currently contains 9,740 observations (visits) and 614 variables, grouped into (68) "concepts" and (13) "domains," such as demographics, family history, genetics, vital signs, medical history, neuropsychological questionnaires, lifestyle, CSF, PET and MRI. While current dataset has been developed using its own data model, tailored to the needs of the project, the AMYPAD PNHS has been selected to work with the European Health Data & Evidence Network (EHDEN) in the adoption of the OMOP data model. This will allow for the systematic analysis of the PNHS database, using a harmonize format as well as a common presentation of terminologies, vocabularies and coding schemes (EHDEN has received funding from the IMI 2 Join Undertaking under the grant agreement No 806968).

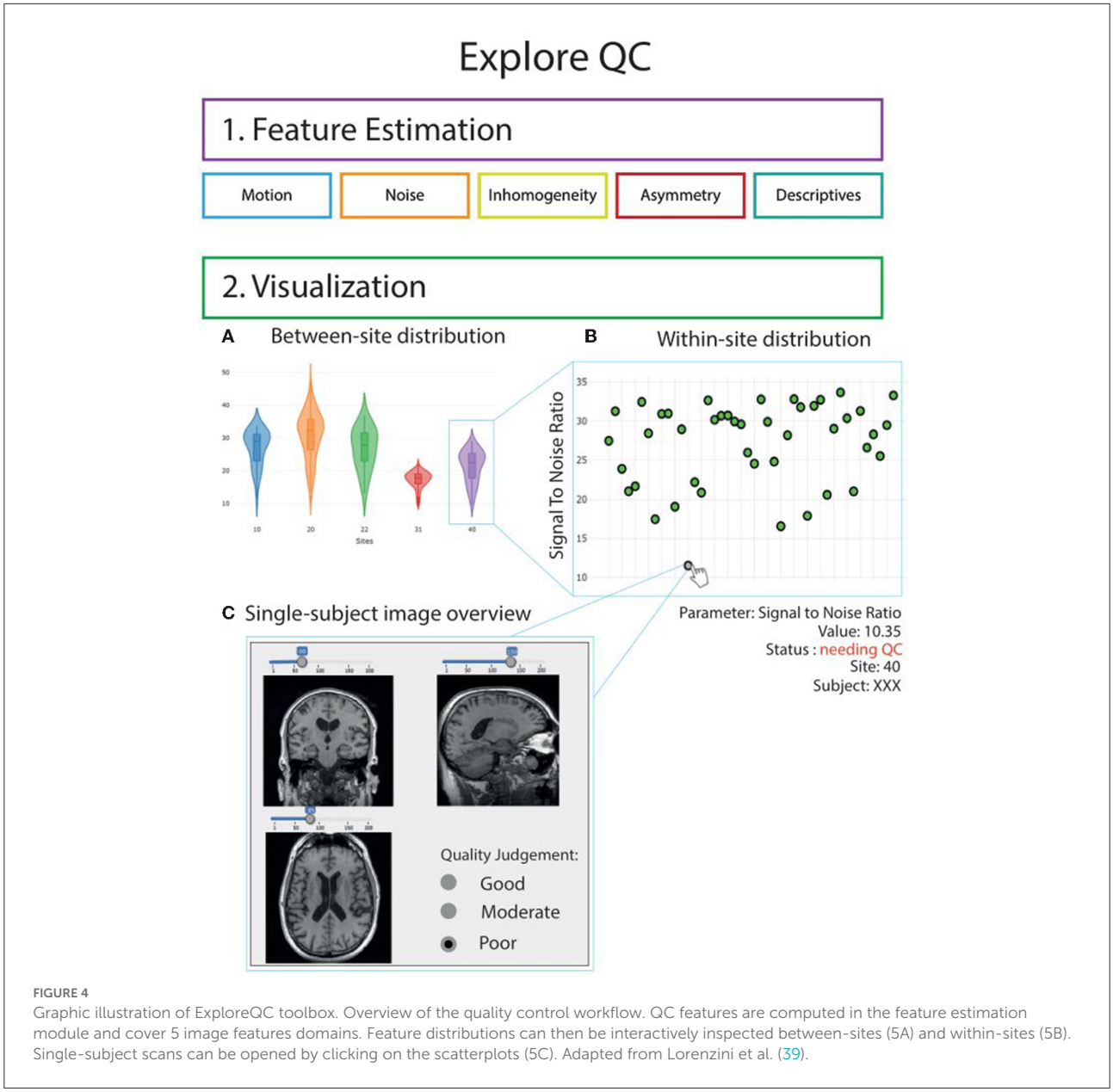

FIGURE 4
Graphic illustration of ExploreQC toolbox. Overview of the quality control workflow. QC features are computed in the feature estimation module and cover 5 image features domains. Feature distributions can then be interactively inspected between-sites (5A) and within-sites (5B). Single-subject scans can be opened by clicking on the scatterplots (5C). Adapted from Lorenzini et al. (39).

All this process of data handling has been performed in close collaboration with the ARIDHIA team, where their expertise in data science has played a major role supporting data integration, harmonization and storage.

8.3. Availability of software

A couple of open-source software packages dedicated to PET imaging in dementia have been developed: NiftyPET for neuro-image reconstruction with basic analyses, and NiftyPAD for dynamic PET analyses.

NiftyPET (https://niftypet.readthedocs.io/) is an open-source software solution for standalone and high-throughput PET image reconstruction, manipulation, processing and analysis with high quantitative accuracy and precision (Figure 5) (44). One of its key applications is brain imaging in dementia using amyloid and tau tracers. The key computational routines are written in CUDA C for fast and efficient execution on NVIDIA GPU devices. The routines are then embedded in Python C extensions to be readily available for high-level manipulation of PET data in Python. Using *NiftyPET*, it has been possible to accurately assess the precision of MR-PET image registration, critical for accurate quantification of amyloid PET data (45). Also, the software was used for comprehensive

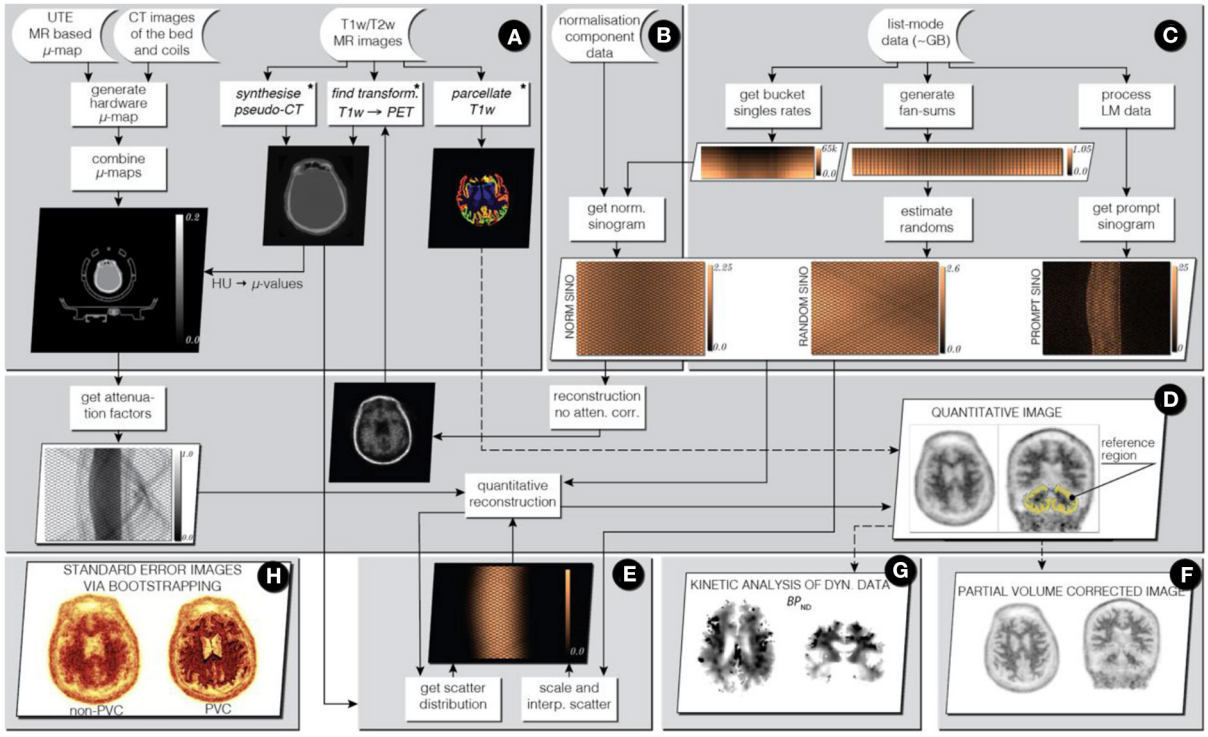

FIGURE 5
Infrastructure for standalone PET image reconstruction and analysis of PET/MR brain data using amyloid PET tracer. Stages **(A–C)** involve processing of input data (raw acquisition and image data), while in stages **(D, E)** image reconstruction is performed followed by image analysis in stages **(F–H)**.

analysis of the American College of Radiology PET phantom to estimate the spatial resolution of PET scanners (46) – information which is essential for performing a robust partial volume correction of amyloid PET images.

NiftyPAD is a freely available open source, Python-based software package for versatile analyses of static, full or dual-time window dynamic brain PET data. The key novelties of NiftyPAD are the analyses of dual-time window scans with reference input processing, pharmacokinetic modeling with shortened PET acquisitions through the incorporation of arterial spin labeling (ASL)-derived relative perfusion measures, as well as optional PET data-based motion correction. The implemented kinetic models were validated by comparing the outcomes with the well-established software packages PPET and/or QModeling. Real dynamic PET data were used from four different amyloid tracers used in clinics. High correlations were earlier validated software indicating reliable model implementation in NiftyPAD. It is freely available (https://github.com/JJiao/NiftyPAD), and allows for multiplatform usage. The modular setup makes adding new functionalities easy, and the package is lightweight with minimal dependencies, making it easy to use and integrate into existing processing pipelines.

8.4. Facilitating an open-access platform

8.4.1. Data access

The AMYPAD PNHS dataset is hosted in the Alzheimer's Disease Data Initiative (ADDI) Workbench, with the first private data release made in November 2021 (Figure 6). Thanks to a 5-year partnership between the AMYPAD consortium and ADDI, the PNHS dataset will remain available to the research community beyond the project duration, with the first public release planned by the end of the first quarter of 2023.

Those researchers interested in using the AMYPAD PNHS data can request access to the imaging, clinical, and biomarker data for scientific research investigation and/or educational activities. The application can be performed *via* the FAIR Data Service of the Alzheimer's Disease Data Initiative (ADDI). In this platform, the user will indicate if the request includes only access to the clinical data or also to the neuroimaging data, the data domains, and the type of data (i.e., raw, harmonized, or derivative). In addition, the researcher should provide a one-page proposal describing the study and the use of the data.

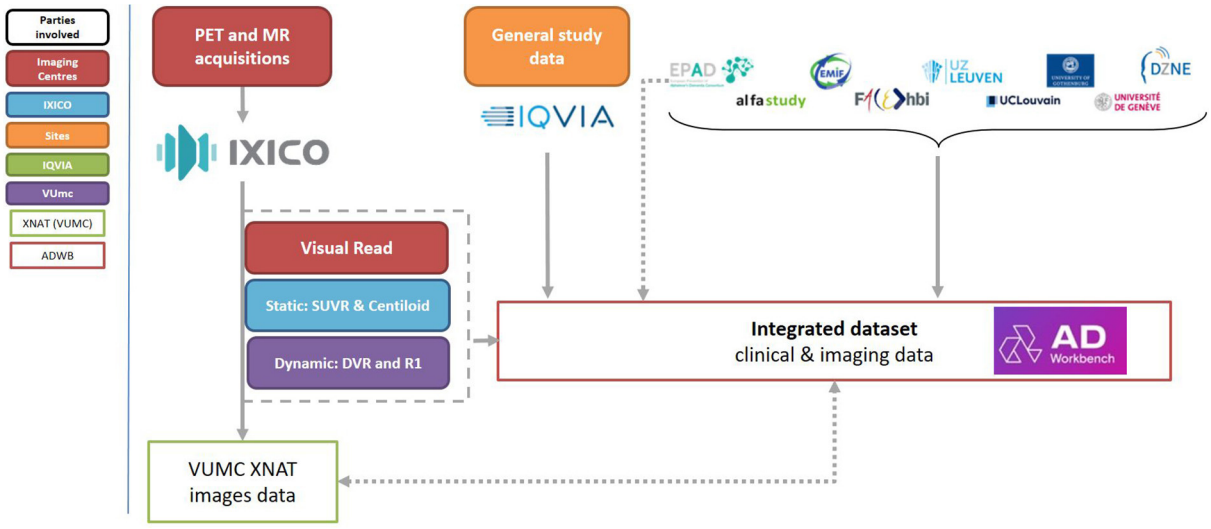

FIGURE 6
Schematic representation of data-flow within the PNHS trial.

The AMYPAD Data Sharing and Publication Committee (DPC) will review the application and the research proposal. Incomplete applications or those without a clear focus will not receive approval. The results of the DPC review will be sent *via* the FAIR platform, and approved application will be processed differently based on the requested data type:

- *Harmonized and derivative data* does not require further approval by the Parent Cohorts, and the access will be granted. This process will take up to 1 month.
- *Raw data* requires specific approval by the Parent Cohorts, which will be contacted with a copy of the proposal. Each cohort will decided if they would grant or not approval. This process will take up to 2 months (1 month for the assessment of the DPC and 1 month for the Parent Cohort).

The results for the data access request will be sent to the researcher *via* the FAIR platform, and approved application will receive access to retrieve the data in the AD Workbench. In case that neuroimaging data was also requested, information to access the XNAT will be also provided *via* the FAIR platform (more details in the next section).

8.4.2. Image data access and XNAT

Imaging data from all sites have been collected by IXICO and have undergone quality control and between-site harmonization. Image data are disseminated by the Amsterdam UMC using an XNAT system (www.xnat.org), an open-source medical image server that allows control of multi-user access and storage of clinical non-imaging data. The image data that is made available, adheres to the PET-BIDS standard (https://bids-specification.readthedocs.io) (47), which ensures transparency of the image provenance and processing history, and enables open and reproducible science.

Together with the EPAD project, the AMYPAD group is working in conjunction with the Alzheimers Disease Data Initiative (https://www.alzheimersdata.org), which will ensure the availability of the main clinical databases for these projects, and support sharing of the imaging data as facilitated by Amsterdam UMC.

9. Conclusion

In summary, the AMYPAD consortium has made a strong contribution to the AD field over the last 6 years. A legacy of over 3,500 amyloid PET scans covering the entire AD *continuum* has been collected across the DPMS and PNHS, which is now curated for sharing with the research community. AMYPAD has expanded the knowledge in both the utility and measurement of amyloid PET beyond the basic dichotomization of a standard negative or positive scan and, in particular, has harnessed the Centiloid metric as a universal tracer-independent method for assessing amyloid load. The consortium has widely demonstrated the robustness and validity of the technique across tracers to enable further research using this technology for both initial diagnosis and prognosis,

and opens possibilities for optimal therapy monitoring and/or patient-management.

Data availability statement

The data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethical Committee of the University Medical Center Amsterdam, location VUmc and all local sites. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

LC has received research support from GE Healthcare (paid to institution). GF is an employee of GE Healthcare. HP is an employee of GE Healthcare. DA received funding by the Fondation Recherche Alzheimer and the Swiss National Science Foundation (project CRSK-3_196354/1). PM received consulting fees from Oncovision. CB is an employee of GE Healthcare. GBF reports grants from Avid Radiopharmaceuticals, Biogen, GE International, Guerbert, IXICO, Merz Pharma, Nestlé, Novartis, Eisai, Piramal, Roche, Siemens, Teva Pharmaceutical Industries, and Vifor Pharma; he has received personal fees from AstraZeneca, Avid Radiopharmaceuticals, Biogen, Roche, Diadem, Neurodiem, Elan Pharmaceuticals, GE International, Lundbeck, Pfizer, and TauRx Therapeutics. AN received consulting fees from Hoffman La Roche. Patent: US patent alpha 7 nicotinic PET tracer. She is deputy chairman of Wennergren Foundations. PP has received research support from GE Healthcare (paid to institution). AS is an employee of Life Molecular Imaging GmbH. RG is an employee of Life Molecular Imaging GmbH. PV has served as member of the advisory board of Roche Diagnostics and received nonfinancial support from GE Healthcare, research support from Biogen and grants from Bristol-Myers Squibb, EU/EFPIA Innovative Medicines Initiative Joint Undertaking, EU Joint Programme–Neurodegenerative Disease Research (JPND and ZonMw). LF is an employee of Janssen Pharmaceuticals. Mark Schmidt is an employee of Janssen Pharmaceuticals. CB is an employee of Alzheimer Europe which has received grant support from Horizon2020, EU/EFPIA Innovative Medicines Initiative Joint Undertaking and the Luxembourg National Research Fund under the aegis of the EU Joint Programme - Neurodegenerative Disease Research (JPND) and sponsorship from AbbVie, Biogen, Danone, Eisai, GE Healthcare, Grifols, Janssen, Lilly, NovoNordisk, Roche and TauRx. JG is an employee of Alzheimer Europe which has received grant support from Horizon2020, EU/EFPIA Innovative Medicines Initiative Joint Undertaking and the Luxembourg National Research Fund under the aegis of the EU Joint Programme - Neurodegenerative Disease Research (JPND) and sponsorship from AbbVie, Biogen, Danone, Eisai, GE Healthcare, Grifols, Janssen, Lilly, NovoNordisk, Roche and TauRx. AM is an employee of GE Healthcare. MB has been a consultant for Araclon, Avid, Bayer, Elan, Grifols, Janssen/Pfizer, Lilly, Neuroptix, Nutricia, Roche, Sanofi, Biogen, and Servier; and received fees for lectures and funds for research from Araclon, Esteve, Grifols, Janssen, Novartis, Nutricia, Piramal, Pfizer-Wyett, Roche, and Servier. RV institution has Clinical Trial Agreements (RV as PI) with Alector, Biogen, Janssen Pharmaceuticals, NovoNordisk, Prevail, Roche, UCB. RV's institution has consultancy agreements (RV as DSMB member) with AC Immune and Novartis. RV was global PI of the Phase 1 and 2 18F-flutemetamol trials. RV's institution had a material transfer agreement (RV as PI) with GEHC for free tracer delivery of the FPACK cohort baseline scans and with Avid Pharmaceuticals, an EliLilly subsidiary. AD Research support: Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, Sofie, Eisai, Novartis/AAA. Speaker Honorary/Advisory Boards: Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA, Bayer Vital. Stock: Siemens Healthineers, Lantheus Holding. Patents: Patent pending for 18F-PSMA7 (PSMA PET imaging tracer). BH received consulting fees

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Elisabetta Vaudano,
Innovative Health Initiative, Belgium

REVIEWED BY
Kristien Aarts,
European Brain Council, Belgium
Pernille Smith,
Aarhus University, Denmark

*CORRESPONDENCE
Claire Hawksworth
✉ claire.hawksworth@nice.org.uk

†These authors have contributed equally to this work

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Participating in innovative medicines initiative funded neurodegenerative disorder projects—An impact analysis conducted as part of the NEURONET project

Claire Hawksworth[1*†], Fatima Salih[2†], Katharine Cresswell[1], Lennert Steukers[3], Carlos Diaz[4], Lewis Killin[4], Laurent Pradier[5], Angela Bradshaw[6] and Dalia Dawoud[2,7]

[1]Department of Science, Evidence and Analytics, National Institute for Health and Care Excellence, Manchester, United Kingdom, [2]Department of Science, Evidence and Analytics, National Institute for Health and Care Excellence, London, United Kingdom, [3]Janssen Pharmaceuticals NV, Beerse, Belgium, [4]SYNAPSE Research Management Partners, Barcelona, Spain, [5]Department of Scientific Strategy and External Relations, Sanofi, Paris, France, [6]Alzheimer Europe, Luxembourg, Luxembourg, [7]Faculty of Pharmacy, Cairo University, Cairo, Egypt

The European Commission's Innovative Medicines Initiative (IMI) has funded many projects focusing on neurodegenerative disorders (ND) that aimed to improve the diagnosis, prevention, treatment and understanding of NDs. To facilitate collaboration across this project portfolio, the IMI funded the "NEURONET" project between March 2019 and August 2022 with the aim of connecting these projects and promoting synergies, enhancing the visibility of their findings, understanding the impact of the IMI funding and identifying research gaps that warrant more/new funding. The IMI ND portfolio currently includes 20 projects consisting of 270 partner organizations across 25 countries. The NEURONET project conducted an impact analysis to assess the scientific and socio-economic impact of the IMI ND portfolio. This was to better understand the perceived areas of impact from those directly involved in the projects. The impact analysis was conducted in two stages: an initial stage developed the scope of the project, defined the impact indicators and measures to be used. A second stage designed and administered the survey amongst partners from European Federation of Pharmaceutical Industries and Associations (EFPIA) organizations and other partners (hereafter, referred to as "non-EFPIA" organizations). Responses were analyzed according to areas of impact: organizational, economic, capacity building, collaborations and networking, individual, scientific, policy, patient, societal and public health impact. Involvement in the IMI ND projects led to organizational impact, and increased networking, collaboration and partnerships. The key perceived disadvantage to project participation was the administrative burden. These results were true for both EFPIA and non-EFPIA respondents. The impact for individual, policy, patients and public health was less clear with people reporting both high and low impact. Overall, there was broad alignment between EFPIA and non-EFPIA participants' responses apart from for awareness of project assets, as part of scientific impact, which appeared to be slightly higher among non-EFPIA respondents. These results identified clear areas of impact and those that require improvement. Areas to focus on include promoting asset awareness, establishing the impact of the IMI ND projects on research and development, ensuring meaningful patient involvement

in these public-private partnership projects and reducing the administrative burden associated with participation in them.

KEYWORDS

Innovative Medicines Initiative (IMI), neurodegenerative disease, impact, survey, public-private partnerships (PPPs), neurodegenerative disorder

1. Introduction

The Innovative Medicines Initiative (IMI), which has recently been succeeded by the Innovative Health Initiative (IHI) was the world's largest public-private partnership (PPP) in the life sciences. The IMI was a partnership between the European Union (EU), represented by the European Commission, and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). EFPIA aims to help members collaborate, innovate and discover new therapies for people across Europe and its members include 37 national associations, 38 pharmaceutical companies and a growing number of small and medium-sized enterprises.

The IMI's core mission was to 'translate health research and innovation into tangible benefits for patients and society and ensure that Europe remains at the cutting edge of interdisciplinary, sustainable, patient-centric health research'. The IMI achieved this through funding over 159 projects since its launch in 2007 followed by launch of the IMI2 from 2014 to 2020. To give an idea of funding amount, the current total budget for its successor IHI is €2.4 billion with approximately half each coming from Horizon Europe and IHI industry partners, and €200 million coming from other life science industries.

IMI2 funded research that aligned with its Strategic Research Agenda (SRA) (1). This laid out the key disease area and research priorities which governed its funding calls. Another initiative specifically relevant in the neurodegeneration disease space, and to this publication, is the EU Joint Programme-Neurodegenerative Disease Research (JPND). This is the largest global research initiative aimed at tackling the challenge of neurodegenerative diseases and in 2019 it published its Research and Innovation Strategy (2) outlining thematic priorities for future research in order to improve prevention, diagnosis, treatment and patient care for neurodegenerative diseases. IMI projects are partnerships between members of EFPIA and other organizations including academic institutions and small and medium sized enterprises (SMEs).

NEURONET was a 3-year Coordination and Support Action that received nearly €2 million in funding through IMI2. It provided coordination and support to other IMI funded neurodegenerative disorder research projects. It aimed to identify research gaps, communicate research findings and create links between the projects that form the IMI neurodegenerative disorders (ND) portfolio. This portfolio currently includes more than 20 different research projects which are improving the diagnosis, prevention, treatment and understanding of neurodegenerative conditions.

A potential benefit of PPPs is that greater transparency at the pre-competitive stage, and in research and development (R&D) could reduce redundancy, duplication of effort, and save money (3). It is assumed too, that spending on R&D will improve innovation and therefore the IMI ND portfolio should generate innovation in the NDD space. The NEURONET project was tasked with investigating this. Logically, this required an impact assessment which needed to establish which factors likely facilitated pharmaceutical innovation (aligned with the SRA mission and priorities) and how the IMI ND portfolio contributed to these factors.

Impact assessments aim to evaluate the significance and reach of both positive and negative effects of research (4). The definition of impact in the context of NEURONET is restricted due to the lack of baseline to assess change. Impact was therefore evaluated in terms of process and activity in relation to the key principles underlining IMI's objectives. In this impact assessment there were two stages. Stage one characterized the project portfolio and conducted network and publication analyses to understand key organizations involved, the degree of collaboration and how the publications addressed ND research priorities. To understand the latter, the SRA priorities for neurodegenerative disease were mapped against themes from the JPND Research and Innovation Framework and the broader JPND report (2).

The network analysis revealed that EFPIA companies are key vehicles for dissemination of knowledge generated between projects due to their prominent feature in the network (5). For example, they were more likely to work on multiple IMI ND projects, connecting them to more organizations. On the whole academic organizations were underrepresented as these 'key nodes' in the network. However, the publication analysis revealed that many were authored by single academic institutions or multiple collaborations between academic partners, a finding that has previously been reported in PPPs (6). The authors concluded that further research was needed to understand if this limited cross-public-private partner collaboration on publications is reflective of an overall lack of collaboration across organizations, or if collaboration across organizations is demonstrated through other mechanisms such as the development of project assets. The publication analysis also revealed a need to more broadly assess how project assets are contributing toward research across the priority scientific areas.

Overall, the first stage provided NEURONET with interesting findings on collaboration, networking and research impact that warranted more in-depth analysis, as well as a broader assessment of impact to align with IMI's objectives. Themes that the second stage was to explore included:

- Reasons for single organization publications and impact this has on knowledge generation and transfer between organizations. Further work could also explore why certain organizations do not participate in publications and whether or not this hinders the transfer of knowledge;
- How the IMI portfolio is linking to global research efforts in this field;
- Qualitative research looking more broadly at the use and impact of project assets, particularly by EFPIA;
- The impact on EFPIA companies of collaborations with other partners through IMI projects;
- Exploration of impact on personal and professional development and the creation of opportunities for early career researchers.

These informed the design of a survey for partners who were involved in the IMI ND projects to understand the broader impact of the projects. The scope for the survey therefore became to understand the scientific and socio-economic impact of the IMI ND portfolio across the EU. Recently various frameworks to measure the impact and value of PPPs have been proposed, and all recognize that wider measures of impact are needed to appropriately reflect their value (7–9). To operationalize scientific and socio-economic impact, we fractioned it into key areas of impact that together would provide insight into the wider impact of the IMI ND portfolio. These areas of impact were: organizational, economic, capacity, collaboration, individual, scientific, policy, patient, societal and health impacts. The survey questions were organized around these key themes.

EFPIA companies were initially targeted for the survey due to the findings from stage one that they represented key organizations in the IMI ND portfolio. After conducting this exercise it was felt that it would be valuable to repeat it for the other organizations involved in the projects which included academic organizations, SMEs patient/carer organizations and other organization types. These could be termed "research-related organizations" and we refer to these as "non-EFPIA" organizations in this publication. Repeating the survey with this group allowed insight into the impact of the IMI ND portfolio from all perspectives.

This paper reports on the conduct and results of the surveys to illustrate the range of project impacts.

2. Methods

2.1. Data collection

To traditionally evaluate impact there needs to be a baseline in which to assess change. The definition of impact in the context of NEURONET is restricted due to the lack of baseline. In addition, NEURONET is not acting as an auditor or evaluator of individual projects or the impact of any specific deliverables against the projects aims. Impact was therefore evaluated in terms of process and activity in relation to the key principles underlining IMI's objectives.

At the time of the survey there were 18 projects in the ND portfolio. See Supplementary Table 1 for the full list. Seven had completed, four were coming to an end and seven were ongoing. The survey was the second stage of the impact analysis. The first stage characterized the project portfolio. For each project data was collected on the partner organizations and number of assets. These were used to conduct a network analysis which visualized the IMI ND portfolio. Every unique organization represented a node and connections between the nodes were defined by the IMI projects in common. Measures of centrality were calculated including the "degree" and "betweenness" of all the network nodes. The degree gave the number of ties that one organization has to all other organizations in the network and the betweenness represented the number of times a node is present in the shortest path between two nodes. This was conducted in Rstudio.

The publication analysis in the first stage of the impact assessment included eight projects that had completed or were about to finish their activity. The following information on the project publications were collected: title, Digital Object Identifier (DOI), first author, first author organization, organizations of all co-authors on the publication. The methodology followed that used by IMI for its annual bibliographical analysis of all IMI projects (10). The number of project organizations for each publication was calculated along with the number of publications per project, the number and percentage of project organizations on at least 1 publication, the number and mean number of publications per organization and the percentage of all project publications each organization was listed on. Two hundred and thirty two publications were included. A network analysis was conducted following the methods and measures for the project network analysis. This indicated how collaborative organizations were. A framework was developed to analyze the project publications against key ND scientific priorities. To do this, the SRA priorities were mapped to the overarching themes from the JPND Research and Innovation Framework, in addition to a number of other sub-categories identified from the JPND report. A visual heatmap was created using MS Excel to show the research priorities and the extent to which these were being addressed. Full details for the methods used in stage one of the impact analysis are documented in the final report (11) and have been published (5).

Stage two of the impact assessment involved developing a survey to elicit more detail on areas of further research generated from stage one, along with data on the broader impact of the IMI ND portfolio. A questionnaire for the EFPIA organizations was developed by Janssen, Belgium, as Task Lead and refined following input from members of the NEURONET Executive Committee (ExCom). Work Package 1 Lead, the National Institute of Health and Care Excellence (NICE), UK, piloted the survey to check face validity and time for completion.

The survey was divided into six categories, informed by stage one of the impact assessment: experience in IMI, impact on company, impact on daily work, impact on professional career, impact on professional network and impact on the field at large. The survey had 46 questions.

The survey was administered online and disseminated between 29th March and 31st August 2021. All EFPIA partners' staff that are or have been involved in one or more of the 18 IMI ND projects that

were part of the portfolio at the time of the survey were invited to complete it. The survey was distributed through the companies *via* a named NEURONET contact person and/or the IMI operational contact person of each EFPIA company. To increase response rates from individual companies a final reminder was sent by the IMI scientific officer on 13 August 2021.

After the EFPIA survey was closed, it was felt that it would be valuable to also survey other project organizations or "non-EFPIA" organizations. The EFPIA survey was reviewed and adapted by a multi-disciplinary group including "non-EFPIA" representation to ensure questions were relevant for a non-EFPIA audience, and therefore facilitate responses. The group included considerations such as the role of the stakeholders, funders or research managers, or executers, the structure of the organization, and terminology and traditional measures of impact in different sectors e.g., publications in academia. This removed questions on economic and regulatory and policy impact. The final survey was drafted by NICE, UK, and refined following input from the NEURONET ExCom. NICE, UK, piloted the survey to check face validity and time for completion. The survey was divided into six categories: experience in IMI, impact on research group or department or personnel, impact on research, impact on collaborations, broader impact on society, research and innovation and impact of assets. The survey had 21 questions.

The survey was disseminated to the individual portfolio projects' partners through their project leads, and through project managers of individual projects. The online survey for non-EFPIA partners was administered between January and March 2022. The online survey tool, Survio®, was used for both surveys.

See Supplementary Tables 2, 3 for the EFPIA and non-EFPIA surveys, respectively.

A pragmatic search was carried out using a pearl growing strategy. Research Rabbit and CitationChaser were used to identify references related (by citation or topic similarity) to known, relevant records which were found by searching PubMed and Google Scholar with search terms including "Innovative Medicines initiative," "impact assessment" and "neurodegenerative disorders."

2.2. Data analysis

The EFPIA survey questions were categorized into 10 areas of impact for data analysis purposes. See Supplementary Table 4 for how they were categorized. These outcome categories were pre-defined and originated from a different task within NEURONET that was developing complementary Key Performance Indicators (KPIs) to estimate impact. These were based on existing IMI KPIs, the IMI1 impact assessment reports and discussions with EFPIA representatives within NEURONET. The outcome areas of impact were:

- Organizational impact (e.g., organizational strategy, objectives, planning, processes, reputation etc.).
- Economic impact (e.g., return on investment).
- Capacity building (e.g., professional development, attracting new staff).
- Collaborations, networks and partnerships.
- Individual impact (e.g., personal development, collaborations and networks, ways of working).
- Scientific impact (e.g., impact on the drug development process, awareness & visibility of IMI ND projects/assets and use of assets in R&D and regulatory/HTA practice).
- Regulatory and policy impact (e.g., impact on regulatory practice, decision makers).
- Patient impact (e.g., research that is including patients and bringing science closer to them).
- Societal impact (e.g., research that is including and empowering the public and generating outcomes and impacts that are relevant for patients/citizens).
- Health impacts (impacts on public health, e.g., life expectancy, prevention of illnesses, quality of life, and the health-care system).

For the non-EFPIA survey, the results were categorized and analyzed according to the seven areas of impact deemed most relevant:

- Organizational impact.
- Collaborations, networks and partnerships.
- Individual impact.
- Scientific impact.
- Patient impact.
- Societal impact.
- Health impacts.

The responses to the survey were exported from Survio to Excel and analyzed. Quantitative and qualitative data were collected. Quantitative data were analyzed using descriptive statistics (counts and percentages of different responses) and responses to the open-ended questions were coded and thematically analyzed using an inductive approach.

3. Results

3.1. Survey respondents

3.1.1. EFPIA

Overall, for the EFPIA survey, 91 responses were received from 24 out of the 31 companies that were invited to participate. See Supplementary Table 5 for the full list of the 24 companies. The majority of responses were from Janssen Pharmaceutica NV and Sanofi (57%, $n = 49/86$). Five respondents indicated that they were not involved in any IMI project and did not qualify for inclusion. The final analysis included 86 responses.

On average, the EFPIA respondents were involved in 2 projects with the majority spending at least 2 hours per week on the projects (74%, $n = 64/86$). Nearly half of those (47%, $n = 30/64$) spent more than 6 h per week on the projects. In terms of project role, the majority (64%, $n = 55/86$) had not been Project Lead (i.e., responsible for the delivery of the whole project) on any project while half of the respondents (50%, $n = 43/86$) indicated they had been Work Package Lead (i.e., responsible for the delivery of the activities of a single work package) on at least 1 project.

3.1.2. Non-EFPIA

Overall, 43 people completed the survey, however one was from an EFPIA organization and excluded from the analyses. The final analysis included 42 respondents. The respondents had roles ranging from Principal Investigator to post-doctoral researchers and project managers (Figure 1). The respondents were split equally between spending 5–10%, 10–50% or more than 50% of their time on the IMI projects.

3.2. Organizational impact

3.2.1. EFPIA

The responses confirmed the visibility of IMI projects within EFPIA organizations. The IMI was known within companies for 100% of respondents and 58% of respondents ($n = 50/86$) thought there were aspects of R&D done differently due to IMI projects.

Over a third of respondents (37%, $n = 32/86$) thought the project they were involved in had a "moderate or high" impact on the company's strategic objectives and ways of working overall, although an equal proportion also thought the impact on this had been "neutral." The majority of respondents (65%, $n = 56/86$) also thought that the IMI ND projects had an impact on the company's presence, visibility and public perception.

Although "I don't know"' was the most popular answer when asked whether the company helps in creating awareness of project outcomes (43%, $n = 37/86$), or helps in creating awareness of the impact of those outcomes (44%, $n = 38/86$), of the remaining respondents, more answered "yes" than "no" to these questions (38 and 35% vs. 19 and 21%, respectively).

3.2.2. Non-EFPIA

Nearly all respondents (88%, $n = 37/42$) felt the projects had resulted in a change to their department. Most thought a "slight" change (45%, $n = 19/42$), followed by a 'moderate' (33%, $n = 14/42$) and "radical" change (10%, $n = 4/42$).

The majority of respondents reported an expansion to current research lines (62%, $n = 26/42$). Nearly half of respondents reported that involvement had led to the creation of new research lines (45%, $n = 19/42$) and an improvement in global positioning (43%, $n = 18/42$). Over a third (38%, $n = 16/42$) also saw new contracts or funding opportunities in their organization due to involvement in IMI ND projects. Other organizational impacts described by respondents include being able to finance staff locally and diversify the staff involved in projects.

3.3. Economic impact

Economic impact was only assessed in the EFPIA survey. Overall, 50% ($n = 43/86$) of respondents selected "neutral" when asked about the impact of the projects on return on investment (ROI). The survey prompted respondents to elaborate on which project outcomes triggered the ROI. Figure 2 shows that the major outcomes were around networking, knowledge and data sharing.

3.4. Capacity building

3.4.1. EFPIA

Of all respondents, 41% ($n = 36/86$) rated the impact on attracting talent as moderate or high. Additionally, 45% ($n = 39/86$) of respondents reported that people had been hired specifically to work on the IMI ND project. The breakdown of the number of hires is shown in Figure 3. Nearly half of those who reported hires (49%, $n = 19/39$) were aware of people who went on to receive a permanent position after being hired for an IMI ND project. Furthermore, 12% ($n = 10/86$) of respondents were aware of people who were hired from an IMI ND project partner to their company.

3.4.2. Non-EFPIA

The majority of respondents reported an increase in the number of staff (64%, $n = 27/42$) due to involvement in the IMI ND project.

3.5. Collaborations, networks, and partnerships

3.5.1. EFPIA

Nearly half of respondents (49%, $n = 42/86$) rated the projects' impact on establishing strategic partnerships as "moderate" or "high." "I don't know" was the most popular answer (53%, $n = 46/86$) when asked if the respondents were aware of any strategic partnerships formed between the company and other IMI partners. Of the remaining, slightly more said yes (26%, $n = 22/86$) than no (20%, $n = 17/86$).

Most people (81%, $n = 70/86$) did report meeting new people internally at their own company and 93% ($n = 80/86$) reported meeting new people from different companies. Around 78% ($n = 67/86$) of respondents also reported establishing new long-term relationships with academic institutions, SMEs, Biotechs and patient organizations and of those 67% ($n = 45/67$) reported forming one to five new long-term relationships.

3.5.2. Non-EFPIA

All respondents reported meeting new people from other organizations and nearly half also met new people in their own organizations (43%, $n = 18/42$). Some of the impacts resulting from these new connections are presented in Figure 4. The most common type of collaboration arising from these connections has been with academic partners, followed by EFPIA partners and then SMEs. Sharing of data and joint publications with academic partners were the most frequently stated activities with academic partners (71%, $n = 30/42$ and 76%, $n = 32/42$ respectively). A third of respondents (31%, $n = 13/42$) had interacted with a regulatory or health technology assessment (HTA) body in relation to IMI ND research as a direct result of participation in IMI projects.

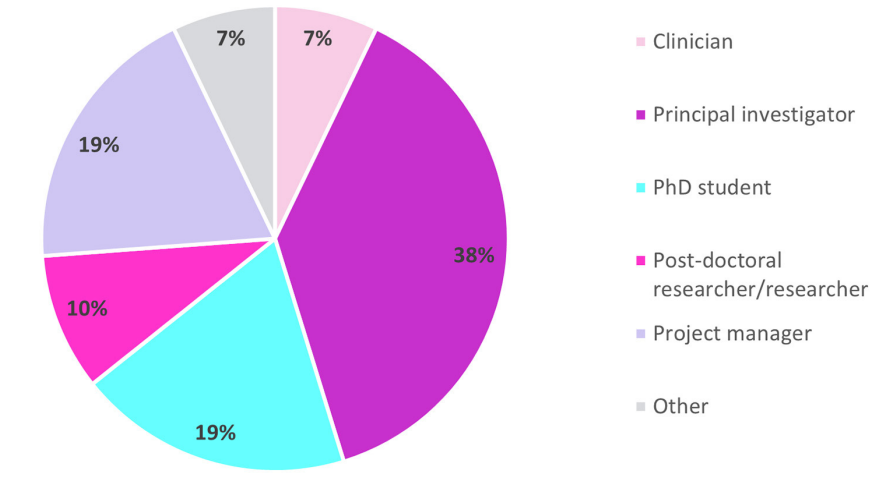

FIGURE 1
Non-EFPIA survey question assessing respondents job role. Respondents selected from Principal Investigator, post-doctoral researcher, clinician, PhD student, project manager, technician, or other. $N = 42$.

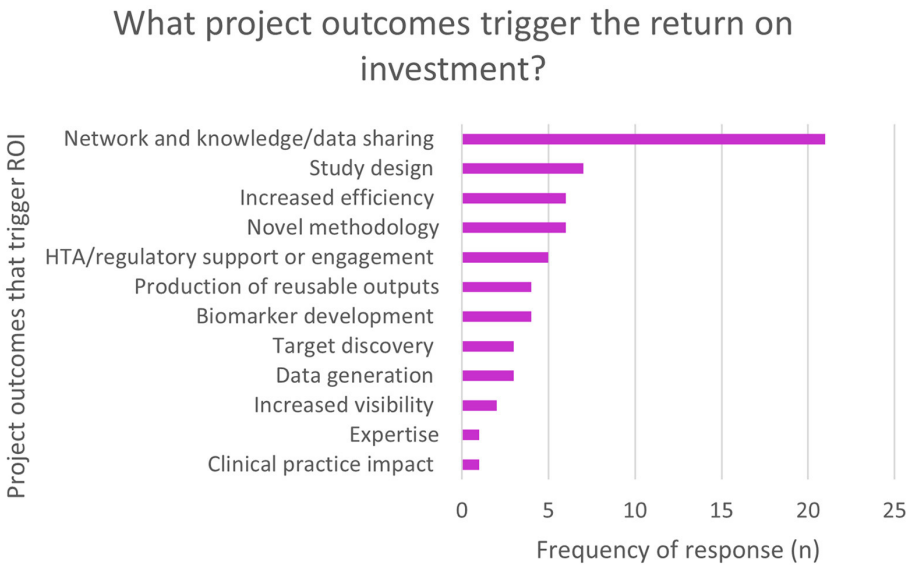

FIGURE 2
EFPIA survey question asking about economic impact. Respondents rated the return on investment in terms of increased efficiency, acceleration of processes, new knowledge etc., and were then asked to elaborate on what project outcomes triggered the return on investment. This figure shows these themes. $N = 56$ for respondent who used free text to detail the project outcomes.

3.6. Individual impact

3.6.1. EFPIA

The reported degree of impact on individuals' daily tasks varied, where 30% ($n = 26/86$) chose "some" or "high" impact and 21% ($n = 18/86$) chose 'no impact' while the remainder were neutral. Overall, 38% ($n = 33/86$) said they do use new tools/datasets/knowledge generated through an IMI project in their daily work whilst 48% ($n = 41/86$) said they did not and 14% ($n = 12/86$) said "I don't know." Some respondents (36%, $n = 31/86$) detailed the impacts on their daily tasks. These are summarized in Figure 5.

In terms of available support, 76% ($n = 65/86$) of respondents said they have or had support from their managers to work on IMI projects while 7% ($n = 6/86$) commented "supportive in theory but no resource commitment or adjustment to other deliverables."

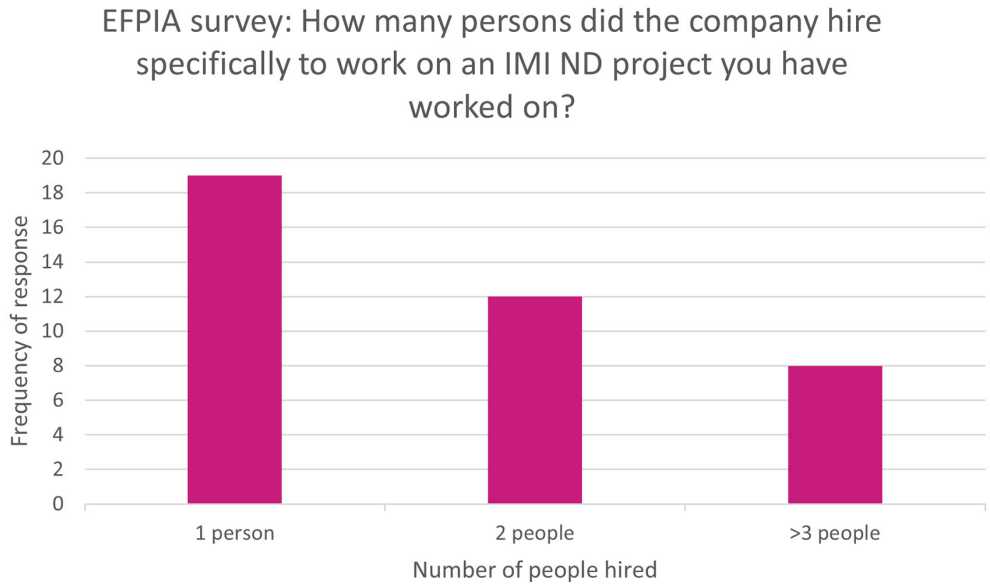

FIGURE 3
EFPIA survey question asking about number of new recruits to IMI ND projects. Respondents were asked "how many persons did the company hire specifically to work on an IMI ND project you have worked on?" $N = 39$ respondents who indicated there had been hires specifically for the IMI ND project. These were grouped into 1, 2, or more than 3.

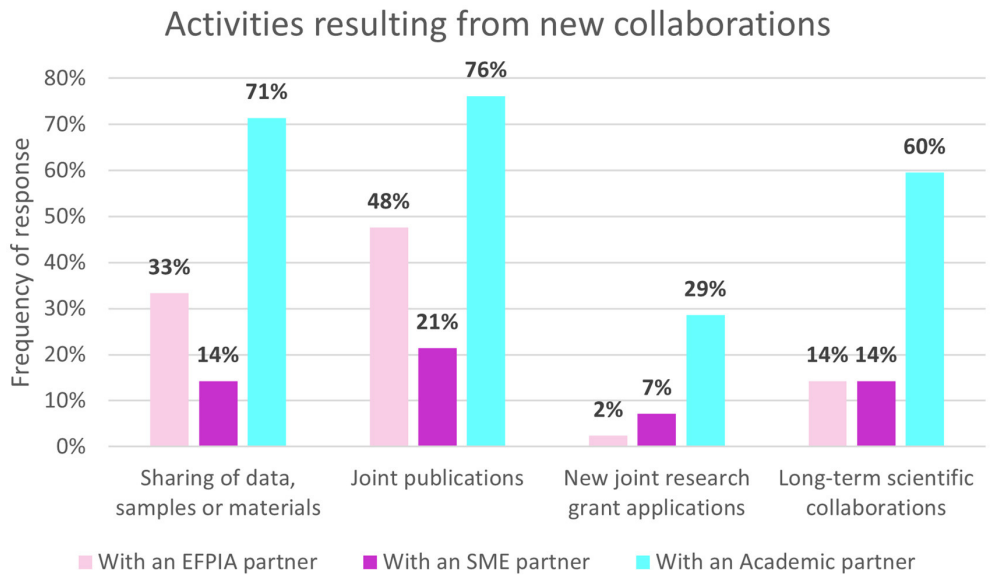

FIGURE 4
Non-EFPIA survey question assessing new collaborations. Respondents were asked "did these new collaborations result in" and could select from: sharing of data, samples or materials, joint publications, new joint research grant applications, long-term scientific collaborations. Respondents indicated whether these were: with an EFPIA partner, an SME partner, academic partner or there was no type of collaboration. $N = 42$.

Additionally, 60% (n = 52/86) of respondents said they received appreciation from their employer for working on IMI projects. In terms of resources, 48% (n = 41/86) of respondents said they did have sufficient resources and time to fulfill their assigned tasks, 44% (n = 38/86) who said they were not sufficiently resourced.

Overall, 81% (n = 70/86) of respondents detailed how IMI had impacted their skillset as shown in Table 1. Furthermore, 81% (n = 70/86) agreed that IMI had expanded their scientific horizons and of these 76% (n = 53/70) specified how, as detailed in Table 2.

When all respondents were asked if any new opportunities came their way directly or indirectly through participation in an IMI project, 53% (n = 46/86) responded with "no," 35% (n = 30/86) responded with "yes" and 12% (n = 10/86) responded with "I don't know."

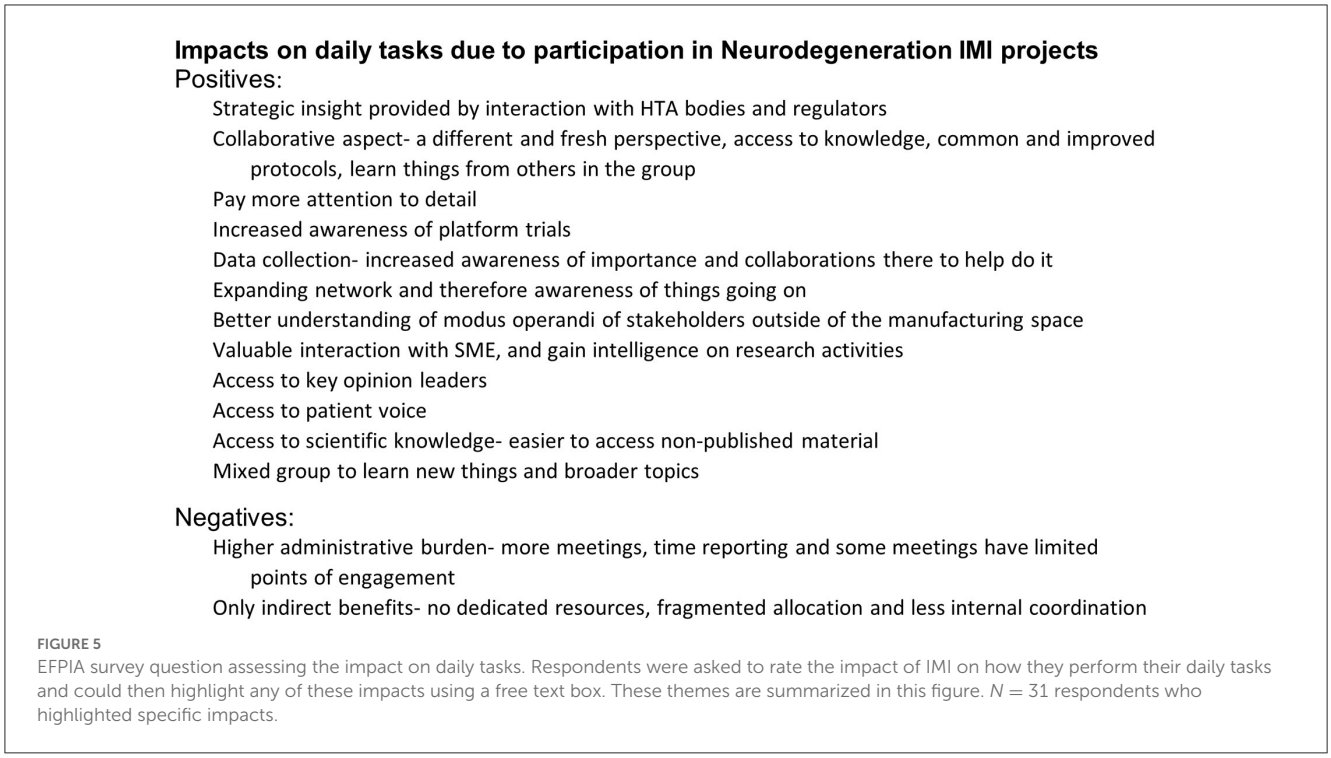

FIGURE 5
EFPIA survey question assessing the impact on daily tasks. Respondents were asked to rate the impact of IMI on how they perform their daily tasks and could then highlight any of these impacts using a free text box. These themes are summarized in this figure. $N = 31$ respondents who highlighted specific impacts.

TABLE 1 Themes and their frequencies when asked how IMI projects had impacted skill set.

Theme describing how IMI has improved skill set	Frequency (%)*
Collaboration for problem solving/networking/communicating externally/project management	46 (66%)
Improved understanding of neurodegenerative disease field/current data and issues	17 (24%)
Knowledge of and access to new techniques/tools/data analytical methods	13 (19%)
Understanding of current research activities	1 (1%)
Not applicable	16 (23%)

*$N = 70$ respondents. Some respondents gave multiple responses.

TABLE 2 Themes and their frequencies when asked how participation in IMI projects had expanded scientific horizons.

Theme describing how IMI has expanded horizons	Frequency (%)*
Broader perspective and understanding alternative approaches by interacting with external colleagues	19 (36%)
Understanding research landscape	14 (26%)
Learning from experts in the field	9 (17%)
Expanding network	7 (13%)
Exposure and access to novel research techniques and technologies	5 (9%)
Knowledge of unpublished data	4 (8%)
Interaction with academic partners	1 (2%)

*$N = 53$ respondents who detailed how. Some respondents gave multiple themes.

3.6.2. Non-EFPIA

On the other hand, 69% ($n = 29/42$) of non-EFPIA respondents felt that involvement in IMI ND projects has resulted in a beneficial impact on their career. The impacts on individuals working on IMI ND projects are shown in Figure 6. These included presenting at scientific conferences and publishing peer-reviewed publications.

Qualitative findings suggest that the benefit of being involved in an IMI ND project may have been particularly useful for early career researchers who, as described by one respondent, were provided with a "unique scientific and networking opportunity."

3.7. Scientific impact

3.7.1. EFPIA

There was greater internal awareness of assets generated through IMI projects that respondents had been involved with compared to projects they were not involved with (Figure 7).

Respondents were not sure if assets were re-used within R&D (45%, $n = 39/86$) or if their company helped in sustaining project assets (69%, $n = 59/86$). Most respondents (53%, $n = 46/86$) were not sure if there is a central database within their company that contains information of assets generated in ND IMI projects, or whether the projects are changing the way that R&D is being conducted (42%, $n = 36/86$).

Overall, 56% ($n = 48/86$) of respondents provided insight into what is possible now, that was not possible before the IMI projects. The resulting key themes are shown in Figure 8.

3.7.2. Non-EFPIA

Most respondents (50%, $n = 21/42$) were unsure if results of the IMI ND projects had impacted the way science/drug development

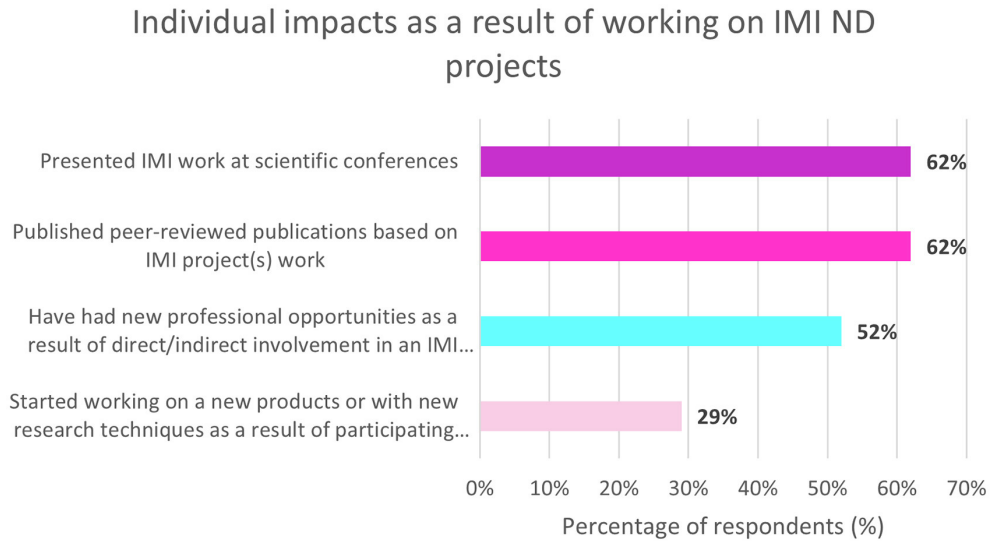

FIGURE 6
Non-EFPIA survey questions assessing the impact on individuals. Respondents were asked four questions: "did any new professional opportunities come your way directly/indirectly through participation in an IMI project?" (yes/no), "have you started working on any new products or with new research techniques as a result of participating in IMI projects?" (yes/no), "have you published any peer-reviewed publications based on your work in IMI projects?" (yes/no) and "did you present any of your IMI project work at scientific conferences?" (yes/no). $N = 42$.

FIGURE 7
EFPIA survey questions assessing asset knowledge. Respondents were asked "how well are assets generated through IMI projects you were involved in, within your company?" (shown in light pink) and "how well are assets generated through IMI projects you were not involved in, within your company?" (shown in dark pink). Rating scale from 1 (not at all known) to 5 (well known). $N = 86$.

is being conducted. Of the remaining, equal proportions said "yes" and "no" (26%, $n = 11/42$ and 24%, $n = 10/42$, respectively).

Examples given of the changes to science/drug development due to the results of IMI projects included:

- Advances to and implementation of new technologies.
- More focused work e.g., focus on a digital biomarker, or greater focus on multiple targets.
- More rigorous processes.
- More integrated approaches.
- Higher level and more global thinking.
- Highlighted challenges in using multiple technologies with physically impaired samples.
- Project results will be used to inform future work.

The majority of respondents were aware of assets from other projects with 60% ($n = 25/42$) aware of "a few" and 14% ($n = 6/42$) aware of "many." Only a quarter

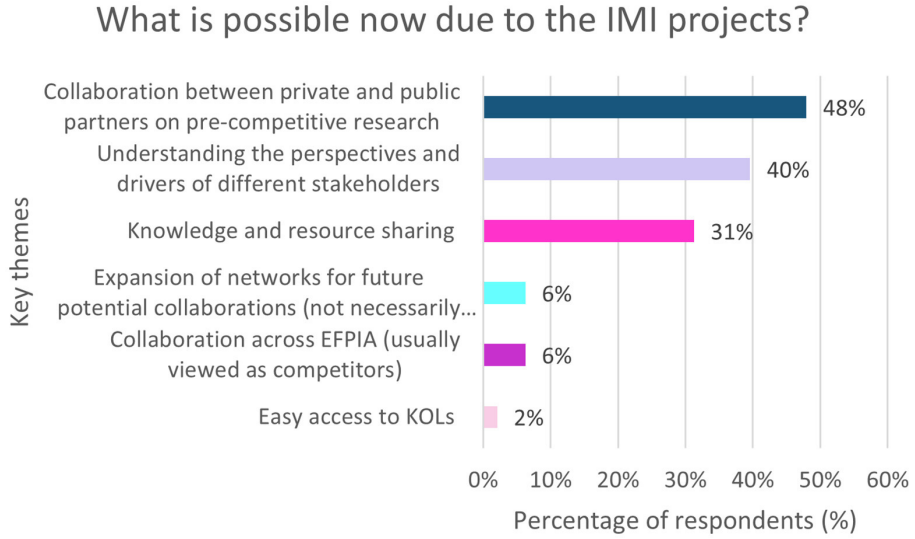

FIGURE 8
EFPIA survey question asking "what is possible now, that wasn't possible before these IMI projects?" This free text question was analyzed by theme which are summarized in this figure. *N* = 48 respondents who answered this question. KOL, Key Opinion Leader.

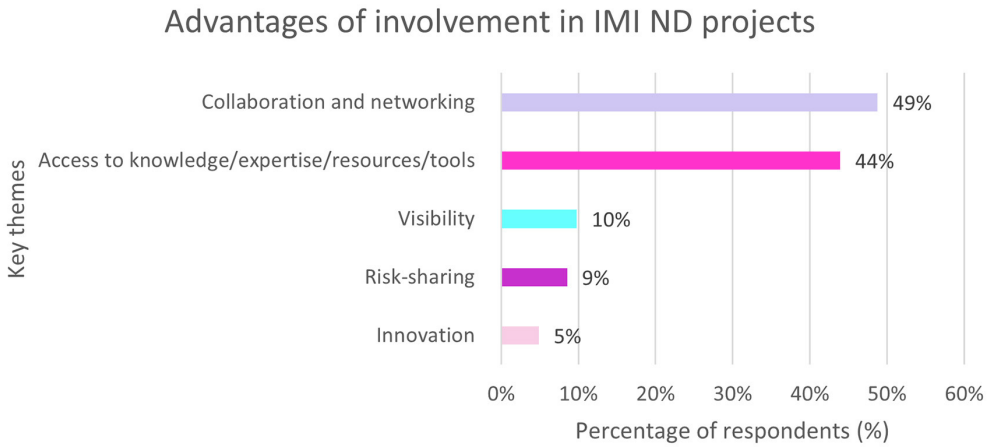

FIGURE 9
EFPIA survey question assessing the advantages of involvement in IMI ND projects. Respondents were asked to describe the main advantage of their company participating as EFPIA partner in IMI. The themes were analyzed and summarized in this figure. *N* = 82 respondents who answered this question.

(26%, $n = 11/42$) of respondents were unaware of other projects' assets.

The majority (93%, $n = 39/42$) of respondents had not received requests for assets from other organizations.

3.8. Regulatory and policy impact

This was only assessed in the EFPIA survey.

Respondents were unsure if the results of the projects had an impact on regulatory practice (48%, $n = 41/86$) with similar proportions selecting yes and no (26%, $n = 22/86$ and 27%, $n = 23/86$, respectively).

3.9. Patient impact

3.9.1. EFPIA

This area asked whether the projects had brought science closer to patients and the general public. Of respondents 40% ($n = 34/86$) selected "yes."

3.9.2. Non-EFPIA

Overall, similar proportions were either unsure (48%, $n = 20/42$), or believed (43%, $n = 18/42$) the IMI ND projects had successfully brought science and patients and the public closer together. One respondent noted that whilst this had not

happened yet, there was a vision to do so once more solid results were available.

Those who felt that the IMI ND projects had brought science and patients and the public closer together, felt it did so through:

- Putting Patient and Public Involvement and Engagement (PPIE) at the core of activities, including study design and communication.
- Having high levels of contact with patients and patient representatives.
- Ongoing and wide dissemination of results.
- Outreach activities such as small group meetings, newsletters, conferences, public discussions and seminars.

3.10. Societal impact

3.10.1. EFPIA

In this section, respondents were asked if the general public and participants had been involved in the research, if it had given them a voice, better informed the public on ongoing research and results and paved the way for new patient-relevant treatment modalities. The most popular responses were "neutral" or "some impact" (37%, $n = 32/86$, and 35%, $n = 30/86$, respectively).

3.10.2. Non-EFPIA

Of non-EFPIA respondents, 78% ($n = 33/42$) reported either "moderate" or "high" impact when asked if the general public and participants had been involved in the research and if it had given them a voice.

3.11. Public health impact

3.11.1. EFPIA

In terms of impact on public health, 14% ($n = 12/86$) said yes, 55% ($n = 47/86$) selected "I don't know," 31% ($n = 27/86$) said no.

3.11.2. Non-EFPIA

The majority of respondents (60%, $n = 25/42$) were unsure if the outputs from the IMI project(s) they worked on had an impact on public health, while 24% ($n = 10/42$) felt they did and 17% ($n = 7/42$) felt they did not. Two respondents thought that whilst they had not had an impact on public health yet, they would in the future.

Examples of impacts on public health reported by respondents included:

- Amyloid Positron Emission Tomography (PET) becoming routine in clinic.
- Possible new guidelines for application of digital health tools in mobility disorders.
- A new hypothesis based on IMI findings currently being tested clinically.
- Increased outreach, interest and knowledge including a number of peer-reviewed publications.

FIGURE 10
Non-EFPIA survey question assessing the advantages of involvement in IMI ND projects. Respondents were asked "from your experience, what were the main advantages and disadvantages of participating in an IMI project?" This figure shows the advantages, and the disadvantages are shown in Figure 12. The results were analyzed thematically. Larger font size indicates more frequent mentions. $N = 33$.

3.12. Advantages of involvement in IMI projects

3.12.1. EFPIA

Of the EFPIA respondents 95% ($n = 82/86$) felt that there were advantages associated with being involved in IMI ND projects. Almost half of respondents (49%, $n = 40/82$) cited "collaboration and networking" closely followed by "access to knowledge or expertise or resources or tools" (Figure 9).

Examples of advantages respondents gave were:

- "Acquiring and sharing knowledge and tools in a highly collaborative mindset."
- "Improved networking; pre-competitive alignments and collaborations (reduce redundant R&D); boost company image for R&D."
- "Discussions with experts in a specific field to solve rapidly existing experimental difficulties."

3.12.2. Non-EFPIA

Opportunities for networking and collaborations was the most commonly cited advantage of being part of an IMI ND project (see Figure 10). Survey respondents stated that they welcomed the chance to build global relationships, have greater exposure to industry and regulatory bodies and strengthen intra-institute relationships. Another benefit was access to key opinion leaders.

A further area that respondents reported advantages in was within research practices and processes. Involvement in IMI projects was seen to provide access to larger sample sizes, image and data sets, and help improve research structures through sharing of best practice.

3.13. Disadvantages of involvement in IMI projects

3.13.1. EFPIA

Overall, 72% of responders reported disadvantages to being involved in the IMI projects. The most common was the time commitment and administrative burden. See Figure 11.

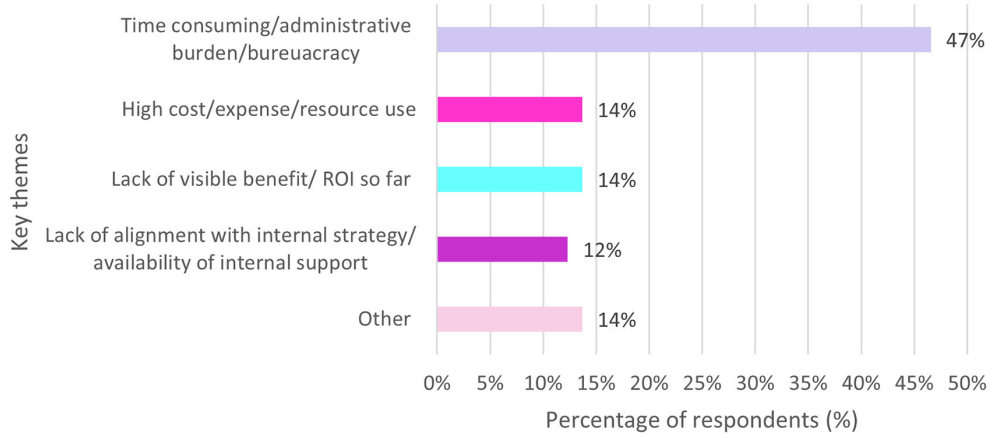

FIGURE 11
EFPIA survey question assessing the disadvantages of involvement in IMI ND projects. Respondents were asked to describe the main disadvantage of their company participating as EFPIA partner in IMI. The themes were analyzed and summarized in this figure. *N* = 62 respondents who answered this question.

FIGURE 12
Non- EFPIA survey question assessing the disadvantages of involvement in IMI ND projects. Respondents were asked "from your experience, what were the main advantages and disadvantages of participating in an IMI project?" This figure shows the disadvantages, and the advantages are shown in Figure 10. The results were analyzed thematically. Larger font size indicates more frequent mentions. *N* = 33.

Examples of disadvantages respondents gave are:

- "Deviation of original plan due to continuous negotiation with public consortium leading to dilute results after 5 years."
- "Requires more effort and time than initially thought it would take to positively contribute to the projects."
- "Workload related to high documentation requirements."

3.13.2. Non-EFPIA

Only a small proportion of respondents (26%, $n = 11/42$) reported disadvantages of participating in an IMI ND project. Bureaucracy, increased workload and complex co-ordination were the most commonly cited disadvantages (see Figure 12). Respondents spoke of the large volume of additional administration required, including significant reporting requirements:

- "HUGE amount of reporting required by IMI, well-above and beyond other H2020 funding schemes." Non-EFPIA survey respondent.

One respondent noted that the work was particularly demanding on SMEs, with no or very low profit.

Respondents felt co-ordination of projects was complex due to the large number of partners involved. Respondents reported that not only did co-ordination of projects require time and effort, but that at times it made delivery difficult because partners were not aligned. Tight timeframes added to this issue, and also made it hard to leverage learnings from data. While some respondents stated the large size of the consortium/projects as an advantage due to the experience and exposure it gave, others saw it as a disadvantage:

- "If too big, these projects become a series of silo projects. My experience with smaller IMI projects is much better than with larger ones"

A small number of respondents commented on what they considered uneven workloads within projects, and one noted the impact of funding allocation on this:

- "EPFIA contributions not clear or not very significant at times (Academic partners seem to be the most involved and put the majority of the effort)."
- "Some partners do much more to advance the project than others but this is not reflected in the amount of funding. So, when partners delay progress due to lack of effort, it is difficult to reallocate funding to a more motivated partner."

4. Discussion

This study, conducted as part of the IMI NEURONET project, has shed light on the perceptions of project partners of the advantages and disadvantages of being involved in these public-private partnership projects. This is the first time this exploration has been undertaken systematically and across the two key

stakeholder groups involved in these projects. Our results showed that the overwhelming advantages to being involved in IMI projects were the networking and collaborative aspects. This was true across both EFPIA and non-EFPIA respondents. It is not a surprising finding since the projects bring together people from different organizations. A bibliometric analysis of IMI research published between 2010 and 2021 found that two thirds of all IMI project papers were co-authored by researchers working in different sectors (12) which evidences the collaborative working. In addition, nearly all respondents reported meeting new people, both internally and externally. This advantage to working in the IMI ND portfolio has previously been cited (5, 13) and fostering radical collaboration between diverse public and private partners was found as a key success in a review of the IMI in 2019 (14). Our finding that the IMI ND projects are impactful in helping forge collaborations aligns with literature on this topic.

Unsurprisingly, the unanimous disadvantage to being involved in the projects was the burden of extra meetings, administration, increased workload and complex coordination. This was to be expected given the number and range of partners. Overall, respondents did not feel they had sufficient time to dedicate to the projects and a widespread comment was that even in cases where their manager or employer was supportive of their involvement, their normal workload was not adjusted. This is an area that should be considered in future projects and should be an important priority for funding bodies to address. This is not the first time this drawback has been documented (5, 14). This administrative burden is potentially jeopardizing the sustainability of interest in participating in these projects particularly for SMEs with limited head counts and administrative capacities and should be a key consideration going forward.

Both EFPIA and non-EFPIA respondents felt that involvement in the IMI ND projects had a clear impact on their organizations including strategic objectives and ways of working overall. However, awareness of assets and project outcomes was low among EFPIA respondents. Only 25% thought project assets were fairly well-known in their company and over half were unaware of a central database detailing project assets. This question assessed awareness of the NEURONET Knowledge Base (15) which had just expanded at the time of the survey. It is a platform that brings together key information and is designed to inform and facilitate similar new projects. This is not the first-time asset awareness has been found to be an area for improvement. This same recommendation was made by a group of experts tasked with evaluating phase one of IMI and performing an interim evaluation of the ongoing IMI2 initiative. One of their conclusions was that access to project outcomes should be broadened (16). Given the IMI objectives of speeding up drug development, it is essential for EFPIA companies to adopt the knowledge generated by projects, if the portfolio is to achieve impact.

Asset awareness did appear to be higher among non-EFPIA respondents. However, it may have been the phrasing of the question that led to this discrepancy. Non-EFPIA respondents were asked about their personal awareness of different assets whereas EFPIA respondents were asked about the awareness within their company. Asset awareness and sharing is a key success factor for PPPs (9). There are different models to achieve this. For example, The Division of Signal Transduction Therapy (DSTT) is a collaboration of six pharmaceutical companies and 20 academic research teams that share all unpublished results, along with reagents, technology and technical know-how. They credit this set up with causing them to publish more effectively (3) and the long-standing collaboration has led to the development and clinical approval of more than 40 drugs (3, 9). However, intellectual property (IP), and the incentives and laws surrounding this are a barrier to such transparent knowledge-sharing (7, 17) and a field of literature exists specifically looking at mechanisms to allow this whilst managing IP. This is arguably less of a concern in the pre-competitive space, which is where the IMI operates. On the basis of our findings, further research should be conducted to concretely determine whether asset awareness differs between these audiences. This would help develop appropriate and effective approaches to increase awareness.

A surprising result of the EFPIA survey was the conflict between whether IMI projects did or did not have an impact on R&D. When asked about changes to R&D through organizational impact the majority of respondents agreed that there were aspects done differently, and one respondent specified that a reduction in redundant R&D was an advantage to being involved in the project. Removing duplication of effort is a perceived advantage of PPPs (3). However, the results were reversed when asked a similar question as part of assessing scientific impact. A recent review demonstrates, with many examples, that PPPs in drug development and discovery do positively impact R&D (9) suggesting a positive impact on R&D is possible. It's important to establish if this survey finding is a true finding, or an artifact of the survey. A previous report examining the socio-economic impact of IMI1 projects specifically found that the projects were changing the manner in which new medicines are being developed, improving the R&D research infrastructure and streamlining the R&D (18). Impact on R&D is a key result considering the NEURONET objectives and further research should clarify if the combined IMI ND project portfolio is impacting R&D.

IMI ND projects are expected to facilitate, among other objectives, the development of new treatments and therefore provide patient impact. However, respondents' perception of this patient impact was uncertain and suggests that patient engagement in the projects might not be optimal. This notion is supported by a review of 75 IMI projects in 2017 which found that European or international patient associations were participating in only 16 of these projects (21%) (19). More could be done to include patients, ensure that the impact for patients is apparent and highlight the value of involving, engaging and communicating with patients at all stages of the pipeline. The authors of the review (19) identified 3 levels at which patient participation occurs: supporting with the dissemination of project results, providing a patient perspective from the start of the project or having a patient led project. The example of a patient-led project used by the authors was EUPATI which trained 100 patients in all aspects of medicine development and on developing an extensive, multi-language training toolbox to be rolled out across Europe (20). The levels of patient engagement outlined in the review could be a framework to increase patient involvement in IMI ND projects.

When the EFPIA respondents were asked about policy impact in terms of regulatory practice most stated they did not know. This could be linked to the types of projects that respondents were working on. The IMI ND projects span the whole pre-reimbursement pathway and whilst there are examples of projects focused on the HTA and regulatory end of the pipeline, many projects are pre-clinical and would not be expected to achieve a high impact on regulatory practice or public health. The long timelines in the life sciences and issues relating to translation of project results from bench to bedside are well-recognized challenges (5, 7, 14, 19), however IMI1 projects have been shown to result in downstream socio-economic impact (18). The review of publications also eludes to the projects having an impact at all stages of the product development timeline (12). This found that the IMI research was wide ranging from basic biological research to clinical practice. This suggests that whilst the projects in the IMI ND portfolio tend to operate upstream, they are likely to have impact further downstream including socio-economic impact and potentially impact on policy, regulatory and public health practice. Translating and aligning scientific results with regulatory requirements is a focus of IMI (21).

Overall, EFPIA staff reported spending less time on the IMI projects than the other partners involved. This could be expected as EFPIA partners provide financial input in addition to their staff time and may have multiple staff working on each project, therefore when surveyed each one reports less working time. It might be believed among non-EFPIA respondents that impact on career progression and opportunities is proportional to time spent on project tasks. This could also help in part explain why non-EFPIA respondents spent a greater number of weekly hours working on the projects.

4.1. Limitations

There were a few limitations in conducting this work. The original ambition was to directly compare responses from the EFPIA and non-EFPIA surveys to understand differences in perceived impact between the two audiences. However, in tailoring the non-EFPIA survey to be appropriate for the audience, the questions that assessed the same areas of impact had slightly different wording and this may have led to different interpretation in some areas. This meant it was only possible to make broad interpretations of the differences rather than direct comparisons. In addition, the adapting of the survey was done using assumptions by the working group about relevancy of themes for a non-EFPIA audience. Whilst this group had input from "non-EFPIA" members, it's possible non-EFPIA organizations could have provided insight into economic impact.

We conducted descriptive analyses but this does not allow conclusions about population parameters. A suggestion would be to perform inferential analyses with these survey data to allow conclusions about confidence, significance and any trends or correlations.

Other limitations relate to how extensively the areas of impact were explored. Lots of insight could be gleaned from the questions assessing the impact on the individual but only one question was asked to understand the impact on patients. Similarly, some questions could have fitted under multiple areas of impact. Finally, it was not possible to calculate a response rate because the number of those who received the survey was not recorded and recipients were asked to forward it to their relevant colleagues without the ability to track the number of recipients.

5. Conclusion

Overall, these surveys provided rich insight into the perceived impact of being involved in IMI ND projects. They revealed clear areas of impact and key advantages and disadvantages which were supported by the literature. Many were universal across both EFPIA and non-EFPIA audiences such as the benefit to collaborations and networking and the organizational impact. The unanimous disadvantage to being involved in the IMI projects was the extra administrative burden and time in meetings.

There were differences between the EFPIA and non-EFPIA respondents in terms of time spent on the project and asset awareness. Generally, the non-EFPIA respondents appeared to be more aware of project assets that had been generated. Further research should establish if this is a true difference to enable the design of appropriate communication strategies. More widespread access to the NEURONET Knowledge Base should help in growing the understanding and breadth of assets available. Further research should also clarify the impact of the IMI ND projects on R&D since this is a key area of impact and the survey gave mixed results.

Patient engagement and involvement is another area that requires focus. The survey indicated that respondents were uncertain of the patient impact and therefore more could be done to involve patients and highlight the value of including patients at every step of the project.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

CH analyzed the data from the EFPIA survey and drafted the manuscript. FS developed and conducted the non-EFPIA survey along with LK who also developed the EFPIA survey and

analyzed the data from the EFPIA survey. KC analyzed the non-EFPIA survey data with support from FS and CH. LP, DD, LS, and CD coordinated the project. All authors provided critical comments on the manuscript and approved the final version of the manuscript.

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Conflict of interest

CH, FS, KC, and DD were employed by the National Institute for Health and Care Excellence. CD and LK were employed by SYNAPSE Research Management Partners. AB was employed by Alzheimer Europe. LP was employed by Sanofi. LS was employed by Janssen Pharmaceuticals NV.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1140722/full#supplementary-material

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Donald C. Lo,
National Center for Advancing Translational Sciences (NIH), United States

REVIEWED BY
Linus Jönsson,
Karolinska Institutet (KI), Sweden

*CORRESPONDENCE
Anna-Katharine Brem
✉ katy.brem@gmail.com

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Digital endpoints in clinical trials of Alzheimer's disease and other neurodegenerative diseases: challenges and opportunities

Anna-Katharine Brem[1,2]*, Sajini Kuruppu[1], Casper de Boer[3,4], Marijn Muurling[3,4], Ana Diaz-Ponce[5], Dianne Gove[5], Jelena Curcic[6], Andrea Pilotto[7,8,9], Wan-Fai Ng[10,11], Nicholas Cummins[12], Kristina Malzbender[13], Vera J. M. Nies[14], Gul Erdemli[15], Johanna Graeber[16], Vaibhav A. Narayan[17], Lynn Rochester[18,19], Walter Maetzler[20] and Dag Aarsland[1,21] on behalf of the RADAR-AD Consortium

[1]Department of Old Age Psychiatry, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [2]University Hospital of Old Age Psychiatry, University of Bern, Bern, Switzerland, [3]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC Location VUmc, Amsterdam, Netherlands, [4]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, Netherlands, [5]Alzheimer Europe, Luxembourg, Luxembourg, [6]Novartis Institutes for Biomedical Research (NIBR), Basel, Switzerland, [7]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [8]Laboratory of Digital Neurology and Biosensors, University of Brescia, Brescia, Italy, [9]Neurology Unit, Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia Hospital, Brescia, Italy, [10]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom, [11]NIHR Newcastle Biomedical Research Centre and Clinical Research Facility, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [12]Department of Biostats and Health Informatics, King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, United Kingdom, [13]Gates Ventures, Kirkland, WA, United States, [14]Foundation Lygature, Utrecht, Netherlands, [15]Novartis Pharmaceuticals Corporations, Cambridge, MA, United States, [16]Institute of General Practice, University Medical Center Schleswig-Holstein, Kiel University, Kiel, Germany, [17]Davos Alzheimer's Collaborative, Geneva, Switzerland, [18]Faculty of Medical Sciences, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom, [19]National Institute for Health and Care Research (NIHR) Newcastle Biomedical Research Centre (BRC), Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [20]Department of Neurology, University Hospital Schleswig-Holstein and Kiel University, Kiel, Germany, [21]Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

Alzheimer's disease (AD) and other neurodegenerative diseases such as Parkinson's disease (PD) and Huntington's disease (HD) are associated with progressive cognitive, motor, affective and consequently functional decline considerably affecting Activities of Daily Living (ADL) and quality of life. Standard assessments, such as questionnaires and interviews, cognitive testing, and mobility assessments, lack sensitivity, especially in early stages of neurodegenerative diseases and in the disease progression, and have therefore a limited utility as outcome measurements in clinical trials. Major advances in the last decade in digital technologies have opened a window of opportunity to introduce digital endpoints into clinical trials that can reform the assessment and tracking of neurodegenerative symptoms. The Innovative Health Initiative (IMI)-funded projects RADAR-AD (*Remote assessment of disease and relapse—Alzheimer's disease*), IDEA-FAST (*Identifying digital endpoints to assess fatigue, sleep and ADL in neurodegenerative disorders and immune-mediated inflammatory diseases*) and Mobilise-D (*Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement*) aim to identify digital endpoints relevant for neurodegenerative diseases that provide reliable, objective, and sensitive

evaluation of disability and health-related quality of life. In this article, we will draw from the findings and experiences of the different IMI projects in discussing (1) the value of remote technologies to assess neurodegenerative diseases; (2) feasibility, acceptability and usability of digital assessments; (3) challenges related to the use of digital tools; (4) public involvement and the implementation of patient advisory boards; (5) regulatory learnings; and (6) the significance of inter-project exchange and data- and algorithm-sharing.

KEYWORDS

Alzheimer's disease, Parkinson's disease, Huntington's disease, neurodegenerative diseases, dementia, digital biomarker, remote measurement technologies, digital health technologies

1. Introduction

Digital endpoints in clinical trials are being investigated increasingly in large-scale international projects. The rapid advancement of technological developments allows entirely new approaches to assessing activities of daily living (ADL), sleep and fatigue, motor, cognitive, social, neuropsychiatric, and autonomous body functions with potential for both trials and clinical practice. The appeal lies in the objective, immediate and continuous measurement in both clinical and home settings, the reduction of visits to research or clinic facilities, the accessibility for under-served populations, the potential for better stratification and more personalised therapies, and the possibility to support otherwise time-intense clinical decisions with Artificial Intelligence (AI). This is of specific importance for Alzheimer's disease (AD), but also other neurodegenerative diseases, such as Parkinson's disease (PD) and Huntington's disease (HD), with a predominantly slow progression over years as well as cognitive impairment and fluctuations, which reduce the validity of data from self-rated or one-time assessments.

Functional decline is a significant indicator of progression of neurodegenerative diseases. A range of questionnaires have been developed to assess ADL (1). However, many of these instruments lack sensitivity to change in early stages of a disease and therefore have a limited utility as outcome measures in clinical trials (2, 3). This is of specific importance considering recent developments in disease-modifying drugs for the treatment of AD, such as aducanumab and lecanemab (4) that are targeting early cognitive impairment and emphasise the need for highly sensitive methods. Similar restrictions apply to standard mobility and neuropsychological testing and the query of social skills, sleep, fatigue, neuropsychiatric symptoms, and autonomous body functions with self- and informant-rating questionnaires. Standard assessments are intermittent, costly, and partly rely on subjective information, which is especially problematic in later stages of a neurodegenerative disease. The common goal of the Innovative Health Initiative (IMI)-funded projects RADAR-AD, IDEA-FAST and Mobilise-D is to define digital endpoints relevant for neurodegenerative diseases that provide reliable, objective, and sensitive evaluation of disability, ADL, and health-related quality of life.

RADAR-AD (EC Grant No.806999; www.radar-ad.org) aims to identify and validate remote monitoring technologies (RMTs) to assess functional impairment in all stages of Alzheimer's disease. The study includes wearables and smartphone apps in the main study ($n = 232$) and passive at-home sensors in a sub-study ($n = 45$). The RMTs measure a wide range of cognitive and functional domains, including spatial navigation, activity, sleep, speech, driving behaviour, and gait (5).

IDEA-FAST (EC Grant No. 853981; www.idea-fast.eu) aims to identify digital parameters in patients with PD and HD, and immune-mediated disorders, which are related to fatigue, sleepiness, and sleep quality. A pilot study (6, 7) has informed the design of a larger clinical observational study using different devices concurrently to capture data on ADL-related activities, sleep, physiological and cognitive/psychological variables. In the latter study, up to 2000 participants (PD $n = 500$; HD $n = 200$) will be recruited at up to 24 sites across Europe.

Mobilise-D (EC Grant No. 820820; www.mobilise-d.eu) (8) aims to validate a suite of digital mobility outcomes to directly monitor mobility performance continuously over a 7 day duration using a single wearable device in PD ($n = 600$) and other diseases associated with mobility impairment (chronic obstructive pulmonary disease, multiple sclerosis, proximal femoral fracture) (9, 10).

In this article, we will draw from the findings and experiences of these different IMI projects in discussing (1) the value of remote technologies to assess neurodegenerative diseases; (2) feasibility, acceptability and usability of digital assessments; (3) challenges related to the use of digital tools; (4) public involvement and the implementation of patient advisory boards to guide clinical trials in terms of protocol design, ethical issues, and selection and applicability of digital tools; (5) regulatory learnings; and (6) the significance of inter-project exchange and data- and algorithm-sharing (Figure 1).

2. The value of remote technologies to assess neurodegenerative diseases

Technological advances in the last decade opened a window of opportunity to introduce digital endpoints into clinical trials. RMTs could provide a useful, objective way to measure decline by collecting data that correspond to various functional domains that are clinically relevant. They assess functional ability either passively (i.e., not requiring any interaction with the device, such as is the case with gait measures) or interactively (i.e., requiring an active interaction with the device such as when assessing functional abilities involving cognition). The benefit of RMTs as compared to standard assessments, is that they

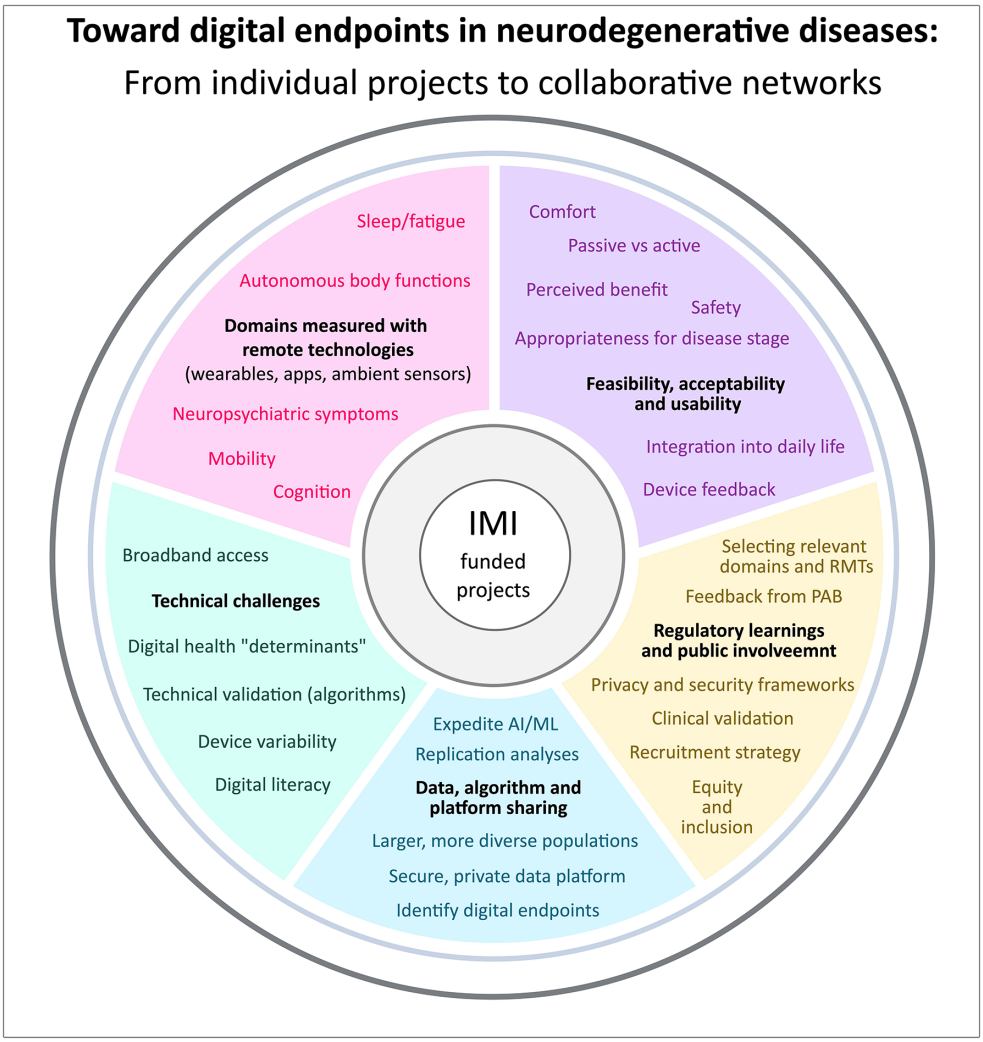

FIGURE 1
Findings and experiences of RADAR-AD, IDEA-FAST, and Mobilise-D in (1) remote technologies to assess neurodegenerative diseases, (2) feasibility, acceptability and usability of digital assessments, (3) challenges related to the use of digital tools, (4) regulatory learnings and public involvement, and (5) data, algorithm and platform sharing.

are objective and can collect data in the real world continuously. They are ideally placed to potentially measure subtle functional changes that are prevalent among individuals in the early, preclinical stages of neurodegenerative diseases, where current methods of cognitive assessments lack the necessary sensitivity (11) and to continuously track changes during the course of a disease. The RMTs used in the different consortia are listed in Table 1.

In the three consortia, different functional domains were measured. Mobility, for example, was evaluated in various ways within the IMI projects. Mobilise-D applied both supervised (in the presence of study staff) and unsupervised testing using a standardised protocol. In addition to that, home mobility was evaluated using an inertial measurement unit (IMU) for 7 days at different time points. In RADAR-AD, mobility was evaluated using a supervised standardised protocol as well, and home mobility using a wrist-worn IMU for 8 consecutive weeks. In both RADAR-AD and IDEA-FAST, heart rate was measured using a wearable. Another functional domain assessed was sleep. IDEA-FAST and RADAR-AD both made use of an app to actively collect data on sleep, asking the participants daily about their fatigue, sleep pattern and quality. Moreover, sleep was measured passively: RADAR-AD made use of a portable EEG device, which a subset of participants wore every night for a month, while IDEA-FAST used a bed sensor with a force-sensitive piezo-electric film, placed under the mattress. Cognition has been addressed in a supervised standardised way in all consortia. Cognitive data was evaluated remotely using several smartphone apps in RADAR-AD and a web-based application of CANTAB in IDEA-FAST and both consortia collected passive information on smartphone use, including keyboard metrics and GPS location tracking.

Future clinical trials will profit from these recent technological developments, which promise improved sensitivity and specificity of endpoint measures, better external validity, and the need of fewer visits to research or clinical facilities and smaller sample sizes due to more detailed datasets per participant.

TABLE 1 Domains assessed in the three IMI-funded consortia RADAR-AD, IDEA-FAST, and Mobilise-D.

	Cohorts	Trial design	Domains assessed	Domains assessed digitally
RADAR-AD	HC $n = 70$ PreAD $n = 38$ ProAD, $n = 65$ MildAD $n = 56$	8 W observation period	• Activities of daily living • Cognitive functions • Sleep quality and fatigue • Life habits • Mobility • Social functioning • Smartphone proficiency • Quality of life • Neuropsychiatric symptoms including depression • Medical history and medication • Physical examination	• Activities of daily living (apps and wearables) • Cognition (apps) • Sleep and circadian rhythm (wearables, sleep EEG) • Mood and fatigue (app) • Mobility SS assessment (IMU) • Mobility US assessment (wearables) • Social (app) • Driving (data logger)
Mobilise-D	PD $n = 600$ MS $n = 600$ COPD $n = 600$ PFF $n = 600$	1 W observation period every 6 M (5 times in total per participant)	• Risk of falls • Cognitive functions • BIA • Fatigue • Disability • Pain • Frailty • Severity of specific conditions	• Mobility SS assessment (6MWT, TUG) • Mobility US assessment (IMU)
IDEA-FAST	HC $n = 200$ PD $n = 500$ IBD $n = 500$ RA $n = 200$ SLE $n = 200$ PSS $n = 200$	1 W observation period every 6 W (4 times in total per participant)	• Sleep quality • Fatigue (mental vs. physical) • Cognitive screening • Disability • Pain • Severity of specific conditions	• Mobility US assessment • Sleep (bed sensors, sleep EEG) • ECG and autonomic function • Fatigue (app) • Cognition (app) • Social (app)

AD, Alzheimer's disease; BIA, body impedance analysis; COPD, Chronic Obstructive Pulmonary Disease; ECG, electrocardiography; EEG, electroencephalography; HC, healthy controls; IBD, Inflammatory bowel disease; IMU, inertial measurement unit; M, months; MildAD, mild-to-moderate AD (dementia, Aβ-positive); MS, multiple Sclerosis; PD, Parkinson's disease; PFF, Proximal Femur Fracture; preAD, preclinical AD (cognitively normal, Aβ-positive); proAD, prodromal AD (mild cognitive impairment, Aβ-positive); PSS, Primary Sjogren's syndrome; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; SS; supervised setting; TUG, timed up and go test; US unsupervised setting; W, week(s); 6MWT, 6 min walking test.

3. Challenges related to the use of digital tools

The use of RMTs can present challenges with respect to a range of aspects including the validity of measurements, related to sensitivity and specificity (e.g., differentiating sensor information in multi-person households), data quality, e.g., choosing the right time granularity (12), data missingness, which is often due to technical and software issues (13), and subsequent analysis. The use of Artificial Intelligence (AI) to combine and analyse RMT signals brings a multitude of challenges itself (14), including privacy and security concerns (15), gaining informed consent (16), and ethical challenges. These can be addressed by creating regulatory frameworks and promoting public-private partnerships (17). Ensuring equity and inclusion when deploying digital tools is another important challenge. Connectivity and broadband access, device variability/obsolescence and digital literacy are "digital determinants of health" that impact equitable access to digital healthcare and the outcomes from and experience with digital tools (18). To date, 37% of the world's population has never used the internet. In the European Union, the percentage of older people (aged 65–74) using the internet varies greatly from 25% in Bulgaria to 94% in Denmark and we face a growing age gap in smartphone ownership in emerging economies around the globe (19). Even if a smartphone or PC is available in a household, access might still be restricted due to financial or technical reasons (20). Digital health studies have developed approaches such as "bring-your-own-device studies" (21), providing funding for internet connectivity, or using sensors that are not (continuously) connected to the internet to help address these challenges. Collocation and sharing of best practices across projects will help address these challenges.

4. Feasibility, acceptability, and usability of digital assessments

It becomes increasingly important to consider the feasibility, acceptance, usability, and ecological validity of digital endpoints in real-world settings. Few studies report on these factors and ageing populations are not well represented in RMT research (22), but are explored in RADAR-AD, IDEA-FAST and Mobilise-D in collaboration with patients and carers. In studies involving wearables and smartphone apps, acceptance to use devices and adherence to protocol are in general positive when they are reported (23, 24). For example, the comfort and

acceptability of a wearable sensor to monitor mobility in the Mobilise-D study was very high (23). However, many studies to date lack information on acceptability, adherence and usability (24). Overall, passive devices/apps requiring little or no interaction with a device show higher feasibility, acceptability and usability than interactive devices and are the most researched to date (25). Research in PD reports that the successful implementation of digital technologies is primarily driven by familiarity with the technology and ease of use, costs, motor symptoms hampering the use, experiencing beneficial effects, and feeling safe whilst using the technology (26). In AD, acceptance and adherence can be facilitated by familiarising participants with the devices and providing personal support, lowering technical demands, co-designing solutions and involving relevant stakeholders, introducing participants to the devices at the earliest stages of the disease, and increasing the perception of effectiveness and safety. Barriers mainly include technology anxiety, system failures, and lack of access (27, 28). However, if these factors are addressed, adherence is generally high (85.7%) in older adults (29).

Some of these barriers became apparent in RADAR-AD. For example, engaging with RMTs led to some participants feeling discouraged, as they acted as a reminder for their declining cognition. Cognitive impairment also led to missing data, e.g., participants removed their wearables before going to bed, meaning sleep hygiene could not be tracked. Study partners are essential when it comes to reducing or overcoming (cognitive) barriers—they help with charging/handling RMTs, provide emotional support, and remind participants to keep wearing/using RMTs. Overall, study partners are vital in the adherence and usability of digital tools in neurodegenerative diseases (Muurling et al., submitted)[1]. In RADAR-AD and IDEA-FAST, participants reported adjustments to daily routines; specifically, acclimating to wearing two wrist-worn wearable devices, using their phone more, and adjusting personal schedules to complete their daily app-based tasks on time. Ergonomic challenges were reported due to the physical design of watches (i.e., watch straps not fitting well or feeling limited in their movements). Similar findings have been collated within multiple systematic reviews on digital tool use in older adults (28, 30, 31). Participants reported individual preferences for the display of the wearable screen (e.g., matching the clock face of their usual watch) and for device feedback (e.g., cognition and activity tracking), which facilitated integration into daily routines. Lack of, or inaccurate device feedback, small screens and small fonts also contributed towards the challenges faced by participants. In the IDEA-FAST pilot study, participants moreover mentioned skin irritations due to adhesive patches, constant worry about the device and insecurities regarding its proper functioning. Also, participants reported being less willing to wear devices that were very visible, complicated to use, or that had to be manipulated at impractical times, e.g., right before sleeping. The roadmap towards translating RMT use from research to clinical practice has to continue to evolve, together with patient and stakeholder involvement, as the benefits and challenges are evaluated (32).

1 Muurling M, de Boer C, Hinds C, Atreya A, Doherty A, Alepopoulos V, et al. and the RADAR-AD Consortium. Feasibility and user experience of remote monitoring in Alzheimer's disease. (submitted)

5. Public involvement and the implementation of patient advisory boards

Public Involvement (PI) is about involving people affected by the condition in all aspects of the research process as partners rather than as research participants (33, 34). PI not only provides the patients' perspective on what research is important and which unmet needs should be addressed, but it is also about understanding and anticipating what aspects of the research may be difficult to manage by the participants, may raise concerns, and how these issues could be addressed. It also involves reflecting about future issues, challenges, and benefits of the project, if and when the results are eventually implemented in the real world. Involving people from minority ethnic groups and other under-served populations is crucial but still remains a challenge (33).

All three consortia involved patients and, in the case of RADAR-AD, also carers in special advisory boards. They provided strategic input to various aspects of consortium activities throughout the projects, including: study protocols and participant-facing documents; digital health technology in general and digital assessments and outcomes in particular; feasibility, usability and acceptability of digital outcome assessment and how it can contribute to improved care; consultation around health technology assessment and regulatory acceptance of digital outcomes; ethical considerations, recruitment and retention strategies; and involvement in promotion activities about the impact and benefits of results. RADAR-AD and IDEA-FAST also collaborated with patient organisations and in IDEA-FAST, two additional groups consisting of patients, consortium members and representatives from patient organisations were formed to develop and review the project activities and to support the design of the two clinical studies.

6. Regulatory learnings

If digital endpoints are to be used in clinical trials aimed to achieve a market authorisation for medicinal products, it is of paramount importance that the endpoints are accepted by the regulatory authorities. In recent years, the use of RMT-based assessments has increased dramatically (35). However, the number of digital endpoint measures that are qualified is still limited (36) and there are no approved primary or secondary digital endpoints for use in clinical trials in AD or PD yet (35, 37). In RADAR-AD, a regulatory strategy was developed early on, including an extensive evaluation of all qualification opinions and advices and scientific advices of the EMA to gain insight in the types of tools that are intended to be used in clinical trials for supporting/submitting applications for obtaining market authorization (registration trials) (36). The EMA recommendations evolved mainly around the relevance, precision, and accuracy of novel endpoints; validation with current gold standards and clinically meaningful legacy endpoints, including those that matter most to patients ("daily-relevant data"); sensitivity and specificity; good compliance and acceptability; and guarantee of optimal data security and privacy. The RADAR-AD consortium had an initial meeting with the Innovation Task Force in 2020 and is currently in the process of having a Qualification Advice discussion with EMA. The Mobilise-D consortium had two consecutive EMA

qualification advices in 2020 (38, 39) and a letter of support was published on the EMA website (40, 41) following each qualification advice. Mobilise-D has furthermore interacted with the Food and Drug Administration (FDA). The IDEA-FAST consortium had two meetings with the EMA between 2020 and 2022. The first meeting with the Innovation Task Force was to discuss the general concepts of developing digital endpoints for fatigue and sleep. The second meeting was to discuss the study design and data analytic plan of a clinical study to identify these digital endpoints which was given general support by the Scientific Advice Working Party.

It is highly recommended for similar consortia to develop a regulatory strategy early on, to ensure that what is being developed will also be accepted in drug trials. It is important to plan for multiple Health Authority meetings utilising Innovation Task Force and EMA Qualification advice meetings as well as meetings with other major Health Authorities, as appropriate. Early advice on study design prior to protocol finalisation/study initiation would be highly desirable. Further development of clear guidance for the use of digital technologies in registration trials could remove some of the regulatory hurdles that currently complicate the development and use of novel improved endpoints (42).

7. The significance of inter-project exchange and data- and algorithm-sharing

To extend and generalise individual project findings and foster deeper understanding of digital outcomes across neurodegenerative diseases, inter-project exchange and data sharing has gained significance. The full value of data collected in large research programmes can only be realised by enabling a wider set of analytics than is possible through individual consortia. This need is only heightened by the current rapidly expanding popularity in AI and Machine Learning research which relies on large datasets. Sharing resources allows for more rapid research to be undertaken, leading to greater efficacy in terms of advancing state-of-the-art than could be otherwise be achieved working on the data in isolation. For example, the sharing of speech data through DementiaBank (43) has enabled a wide range of different machine learning approaches to be compared and assessed on a common database (44). In such a rapidly growing area of research it is also important to conduct replication analysis and robust generalised testing of proposed digital phenotypes. Sharing and open sourcing algorithms enables these vitally important verification steps.

The sharing of data requires careful considerations to preserve the privacy of participants in a manner that not only meets ethical and statutory requirements, but also meets participants' expectations regarding distribution of their data. Entire IMI-projects have developed around this topic. For example, the European Platform for Neurodegenerative Diseases (EPND, www.epnd.org) aims to accelerate the discovery of diagnostics and treatments for neurodegenerative diseases by removing barriers to data and sample sharing (45). This includes sharing of digital data, by building a robust and secure data sharing infrastructure and funding a case study of prospective digital (bio)marker data collection. EPND aims to build connections to existing data platforms and facilitate the discoverability of resources; provide secure, private cloud-based workspaces where researchers can perform and save analyses; collaborate with other permissioned users; and develop ethical, legal, and regulatory principles guiding platform design and discovery and sharing of data.

The access to and reuse of research data generated by Horizon 2020 projects is available through the Open Research Data Pilot (ORD Pilot), which is in line with the FAIR (Findable, Accessible, Interoperable, Reusable) principles[2] and ensures open access to publications and research data (curated and raw data) including access to, e.g., specialised software or software code, algorithms, and analysis protocols. This allows to build on previous research findings, foster collaboration, promote innovation, and improve transparency in research (46). New projects can be greatly strengthened by reusing infrastructure, such as RADAR-base, and sharing algorithms between consortia that use similar RMTs, such as RADAR-CNS, in the case of RADAR-AD.

We argue that sustainability should be plannable and funded beyond the duration of a project, ideally via IMI-funded platforms, to guarantee a lasting impact and allow following projects to profit from the large data volumes produced by RMTs, previous experiences, including cross-learning about device selection and barriers/facilitators of using digital health technology, especially for studies that are targeting similar demographics and conditions.

8. Conclusion

Technological advances and collaboration between IMI-funded and other consortia bring new opportunities to develop and introduce digital endpoints into clinical trials that can revolutionise the assessment and tracking of neurodegenerative symptoms. The digitalization of endpoints allows for objective, immediate and continuous measurement in both clinical and home settings, the reduction of visits to research or clinic facilities, greater accessibility for under-served populations, better stratification and more personalised interventions, and AI-supported clinical decisions.

RADAR-AD consortium

Dag Aarsland, Halil Agin, Vasilis Alepopoulos, Alankar Atreya, Sudipta Bhattacharya, Virginie Biou, Joris Borgdorff, Anna-Katharine Brem, Neva Coello, Pauline Conde, Nick Cummins, Jelena Curcic, Casper de Boer, Yoanna de Geus, Paul de Vries, Ana Diaz, Richard Dobson, Aidan Doherty, Andre Durudas, Gul Erdemli, Amos Folarin, Suzanne Foy, Holger Froehlich, Jean Georges, Dianne Gove, Margarita Grammatikopoulou, Kristin Hannesdottir, Robbert Harms, Mohammad Hattab, Keyvan Hedayati, Chris Hinds, Adam Huffman, Dzmitry Kaliukhovich, Irene Kanter-Schlifke, Ivan Koychev, Rouba Kozak, Julia Kurps, Sajini Kuruppu, Claire Lancaster, Robert Latzman, Ioulietta Lazarou, Manuel Lentzen, Federica Lucivero, Florencia Lulita, Nivethika Mahasivam, Nikolay Manyakov, Emilio Merlo Pich, Peyman Mohtashami, Marijn Muurling, Vaibhav Narayan, Vera Nies, Spiros Nikolopoulos, Andrew Owens, Marjon Pasmooij, Dorota Religa,

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Gaetano Scebba, Emilia Schwertner, Rohini Sen, Niraj Shanbhag, Laura Smith, Meemansa Sood, Thanos Stavropoulos, Pieter Stolk, Ioannis Tarnanas, Srinivasan Vairavan, Nick van Damme, Natasja van Velthogen, Herman Verheij, Pieter Jelle Visser, Bert Wagner, Gayle Wittenberg, and Yuhao Wu.

Mobilise-D consortium

Full membership of the Mobilise-D consortium is available on the website http://mobilise-d.eu/wp-content/uploads/2023/06/v9-logos_06.17.2022_Mobilise-D-consortium-members-names.pdf.

IDEA-FAST consortium

Wan-Fai Ng, Christopher Bull, John Isaacs, Chris Lamb, Alison Yarnall, Lynn Rochester, Silvia Del Din, Chloe Hinchliffe, David Halliday, Ashur Rafiev, Bing Zhai, Dan Jackson, Peter Gallagher, Victoria MacRa, Leigh Denley, Ellen Silva, Philip Brown, Helen Gallon, Sean Scott, Phillip McGrouther, Dean Miller, Darren Storey, Lee Briton, Walter Maetzler, Kirsten Emmert, Robert Goeder, Jennifer Kudelka, Corina Maetzler, Hanna Kaduszkiewicz, Tanja Lange, Marie Bornhorst, Hanna Grasshoff, Stefan Schreiber, Sophia Hinz, Friso Muijsers, Kristina Brandt, Tina Hagen-Hurley, Robbin Romijnders, Clint Hansen, Linda Pialek, Kirstin Hansen, Johanna Graeber, Susanna Nikolaus, Florian Schrinner, Pia Görrissen, Paula Cullen, Maren Williams, Andrea Pilotto, Alessandro Padovani, Sabrina Denardi, Giulio Bonzi, Marcello Catania, Valentina Chirico, Fiorenza Cavagnini, Christen Janneke van de Woude, Nynke Borren, Monique Devillers, Nicole Larmonie, Denise Schenk, Hans van Leeuwen, Jorina van der Salm, Iain McInnes, Neil Basu, Joe Galloway, Norelee Kennedy, Alexander Fraser, Hayley Connolly, Sadhbh Ni Mhidigh, Imelda Doolan, Cathal Linnane, Jacques Demotes-Mainard, Linda Stöhr, Neshat Chareh, Hanna Schrinner-Fenske, Martina Esdaile, Alicja Szofer-Araya, Costantino Pitzalis, Michele Bombardieri, Louise Warren, Myles Lewis, Paul Giuliani, Sharon Palmer, Vicky Byers, Yi-Ke Guo, Kai Sun, Danilo Mandic, Mary Morrell, Siyao Wang, Florian Guitton, Yifeng Mao, Ailsa Hart, Shaun Power, Guanyu Tao, Benjamin Vandendriessche, Arno Bossaert, Rebeca Munoz, Hans De Clercq, Pierrick Arnal, Bertrand Fatus, Evgeniia Kurash, Maya Dorsey, Miles Parkes, Sree Subramanian, Louise Stockley, Rona Smith, Renata Schaeffer, Jérôme Kalifa, Jonathan Chauvin, Clémence Pinaud, Adrien Bennetot, Alexandra Belfiore, Laura Carrasco Marin, Mayca Marín, Jennifer Jimenez, Miriam Grande, Susana Donate, Evert-Ben van Veen, Daniel Groos, Martin Boeckhout, Beatrice van der Velden, Olenka van Ardenne, Denis Groot, Nebo Savic, Irene Schluende, Franziska Klepka, Simon Beniston, Veli Stroetmann, Rainer Thiel, Daniel Schmidtmann, Karin Breuer, Jessica Paul, Shahan Tariq, Alexandra Prodan, Griselda Marku, Tiago Guerreiro, André Rodrigues, Diogo Branco, Livia Moreira, Carla Marques, Hélia Rodrigues, Fabio Roli, Davide Ariu, Stefania Casula, Battista Biggio, Luca Piras, Luca Didaci, Matteo Mauri, Joaquim Ferreira, Leonor Correia Guedes, Inês Dias, Ana Teresa, Joana Costa, Mariana Matos, Teemu Ahmaniemi, Luc Cluitmans, Jani Mäntyjärvi, Juha Kortelainen, Rajdeep Nath, Emmi Antikainen, Kinga Koski, Francesca Cormack, Michele Veldsman, Laura Keylock, James Dobson, Janet Griffiths, Nick Taptiklis, Julian Fierrez, Aythami Morales, Ruben Tolosana, Alejandro Pena, Luis Gomez, Rafael Oliveros, Ruben Vera-Rodriguez, DaQing Zhang, Xujun Ma, Mossaab Hariz, Pei Wang, Djamal Zeghlache, Jordi Evers, Laura Siepman, Martijn Niessen, Ralf Reilmann, Robin Schubert, Atbin Djamshidian-Tehrani, Grzegorz Witkowski, Halina Sienkiewicz-Jarosz, Malgorzata Dusza-Rowinska, Klaus Seppi, Katarina Schwarzova, Corinne Horlings, Samuel Labrecque, Anita Malik, Wolfram Rieneck, Maria B. Lauvsnes, Roald Omdal, Katrine Norheim, Svein Skeie, Anne Hjelle, Hilde Norvik, Dave Wenn, Mike Jackson, Luisa Avedano, Bella Haaf, Tatiana Negurita, Susanne de Bot, Carola Buitelaar, Kasper van der Zwaan, Laura Kuijper, Adrie van Weeghel, Ian Bruce, John McBeth, Liz Fay, Joanna Jozefiak, James Prior, Denise Faulkner, Ioannis Pandis, Nikolay Manyakov, Stefan Avey, Meenakshi Chatterjee, Kenneth Mosca, Cesar Calderon, Rana Rehman, Melissa Mendez-Nguyen, Lori Warring, Marc Walton, Bethany Paxson, Diana Koletzki, Shyla Jagannatha, Zhi (Carrie) Li, Drew Elias, Kai Langel, Dario Masullo, Matthew Roche, Victoria Zolfaghari, Sarah Weingast, Maurizio Facheris, Tony Bannon, Matt Czech, Jie Shen, Shiv Patel, Michelle Crouthamel, Josh Cosman, Sean Turner, Magnus Jörntén-Karlsson, Tim Ruckh, Folke Folkvaljon, Jörgen Jensen, Neil Newman, Susan Forda, Birgit Steckel-Hamann, David Dexter, Nikul Bakshi, Joe Mather, Seleen Ong, Carla Cox, Yiorgos Christakis, Hao Zhang, Carrie Nothcott, Elaine Borthwick, David Nobbs, Jens Schjodt-Eriksen, Sebastian Holst, Florian Lipsmeier, Jason Hannon, Nadir Ammour, Haneen Njoum, Hillol Sarker, Imane Brigui, Raolat Abdulai, Xavier Benain, Jimena Diaz DeLeon, Manon Cariou, Fabrice Bonche, Vincent Mittoux, Sheila Thomas, Caroline Zutterling, Juliette Muszka, Frederique Guilbert, Xavier Brusson, Gwenaelle Corre, Babak Boroojerdi, Coralie Domange, Phil Scordis, Kasper Claes, Valentina Ticcinelli, Chengliang Dai, Giovanni Campana, Sarah Bilali, Oliver Stumpp, Mireille Delval, David Marquet, Gwenaelle de Keyser, Claudia Mazza, Alexandra Auffret, Jeremy Edgerton, Juha Rouru,Minna Korolainen, Sammeli Liikkanen, Mikko Kuoppamäki, Marina Lindford, Anssi Mäkiniemi, Toni Sarapohja, Olavi Kilkku, Antonella Chiucchiuini, Brian Tracey, Dimitri Volfson, Tairmae Kangarloo, Francesco Onorati, Wojtek Piwko, Geert van Gassen, Todd Swick, Armella Escher, Pietro Artoni, Robert Latzman, Mike Chambers, Elizabeth Amstutz, Nick Bott, Laura Rosen, Ieuan Clay, Aiden Doherty, Sara Riggare, Dina de Sousa, Cate Titterton, Heather Hunter, Ulli Funken, Jill Shutt, Werner Rammele, Jean Heather, Paul Howard.

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EDITED BY
Sudeshna Das,
Harvard Medical School, United States

REVIEWED BY
Cortney Ann Turner,
University of Michigan, United States
Linus Jönsson,
Karolinska Institutet (KI), Sweden

*CORRESPONDENCE
Magali Haas
✉ magali.haas@cohenbio.org

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Models and methods: a perspective of the impact of six IMI translational data-centric initiatives for Alzheimer's disease and other neuropsychiatric disorders

Hilary North[1], Martin Hofmann-Apitius[2], Martien J. H. Kas[3], Hugh Marston[4] and Magali Haas[5]*

[1]Scientific Advisor to Cohen Veterans Bioscience, New York, NY, United States, [2]Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Bonn, Germany, [3]Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, Netherlands, [4]Boehringer Ingelheim Pharma, Biberach, Germany, [5]Cohen Veterans Bioscience, New York, NY, United States

The Innovative Medicines Initiative (IMI), was a European public–private partnership (PPP) undertaking intended to improve the drug development process, facilitate biomarker development, accelerate clinical trial timelines, improve success rates, and generally increase the competitiveness of European pharmaceutical sector research. Through the IMI, pharmaceutical research interests and the research agenda of the EU are supported by academic partnership and financed by both the pharmaceutical companies and public funds. Since its inception, the IMI has funded dozens of research partnerships focused on solving the core problems that have consistently obstructed the translation of research into clinical success. In this post-mortem review paper, we focus on six research initiatives that tackled foundational challenges of this nature: Aetionomy, EMIF, EPAD, EQIPD, eTRIKS, and PRISM. Several of these initiatives focused on neurodegenerative diseases; we therefore discuss the state of neurodegenerative research both at the start of the IMI and now, and the contributions that IMI partnerships made to progress in the field. Many of the initiatives we review had goals including, but not limited to, the establishment of translational, data-centric initiatives and the implementation of trans-diagnostic approaches that move beyond the candidate disease approach to assess symptom etiology without bias, challenging the construct of disease diagnosis. We discuss the successes of these initiatives, the challenges faced, and the merits and shortcomings of the IMI approach with participating senior scientists for each. Here, we distill their perspectives on the lessons learned, with an aim to positively impact funding policy and approaches in the future.

KEYWORDS

innovative medicines initiative, pharmaceutical industry, public–private partnership, European Union, neuropsychiatric disorders

Introduction: overview of the innovative medicines initiative

The IMI Joint Undertaking (IMI-JU) is a European initiative to increase the competitiveness and success of European pharmaceutical research through a unique model that combines intellectual collaboration with academia and public funding.[1] Officially, the partnership is executed by DG Research and Innovation of the European Commission, of European Communities, and EFPIA (European Federation of Pharmaceutical Industries and Associations). Briefly, the collaborative projects are initiated by participating pharmaceutical companies, who identify a need for collaborative support from the academic community. Academic groups apply to be considered for the role, and the IMI decides which is best suited to partner with the industry participants. The funding is provided one-to-one by both the industry participant and the IMI. This approach is intended to scale funding and remove bottlenecks, giving industry undertakings direct access to academic expertise that would otherwise take years to materialize. Initiated in 2007, the IMI has had a budget of 5.2 billion euros, making it the largest public–private partnership in the world. It is therefore critical to review the successes of the initiative to date and determine areas for improvement as new projects are initiated for the future.

IMI projects in support of neurological data science

A large portion of projects funded by the IMI, since its inception, have had a focus on neurodevelopmental, neurodegenerative or neuropsychiatric disorders, as these conditions collectively directly impact 1 in 3 people world-wide (2). As a leading cause of illness and of disability, these disorders significantly reduce human capabilities and productivity. By one estimate, the cost to the global economy is currently between $2.5 trillion USD and $8.5 USD trillion per year (3). Many IMI projects were focused on Alzheimer's disease, where one might argue that, prior to 2008, little progress or investment had been made by industry, and only symptomatic treatments were available. At the genesis of the IMI efforts, we lacked precision medicine solutions for most of these and diseases and, even more discouragingly, many large drugmakers began to redeploy their investments away from neuroscience pipelines (4). This departure was hastened by stacked up clinical failures in the years prior, imminent patent expirations, and a lack of a pipeline caused by a combined lack of a biological or mechanistic understanding of these diseases and other challenges unique to brain research (e.g., blood–brain barrier) and exponentially rising costs of R&D.

Across many global initiatives (e.g., the European College of Neuropsychopharmacology (ECNP), the International College of Neuropsychopharmacology (CINP), the National Institutes of Health (NIH), etc.) common challenges were identified that were hampering progress, including, but not limited to:

- Defining the pathological phenotype precisely and ability to diagnose it.
- A lack of objective diagnostic tests and treatment responsive biomarkers.
- Intermediate phenotyping to characterize multiple risk factors and address pleiotropy of complex disorders.
- Mechanism-based modeling and simulation approaches for quantitative understanding of the pathology.
- New drug targets involved in the pathology of interest.
- Lack of translational validity: promising effects of novel compounds in animals did not reliably predict efficacious effects in patients.
- Novel tools and technologies for measuring the brain at a molecular, circuit, and systems level.
- Limitations of standard study designs (e.g., double-blind, randomized, controlled trials).
- Transfer of small molecules and biologics across the blood–brain barrier.

The field recognized that new large-scale, data collection and analysis efforts were necessary to understand these heterogeneous, polygenic disorders and would require broad collaboration and sharing of tools and data.

Significant re-investment and re-engagement by industry in neurodegenerative diseases, including AD, certainly correlates with IMI's tenured investment. Generation of numerous databases and access to AD data, infrastructure for conducting large-scale trials, were fostered by IMI, as well as a new molecular-based taxonomy. It is indiscernible, however, whether these have been utilized or integrated into any of the drug programs (Aducanumab (Aduhelm™) and Leqembi (lecanemab-irmb)) that have recently been approved by the U.S. Food and Drug Administration (FDA). To evaluate the strengths and weaknesses of the IMI framework for advancing precision medicine solutions for neuroscience, we interviewed key contributors to six funded efforts: Aetionomy, the European Medical Information Framework (EMIF) project, the European prevention of Alzheimer's dementia consortium (EPAD), eTRIKS, and Enhancing Quality in Preclinical Data (EQIPD) and Psychiatric Ratings using Intermediate Stratified Markers (PRISM), see Table 1. Total funding by IMI between IMI1 (2008–2013) and IMI2 (2014–2020) amounts to €5.276 billion. Of this €182,384,533 was invested in the initiatives outlined within this review (1).

IMI projects represented in this review

The EMIF project was a public–private consortium with 57 partners that operated for 5.5 years, from January 2013 to June 2018 with the goal of improving access to patient-level data. With patient data housed in disparate locations and in different systems, typically in isolation and not accessible from the outside, it is not possible to fully leverage its potential. EMIF sought to develop common technical and governance solutions and improve access and use of health data. To this end, EMIF built a common Information Framework (EMIF-Platform) to link up and facilitate access to diverse medical and research data sources. By integrating data from various sources such as electronic health records, biobanks, and clinical trials, EMIF enabled researchers to access a wealth of diverse and large-scale data

1 http://www.emif.eu/

TABLE 1 Overview of selected CNS and data management IMI initiatives.

IMI initiative	Dates	Project goals	Accomplishments	Resources
The AETIONOMY Project	01/01/2014 to 31/12/2018	Facilitate the use of precision medicine in neurodegenerative disorders	Integrated a broad range of datasets and dissected underlying mechanisms of disease; developed prototype Parkinson's disease taxonomy	https://www.aetionomy.eu/
EMIF – The European Medical Information Framework Project	01/01/2013 to 30/06/2018	Improve access to patient-level data	Built a common information framework platform to streamline organization of and access to diverse data sources	http://www.emif.eu/
EPAD – The European Prevention of Alzheimer's Dementia Consortium	01/01/2015 to 31/10/2020	Enhance design of clinical trials for AD drug candidates through adaptive trial design and focus on pre-symptomatic disease phase	Combined existing national and regional registers of potential pre-symptomatic AD patients and performed follow-up testing to characterize the subject pool	https://ep-ad.org/
The eTRIKS Collaboration	01/10/2012 to 30/09/2018	Centralize metadata for use in translational research	Developed a searchable IMI data repository and facilitated research collaboration	https://www.etriks.org/consortium/
EQIPD – Enhancing Quality In Preclinical Data	01/10/2017 to 30/09/2021	Improve the quality of data in non-regulated drug discovery research	Developed a novel quality management system and other open-access tools to help researchers generate reliable data	https://go-eqipd.org/
The PRISM Project	PRISM:01/04/2016 to 30/09/2019, PRISM 2:01/06/2021 to 31/05/2024	Develop a new understanding of neuropsychiatric disorders and an improved transdiagnostic approach	Conducted biomarker research across cohorts of patients with different conditions and overlapping symptoms to uncover common underlying pathologies	https://prism-project.eu/en/prism-study/

sets. In its 5 years, EMIF successfully leveraged data from than 62 million EU adults and children through federal databases and cohorts from 7 different countries, improving access to and providing tools and workflows to discover, access, assess, and (re)use human health data. To explore whether the platform might be applicable across disciplines, EMIF included two therapeutic areas: AD (EMIF-AD, with a focus on pre-dementia AD) and metabolic complications of obesity (EMIF-Metabolic). Through this multi-disease approach, EMIF facilitated the identification of commonalities, patterns, and insights across diseases and patient populations, allowing researchers to gain a better understanding of disease mechanisms, risk factors, and treatment outcomes.

The EPAD consortium[2] aimed to pioneer a novel, more flexible approach to clinical trials of AD drug candidates. To this end, the EPAD focuses on adaptive trial designs that will enable investigators to gather results faster and at a lower cost, with the pre-symptomatic phase of disease in mind for the prevention or delay of advanced symptom onset. Challenges to this approach include the difficulty of identifying people who are likely to develop AD, considering an inadequate understanding of early stages of the disease, as well as the lack of flexibility in how clinical trials are conducted. To overcome these challenges, EPAD pooled existing national and regional registers of individuals at risk of developing AD to create a single, pan-European register of around 24,000 people. Of these, the 6,000 deemed to be at greatest risk of AD were placed into a specialized, at-risk subject cohort that underwent standardized tests and follow-up. Finally, 1,500 of these subjects participated in early stage 'adaptive' clinical trials of therapeutics intended to prevent the progression of AD. The compiling and streamlining of these disparate datasets led to the identification of four distinct subgroups based on cognitive function (5).

The overall aim of the PRISM project[3] was to develop a quantitative, transdiagnostic neurobiological approach to the understanding of neuropsychiatric disorders in order to accelerate the discovery and development of better treatments for patients with those disorders (6). Elucidation of common underlying pathologies across conditions could facilitate development of therapeutics that address those symptoms directly, outside of the constraints of treating the diseases as a whole. The development and implementation of such an innovative transdiagnostic framework requires a multi-staged approach. First, transdiagnostic and translational quantitative biomarkers need to be identified and implemented in clinical and pre-clinical domains. Second, proof-of-concept needs to be provided for identified biomarkers, showing that they allow for stratification of patients on the basis of quantitative biological measures. To this end, the project partners carried out a range of tests on patients with neuropsychiatric disorders (7) in a bid to determine which biological parameters can be matched with specific clinical symptoms like social dysfunction (8). They identified quantitative biological parameters that allowed the grouping of patients into clusters based on symptoms and underlying causes. For example, PRISM found that social

2 https://ep-ad.org/

3 https://prism-project.eu/en/prism-study/

TABLE 2 Pros and Cons to the IMI approach.

Pros and Cons to the IMI approach	
Positive impacts	Room for improvement
Correlated with major advancements in the field of AD research	Need for central management of databases and biomarker repositories
Unique, disruptive approach; emphasis on goal-oriented progress	No mechanism for sustainability of projects beyond funding period
Successfully fostered new ideas and transformed funding landscapes	Process for matching academic collaborators to industry sponsor not always successful; unclear alignment of IP and profit incentives
Facilitated new collaborations across industries/communities	Excessive bureaucratic and administrative burden

dysfunction is transdiagnostically associated with default mode network disconnectivity in schizophrenia and Alzheimer's disease (9). They also developed new behavioral readouts using passive remote smartphone monitoring with the aim of identifying novel digital biomarkers (10, 11). Finally, a preclinical testing battery with parameters homologous to those studied in patients was implemented to allow for back-translation of human findings and deliver predictive model systems to accelerate the drug discovery process (12). The PRISM project was one of the rare IMI endeavors that successfully received follow-on funding to build upon these results, through PRISM2 (13).

The Aetionomy project[4] innovated classification approaches for neurodegenerative diseases by applying computational tools to molecular and biological data (mechanistic data) based data of Alzheimer's disease (AD) and Parkinson's disease (PD) that might contribute to a 'taxonomy' of these conditions, and help the community move towards a precision-medicine approach, instead of relying solely on clinical or symptom-based approaches. Aetionomy used a broad range of datasets, ranging from molecular to symptom data, and organized, structured, integrated them to dissect the underlying mechanistic causes in order to bring structure to the classifications. The consortium successfully demonstrated that their prototype taxonomy could be used to identify patient subgroups in Parkinson's disease (PD). These efforts resulted in an open-access knowledge base with inventories of mechanistic hypotheses that form the basis for the prototype taxonomies.

The eTRIKS collaboration[5] with ELIXIR-Luxemburg Node is an IMI data repository that centralizes ongoing and past IMI project level metadata for translational research scientists who require information about study projects. eTRIKS places an emphasis on the findability of research study descriptions with the aim of linking global data in a way that can be optimally leveraged to improve biomedical research, creating value for public and private organizations and driving research collaboration towards precision medicine. eTRIKS aimed to improve the technological platforms that scientists can use to share data.

The EQIPD project[6] sought to generate simple and sustainable solutions to improve data quality in non-regulated drug discovery. One of the main outcomes of the project was a novel quality management system as well as a range of other open-access tools and learning materials. EQIPD sought to provide various stakeholders groups with resources that would facilitate collaboration and ensure generation of robust and reliable data. The EQIPD project, which was active from 2017 to 2021, was advanced by 30 consortium members as well as several dozens of stakeholders representing academic institutions, industry, CROs, academic core facilities, funders and research tool manufacturers. A non-profit organization Guarantors of EQIPD e.V. was founded in 2021 to maintain, further develop and to disseminate the project's output.

Lessons learned from a decade of the IMI

Drs. North and Haas conducted interviews and synthesized feedback from six of the program leaders, representing the academic and industry viewpoints and contributions to these IMI initiatives: Anton Bespalov, Hugh Marston, Martien Kas, Martin Hofmann-Apitius, Simon Lovestone, and Bart Vannieuwenhuyse. We asked each for their reflections on the strengths and weaknesses of the IMI approach (Table 2), with a focus on whether or not the unique governance and funding models worked as intended, whether the resulting platforms and data represented significant contributions to the field, and what pitfalls could be avoided in the future. The views in this section also represent those of the last author, who is not an EU citizen, who did not directly participate in any of these funded projects but, was integrally involved in all of them either at inception (generating & designing proposals, serving on a scientific advisory board, or serving as an independent reviewer on behalf of IMI) over a decade, and was invited to prepare this manuscript by the editors as an independent party.

The fundamental question at hand is whether mechanisms like the one created by the IMI are indeed successful in advancing precision solutions for some of the over 800 diseases of the brain on behalf of EU citizens, or the world. First, one must ask, what are our metrics to assess such success? The number of new drug targets? Actionable advancement in disease understanding? Patents filed? Datasets generated? New investment by industry founded on the results within these programs?

Prior to the IMI, no comparable major public–private partnerships and investment had existed within this healthcare space. Thus, IMI was forced to blaze a trail that would scale across hundreds of projects and apply across geographies, addressing governance, program management, monitoring, and balancing of incentives between multiple interested parties. Many groups have since been able to leverage IMI protocols and procedures as templates to guide their own initiatives.

The overall impressions of the six contributors were aligned in that the IMI funding scheme provided a unique boost to collaboration unlike any other opportunity previously available. The authors felt that

4 https://www.aetionomy.eu/
5 https://www.etriks.org/consortium/
6 https://go-eqipd.org/

the initiative has been very successful, has fostered new thoughts and notions, and has even been transformative to both the EU and US funding and policy landscapes, noting that ambassadors from the IMI had spoken to a congressional panel to encourage more public–private partnership in the drafting of a landmark piece of US research legislation, the 21st Century Cures Act. One author summarized his perspective on the initiative as "totally thrilling, controversy-arising, and disruptive - in a good way." Another author insisted that, compared to traditional funding approaches, "IMI is more impactful, has more traction in reality, and is more focused on solving problems." Many authors noted that they felt they would not have accomplished what they had with a funding scheme other than IMI. Most importantly, the IMI has provided the unique opportunity for collaboration between a range of participants – industry, academia, and policymakers – where the expressed goal of each project is to meet the needs of patients. "When the goal is to improve patients' lives, all stakeholders need to be involved from the beginning."

The most widely cited advantage of the IMI approach was that it uniquely fostered collaboration between industry and academia early in a project's life cycle and in a precompetitive "demilitarized zone." The approach allowed partnerships that otherwise would have been competitive to instead be collaborative. Bringing academic partners into industry-driven initiatives is particularly important for facilitating multi-disciplinary work: it would not be possible for companies to employ experts in every relevant field of study pertaining to their project. The interviewees attested that "the IMI has boosted multi-disciplinary collaboration across Europe like never before." Beyond the furtherance of collaboration *between* industry and academia, the IMI has also fostered collaboration *within* academia and *within* industry, as well.

Importantly, they observed that the initiatives and the "calls for funding" are industry-driven: the IMI allows industry to source academic support in a way that will accelerate industry initiatives, rather than industry attempting to piece together what they need from academic research that is already occurring. This allows the pharmaceutical partner to drive and explore proof of principle. Having industry input, as well as the input of other stakeholders such as patient groups, early in the research planning process is "crucial" to ensuring the studies are designed in a way that will benefit the drug development process. While academia produces important and interesting science, it is often not generated in form that is not workable for industry. One contributor even remarked that the "academic key opinion leaders have much less impact in [some of the IMI partnerships than they do] in other funding schemes, and this is a key to its success!"

While most contributors spoke about the advantages of IMI from an industry perspective, those who joined IMI projects from the academic side also cited numerous positive attributes. In general, IMI moved academic research forward, increased the amount of funding available for academic research, cross-academic fertilization, and collaboration across all of Europe in a way that has not happened in other cross-country funding schemes. Furthermore, the involvement of industry has encouraged a focused, goal-oriented ethos with elevated problem-solving capability and introduced industry-style project management, which is generally an improvement upon the administrative and operational capabilities of academic research centers. The projects have also led to a positive impact on flow of people between academic and industry. IMI has "taken the interesting science produced in academia and elevated it to a position of global impact."

Despite the overwhelming positives the contributors recounted, IMI was described as having a number of disadvantages or areas for improvement. Most notably, the contributors felt that IMI projects were not sustainable and were in need of a mechanism for more follow-up time. The 3 year (extendable to 5 year) grant term was universally thought to be too short without a mechanism or framework for sustainability thereafter in place, and progress made in many of the projects was lost when the funding term came to an end. Several of the projects were proof-of-concept and need further investment and time to determine whether their results can be independently replicated (e.g., PRISM, AETIONOMY). Some of the projects had to establish independent sustainability models to ensure that the product of their efforts would be maintained after the funding cycle was over (e.g., EQIPD, eTRIKS). While some projects were selected for renewal, the majority were not. One author who did succeed in continuing funding of the project through a related grant noted that this had required perseverance and an innovative approach to the application process, but also a loss of valuable time. These cases suggest an opportunity for IMI to consider how it transitions projects at the end of their lifecycle to ensure that valuable (public) assets are not lost.

The need to generate digital data repositories and open-source software tools and promote data sharing were addressed by several of the programs. Indeed, eTRIKS was explicitly designed with the intention that all relevant IMI projects could utilize its common platform to avoid each project having to invest in their own knowledge management system and avoid duplicative efforts. However, there appears to be no central strategy within the IMI for knowledge management, central management of legacy data or establishment of common data standards across programs, although IMI-funded Neuronet[7] seeks to address some of these challenges. The implementation of a strategy for an integrated, comprehensive international digital infrastructure for research data would be a substantive boon to the next generation of IMI. To realize such a transformative opportunity, we will need consensus and coordination across critical agencies, such as the European Medicines Agency (EMA), the U.S. National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA), among others.

Similarly, the need for objective biomarkers, and the collection of biosamples across multiple centers, was a focus of several of the programs. However, each program addressed methodological issues of sample collection, handling, long-term storage, retrieval and analysis, independently, and under unique governance and practice frameworks. The establishment of an IMI core research infrastructure to promote high-quality, streamlined procedures under appropriate governance, leveraging best practice guidelines (14) for establishing repositories, is highly recommended.

The funding scheme employed by IMI in these initiatives is generally termed a "public–private partnership" (PPP). In a public–private partnership model, various stakeholders from the public and private sectors come together to collaborate on a shared goal or

7 https://www.imi.europa.eu/projects-results/project-factsheets/neuronet

project. While such partnerships can yield numerous benefits, they also have the potential to give rise to conflicts of interest among the stakeholders involved. In a public–private partnership model involving academic and industry stakeholders, conflicts of interest can emerge due to the divergent goals and motivations of these two sectors. Academic stakeholders, such as universities and researchers, typically prioritize knowledge generation, particularly for discovery & innovation, academic freedom, and the pursuit of unbiased scientific inquiry and generation of publications. They strive to contribute to the advancement of knowledge and the public good. On the other hand, industry stakeholders, including corporations and businesses, may be driven by a focus on product development, reproducibility and robustness of results, and commercial interests, such as profit maximization, and gaining a competitive edge in the market. These differing priorities can lead to conflicts when it comes to issues such as research direction, data sharing, intellectual property rights, and publication of research findings. Academic stakeholders may seek to publish research that contributes to the public domain, while industry stakeholders may prefer to protect proprietary information. Additionally, concerns about potential bias or undue influence can arise when industry funding is involved in academic research, raising questions about the objectivity and integrity of the findings. Addressing these conflicts of interest requires clear guidelines, transparent communication, and robust safeguards to maintain scientific rigor, maintain academic independence, and ensure the public's trust in the research outcomes.

Participants did, in fact, raise concerns about the process by which IMI "matches" academic applicants to the industry partners, where the inevitable mismatching of personalities or working styles of the groups, inherent differences in the academic and pharmaceutical working cultures, and unclear incentive alignment. While the industry participants indicated that they were able to provide guidance to the IMI to steer them towards the most suitable academic match, successfully influencing this process required significant finesse, diplomacy, and a bit of luck. In some cases, tension or disputes arose over the division of labor and assets: some industry participants bristled at the common desire among academics to work independently and without outside influence, and some academic partners wondered whether the industry partner was contributing enough to justify their ownership of the IP. Incentives (both for academics and for industry partners) within the IMI framework is a consistent area of challenge. One might consider whether new models can be developed that more equitably incentivize academic involvement in research that has the potential to lead to profits solely for private companies. The IMI could also consider whether the products generated by these programs are truly 'translating' into know-how, IP or technologies that can be readily incorporated into R&D efforts. Overall, while the mixing of backgrounds and IP incentives did lead to some real tension, the contributors felt that this was not all bad: the mingling of different viewpoints and goals, in their estimation, improved the perspective and understanding of all. Nevertheless, it is clear, that further investment to optimize the matching, incentives and IP and communication frameworks for PPP by IMI is required.

Finally, by strong consensus, one of the biggest detractors from the IMI experience was the overbearing administrative demands, although there were dedicated project management agencies engaged for much of the bureaucratic work. One author exclaimed that the red tape and bureaucracy were simply "crucifying." There was a strong emphasis on formal reporting, for which deliverable timelines were highly important, while deliverable content was a mere formality. Some of the contributors felt that, in contrast to the IMI, the US NIH has a more practical approach to funding, with a stronger orientation towards goals and achieving results. Going forward, the IMI could accomplish more for drug development and better improve the lives of patients with more flexibility and a stronger emphasis on accomplishment, and less insistence on administrative procedures. Still, not all feedback in this area was negative: the application process was noted as being agreeable, with a reasonable amount of work required for the first round and the bulk of the application work only necessary for finalists who stood a high chance of success. Still, the benefits to science were unanimously seen as outweighing the bureaucratic frustrations. "IMI has had a lot of red tape, but for drug development, it has gotten it done."

As the proverb goes, "hindsight is 20/20" and one can always find room for improvement. But if we look back at where neuroscience R&D was in 2007, before IMI was launched, and where we are headed now, with new tools and new insights largely driven by the trails blazed by IMI, one has to conclude that these were investments well worth making. Many of these efforts would now be categorized as 'Learning Health Systems" models, seeking to achieve continuous rapid improvement in health and healthcare and to transform organizational practice. As such, perhaps future initiatives might be informed by the insights garnered in this field, including rapid evidence-to-implementation cycles and relevant metrics of success.

Conclusion

The IMI approach to funding biomedical research has been a unique approach to fostering collaboration between industry and academia. Participants in a number of IMI projects shared their opinions that the funding scheme was highly successful and facilitated ideas and innovation that would not have occurred under other traditional funding mechanisms. The IMI approach could be strengthened through the addition of mechanisms to ensure sustainability of projects after initial funding terms, centralization of database and biomarker repository management, a better method of matching academic and industry partners, alignment of IP and profit incentives, and a reduction in bureaucratic administrative demands.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.imi.europa.eu/projects-results/project-factsheets.

Author contributions

HN and MH conducted interviews and drafted the manuscript. MH-A, MK, and HM contributed project-specific content and opinions for the review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Sudeshna Das,
Harvard Medical School, United States

REVIEWED BY
Esther Schenker,
Independent Researcher, Levallois-Perret, France
Brendan Behan,
Ontario Brain Institute, Canada

*CORRESPONDENCE
Angela Bradshaw
✉ angela.bradshaw@alzheimer-europe.org

†PRESENT ADDRESSES
Andrew Owens,
Human Sciences Research,
Jaguar Land Rover Research Department,
National Automotive Innovation Centre,
University of Warwick, Coventry, United Kingdom
Rodrigo Barnes,
14/16 Bvd. Poissonniere, Paris, France

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Data sharing in neurodegenerative disease research: challenges and learnings from the innovative medicines initiative public-private partnership model

Angela Bradshaw[1]*, Nigel Hughes[2], David Vallez-Garcia[3], Davit Chokoshvili[4], Andrew Owens[5†], Clint Hansen[6], Kirsten Emmert[6], Walter Maetzler[6], Lewis Killin[7], Rodrigo Barnes[8†], Anthony J. Brookes[9], Pieter Jelle Visser[10], Martin Hofmann-Apitius[11], Carlos Diaz[7] and Lennert Steukers[2]

[1]Alzheimer Europe, Luxembourg Ville, Luxembourg, [2]Janssen Pharmaceutica NV, Beerse, Belgium, [3]Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [4]Bioinformatics Core, University of Luxembourg, Belvaux, Luxembourg, [5]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [6]Department of Neurology, University Hospital Schleswig-Holstein, Campus Kiel and Kiel University, Kiel, Germany, [7]Synapse Research Management Partners, Barcelona, Spain, [8]Aridhia Informatics Ltd., Edinburgh, United Kingdom, [9]Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom, [10]Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, University of Maastricht, Maastricht, Netherlands, [11]Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin, Germany

Efficient data sharing is hampered by an array of organizational, ethical, behavioral, and technical challenges, slowing research progress and reducing the utility of data generated by clinical research studies on neurodegenerative diseases. There is a particular need to address differences between public and private sector environments for research and data sharing, which have varying standards, expectations, motivations, and interests. The Neuronet data sharing Working Group was set up to understand the existing barriers to data sharing in public-private partnership projects, and to provide guidance to overcome these barriers, by convening data sharing experts from diverse projects in the IMI neurodegeneration portfolio. In this policy and practice review, we outline the challenges and learnings of the WG, providing the neurodegeneration community with examples of good practices and recommendations on how to overcome obstacles to data sharing. These obstacles span organizational issues linked to the unique structure of cross-sectoral, collaborative research initiatives, to technical issues that affect the storage, structure and annotations of individual datasets. We also identify sociotechnical hurdles, such as academic recognition and reward systems that disincentivise data sharing, and legal challenges linked to heightened perceptions of data privacy risk, compounded by a lack of clear guidance on GDPR compliance mechanisms for public-private research. Focusing on real-world, neuroimaging and digital biomarker data, we highlight particular challenges and learnings for data sharing, such as data management planning, development of ethical codes of conduct, and harmonization of protocols and curation processes. Cross-cutting solutions and enablers include the principles of transparency, standardization and co-design – from open, accessible metadata catalogs that enhance findability of data, to measures that increase visibility and trust in data reuse.

KEYWORDS

neurodegenerative disease, data sharing, innovative medicines initiative, GDPR, digital endpoint, real world data

1. Introduction

Data sharing is the process of making data available to people other than the data generators, collectors, custodians or stewards, forming a cornerstone of Open Science, wherein data is easily accessible, comprehensible, reproducible, replicable, and verifiable (1). Researchers and funding organizations are increasingly aware that data sharing is essential for effective and efficient biomedical research, and can also improve the accuracy and reproducibility of research, inform risk/benefit analyses of treatment options, strengthen collaborations, and enable large-scale analyses (2). Recognizing these practical and scientific benefits, journals in a variety of research fields, including medical science (3), have implemented data sharing policies, mandating data sharing statements and, in some cases, applying stringent requirements for data sharing.

However, these policy changes have not yet led to a substantial increase in data sharing from published research studies. For example, a cross-sectional analysis of 487 clinical trials published in *JAMA*, *Lancet*, and *New England Journal of Medicine*, reported that only 2 (0.6%) out of 334 articles agreed to data sharing, providing de-identified participant-level datasets or making them publicly available on journal websites. The same analysis also found that of the 89 articles stating they had provided individual participant data via a secure repository, only 17 articles had actually done so (4). Similarly, a 2021 study analyzing compliance of biomedical researchers with their Data Access Statements found that of 1792 manuscripts where datasets were "available upon reasonable request," only 6.8% (123 manuscripts) provided the requested datasets upon request (5).

To further promote Open Science, the European Union (EU) has established minimal guidelines for data sharing in EU-funded projects (6). Under Article 29.2 of the Horizon 2020 model grant agreement, it was mandated to have unrestricted access to all peer-reviewed publications, including the right to download and print them. Moreover, a machine-readable electronic copy of the published version must be stored in a repository for scientific publications, together with bibliographic metadata providing the name of the action, project acronym and grant number (7). A similar provision to provide open access to peer-reviewed publications was also included in the European Innovative Medicines Initiative 2 joint undertaking (8). In Horizon Europe, the €95 billion Framework program for research and innovation that has succeeded Horizon 2020, the Open Science concept has been considerably expanded, imposing additional mandatory practices. These practices include an obligation to provide digital or physical access to the results needed to validate the conclusions of scientific publications, and an obligation to provide Open Access to research data under the principle "as open as possible, as closed as necessary" (9).

Alzheimer's disease (AD) is the most common cause of cognitive impairment in individuals older than 65 years and is also one of the leading causes of death worldwide (10). According to estimates, neurodegenerative diseases such as AD are projected to create an economic burden of around €267 billion in Europe by 2030. The total cost of drug development for AD is estimated to be around $5.6 billion with an average duration of 13 years from preclinical studies to drug approval (11). Although advances in AD therapy have been achieved (e.g., FDA approval of aducanumab in 2021, as the first disease-modifying therapy for AD) (12), the failure rate in AD drug development remains very high (13, 14). Faced with such high human and economic costs, many public-private partnerships (PPP) have been established to improve the diagnosis, treatment and care of AD. As collaborative consortia which bring together key actors in the drug development process, PPPs are well-positioned to develop new therapies and lower the economic burden associated with devastating neurodegenerative diseases such as AD. From basic biomedical research and translational research to product registration and post-marketing surveillance, PPP aim to accelerate drug development by implementing non-linear, adaptive processes and strengthening collaborative approaches for the life-cycle management of therapies. Through a multidisciplinary and collaborative strategy in which stakeholders share knowledge, competencies, resources, and risks, PPPs have the potential to accelerate the translation of biological discoveries into clinical practice (12). PPP models can also identify new options to revisit discontinued products, call for funding for areas with unmet health needs, enhance knowledge of disease and promote learning from others, and sharing data (12). Since 2008, the Innovative Medicines Initiative (IMI), Europe's largest public and private collaboration in the life sciences, has funded over twenty PPP on neurodegenerative diseases, accelerating research across a wide spectrum from preclinical science to applied clinical research.

In the field of neurodegeneration, the availability of data from small and large projects has resulted in unprecedented research and innovation (15) boosting the utility of data, accelerating research, and improving our understanding of disease causes, treatment, prevention, and care. Numerous initiatives for data sharing have been established, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), Global Alzheimer's Association Interrogation Network (GAAIN) and Alzheimer's Disease Data Initiative (ADDI) in the United States, the Australian Imaging Biomarker & Lifestyle Flagship Study of Aging (AIBL) in Australia, the European Platform for Neurodegenerative Diseases (EPND) in Europe (16), the French National Alzheimer's Information System, and SveDem-the Swedish Dementia Registry (17, 18). Funded through the IMI, projects such as the European Medical Information Framework (EMIF) and the European Prevention of Alzheimer's Dementia [EPAD; (19)] have worked with research cohorts to undertake novel, large-scale research and develop systems and tools for data sharing (20). However, challenges in sharing data still remain.

Neuronet was a coordination and support action aimed at supporting and integrating projects in the IMI neurodegenerative disorders (ND) portfolio. Working on various themes and across different disease areas, twenty-four projects and 270 distinct organizations form the IMI neurodegeneration portfolio, including over 140 academic institutions, thirty-three companies that are members of the European Federation of Pharmaceutical Industries and Association (EFPIA), 55 SMEs (small and medium-sized enterprises) and 7 patient/carer organizations, among others (21). Neuronet aimed to support projects of the ND portfolio, to multiply its impact and visibility while enabling synergies and collaborations between partners in Europe, and around the world.

A Working Group (WG) on "data sharing and reuse" was established by Neuronet in 2019, bringing together experts from IMI ND projects. WG members were nominated by their respective projects (ADAPTED, AETIONOMY, AMYPAD, EMIF, EPAD, IMPRiND, PD-Mitoquant, RADAR-AD, RADAR-CNS) based on their expertise and experience in data sharing, with representatives from European academic institutions, industry, SMEs and patient

FIGURE 1
Challenges to data sharing in IMI neurodegeneration research projects. The Neuronet Working Group on data sharing identified five main categories of challenges that can impede data sharing (listed above), providing recommendations on how to address these challenges based on experiences of participation in IMI neurodegeneration projects (Boxes 1–5).

organizations (further details on the WG composition and activities can be found on the Neuronet website). Experts contributed to discussions during quarterly online meetings, and also participated in a face-to-face workshop organized by Neuronet partners in early 2020, prior to the COVID pandemic. The WG aimed to share lessons learned, discuss common challenges and needs, and identify priorities and opportunities for synergy and collaboration across projects, with the expectation of having more consistent and informed decision making, improved reuse of results, improved networking across projects, greater exposure to expert knowledge, and more uniform application of standards. In this policy and practice review, we outline the challenges and learnings of the WG, providing the neurodegeneration community with examples of good practices and recommendations on how to overcome obstacles to data sharing.

2. Challenges and enablers for data sharing: insights from the Neuronet WG

Sharing data has the potential to improve public health in several ways, including facilitating research that provides a more thorough understanding of health issues, enabling the creation of innovative solutions, and ensuring that decisions are grounded on the best available evidence (22). PPP projects have great potential for data discovery and exchange to maximize innovation, but are subject to particular obstacles linked to their cross-sectoral scope and scale. These issues, which are influenced by different expectations and regulations at the funder, institution and state levels, were the subject of extensive discussions in the Neuronet WG on Data Sharing. Where relevant, discussions involved experts from other IMI projects outside the ND field (e.g., BigData@Heart, FAIRplus), who were invited to describe data sharing challenges they had encountered and resolved.

In this section, we outline the key learnings from these discussions, identifying key challenges, ways to address them, and providing examples of good practices from IMI PPP projects. Five main categories of challenges were identified by the WG, related to organizational and legal, data protection, psychological/social and technical issues. It should be noted that the challenges and good practices are primarily presented from a European perspective; for example, discussions on data protection are centered on the EU General Data Protection Regulation (GDPR), which regulates the processing of personal data from European citizens (Figure 1). Beyond the legal context, however, many data sharing challenges, barriers and enablers are shared between Europe and the rest of the world, expanding the relevance and utility of this review. Similarly, while the review draws primarily on experiences from sharing clinical data about human research participants and patients, there are overlaps in challenges experienced when sharing preclinical data.

2.1. Organizational challenges

From direct patient-clinician interactions to the research institutions or healthcare organizations involved, clinical studies in PPP projects on neurodegenerative disease typically have a complex hierarchy of relationships. These institutions or organizations may be part of regional consortia, provide data to a repository, or may be involved in data sharing networks. As a result, agreements on data sharing become multi-layered, multi-partner documents that are built on an initial agreement between patients and clinicians. Interactions between stakeholders at various levels of this hierarchy can therefore impact data sharing, influenced by sociotechnical factors such as trust. For example, a narrative review of empirical evidence addressing views and attitudes toward the use of health data for research reported that, despite being aware of the potential benefits of data sharing, participants were concerned about potential breaches of confidentiality and data abuses (23).

The organizational challenges linked to data sharing in clinical PPP studies exist at multiple levels and are influenced by questions surrounding rights to the data. For example, in clinical trials and cohort studies, participants have rights as data subjects, while also having a relationship with the clinical sites they visit, as well as the organizations with whom the data gets shared. In studies involving the use of real-world data (RWD), patients have rights as data subjects, maintaining interpersonal relationships with the clinicians involved in their care, and the hospitals or facilities where healthcare interventions take place. Consequently, there are particular challenges linked to the way individual studies are structured or governed, further complicated by the different objectives, interests and incentives for data sharing as viewed by the diverse range of institutions that participate in PPP consortia.

TABLE 1 Different actors in the organizational model.

	Legal basis	Data sharing degrees of freedom
Citizen	National and international law.	1. Can give consent to data sharing models, case by case. 2. Can control downstream use of data (under GDPR).
Clinical Researcher	Staff contract, professional qualification.	Staff contract, professional qualification.
Medical Research Organization	Legal entity, subject to regulation in legal territory, e.g., as a charity or registered as a data controller.	1. High degree of freedom. 2. Acts as data controller on receipt or creation of data. 3. Can share data with researchers or subcontractors. 4. Can take custody of 3rd party data on behalf of researchers. 5. Can initiate and collaborate on projects with data sharing.
Pharmaceutical Company	Legal entity, subject to regulation in legal territory including company law.	1. High degree of freedom. 2. Acts as data controller on receipt or creation of data. 3. Can share data with internal researchers or subcontractors. 4. Can initiate and collaborate on projects with data sharing.
Consortium	Partnership agreement.	Partnership agreement establishes a clear and usually constrained framework for data sharing inside and outside the protocol of a study.
Data sharing network	May be a legal entity (often not).	If legal entity, can contract data processors and facilitate and host data sharing agreements.

Box 1: Recommendations on addressing organisational challenges to data sharing.

Organisational challenges

- Complex hierarchy of rela tionships between parties in PPPs, involving multiple actors across different sectors, who may have varying objectives, motivators, abilities and incentives to share data
- As a result, data sharing often involves multi-layered, multi-partner agreements that must satisfy intellectual property concerns in accordance with data protection regulations, reflecting this high degree of structural complexity.

Recommendations

- Transactional roles (e.g. principal investigators, data controllers, legal signatories) should be clearly defined and adequately resourced by PPPs, both financially and in terms of expertise
- Where suitable, applying a capability maturity model could help PPPs to define these actors and support their roles in data sharing processes, identifying and meeting training needs
- The use of existing Open Access infrastructures such as data catalogues, repositories or data sharing platforms can reduce some of the administrative burdens on individual researchers in PPPs, also supporting record-keeping, data governance and compliance.

2.1.1. Addressing organizational challenges

To address the organizational challenges outlined above, it is important to first have a good understanding of the placement of individual actors within the PPP or organizational structure, the laws, rules and regulations to which they are subject, and the aspects of data sharing each actor controls (Table 1). Organizational challenges may arise when the role of the different parties in data sharing agreements are unclear or not sufficiently defined. To address this issue, and under data protection legislation, the transactional roles of individual parties should be clearly defined. For example, data controllers must be identified by name in clinical studies, with principal investigators (PIs) or clinical research sponsors at a research institution often taking this role. Organizations or individuals with data processing roles should also be identified (e.g., legal entities providing technical services). Likewise, other roles that may be involved in data sharing, including data custodians (individuals who manage the data), data stewards (individuals who are responsible for the quality and correct usage of the data) and the data recipient (individuals or parties to whom the data is disclosed) should also be defined.

Organizational issues may also arise when individual parties are unable to act in the role required by legal frameworks that govern data sharing in PPP projects. To address these issues, as well as clearly defining which role each party plays, it is important to ensure each party has sufficient resources to fulfill that role. Organizations and individuals should invest sufficient time in training to effectively operate within this framework. The capability maturity model (23) is an organizational IT improvement strategy which could be applied to facilitate data sharing and collaboration. For example, it can be helpful to incorporate methods to obtain and record continuous feedback from individuals fulfilling different roles when sharing data, then use this feedback to adapt data flows, processes and infrastructures to facilitate data sharing. This can also identify process improvements and training needs to share data more effectively, providing paths for interactions and dialogs between organizational units and individuals to clarify priorities, requirements and limitations.

To further mitigate organizational issues in a sustainable way, researchers can also consider depositing de-identified data in a repository for long-term data preservation, creating a public record of the deposition, and formal metadata (e.g., digital object identifier (DOI) for citation) that can be more easily shared. This is still possible for datasets that require controlled access measures and can provide numerous advantages over managing data use agreements (DUAs) by email, with the platform handling aspects such as user registration, providing access to the DUA, enabling audit trails, etc. Not only does this remove some administrative burden for the researcher, but it also

BOX 2: Recommendations on addressing legal challenges to data sharing.

Legal challenges

- As cross-sectoral consortia involving multiple organizations of varying size, structure and complexity, PPPs raise particular issues around data ownership, access rights, usage limitations and privacy restrictions.
- Legal agreements in PPPs can be limited to specific purposes, with insufficient scope for application to the broad range of processes that can be involved in data sharing. Conversely, multi-layered, multi-partner agreements are often complex to negotiate and comply with, particularly when transactional roles of individual partners are not clearly defined.

Recommendations

- Where relevant, legal teams and/or signatories responsible for business, intellectual property and regulatory approvals should be identified, involved and informed from the early stages of PPP development.
- Establishing standard policies and template agreements for data sharing operations (e.g., data transfer agreements) in collaboration with all PPP partners can help contextualize and accelerate legal processes.

removes the reliance on the PI being available in perpetuity to deliver the data, and can improve record keeping and compliance.

2.2. Legal challenges

Discussions within the WG identified several legal issues that must be clarified when data is shared between beneficiaries, between IMI consortia, or with third parties. These include ownership of the data; access rights with conditions and usage limitations; possible embargo periods and associated time-limits for exercising access rights; how to provide access rights to affiliates, contractors or third parties; privacy restrictions; and ownership of, or access rights to results generated from shared data. To address these issues, many PPP projects establish additional legal agreements, some of which may be multi-party agreements that involve all consortium partners. Some contracts are mandatory due to the respective consortium agreements, and, in some cases, the process is streamlined by knowing who owns the data and who will be using it. However, these agreements are sometimes limited to specific purposes and are not wide-ranging to simplify and accelerate the process.

Beneficiaries of two IMI consortia can also enter into collaboration agreements to share specific data sets for particular purposes. In such scenarios, especially when all beneficiaries need to approve the collaboration agreement, the entire process becomes time-consuming and undermines timely collaboration. Data sharing agreements are also made between other beneficiaries, associated partners, linked partners, third parties, and other stakeholders. In a survey conducted by Neuronet to identify obstacles associated with project collaboration (24, 25), it was found that long delays involved in the preparation of agreeable terms and conditions for such collaboration documents and collection of signatures were the main issues.

2.2.1. Addressing legal challenges

To share sensitive data sets with third parties, internal approval from business, intellectual property (IP), and regulatory groups involved in PPP projects should be obtained. This can help determine whether the data are proprietary or under license, and can identify potential use restrictions linked to research ethics (e.g., informed consent). Although challenges connected with research ethics/REC approvals were not addressed in discussions of the data sharing WG, the WG on Ethics and Patient Privacy identified the following enablers that may help address these challenges: (1) clearly identifying the roles and responsibilities of entities/individuals involved in clinical data collection, use, and storage (and providing concise explanations in consent forms), (2) adapting and aligning procedures for consent and management of data access requests across clinical sites through collaborative engagement with relevant site personnel; and (3) preparing multi-site study documentation with reference to prior REC approvals and involving REC experts where feasible, using accelerated processes (such as the Proportionate Review process in the UK) if available (26).

When sharing or reusing data, PPP consortia should discuss and evaluate the requirements for data privacy and data transparency (e.g., what data are sufficient to achieve the scientific objectives of research) and determine the appropriate level of data identifiability to be used (e.g., pseudonymised, anonymised, or synthetic), to support decision making that strikes a balance between data privacy and scientific value. It is also important to involve institutional legal teams from the early stages of the project, so that they know the context for any legal agreements needed; establishing policies and templates for data transfer and other data sharing agreements can help accelerate legal processes in a sustainable way. To this end, adequate resources need to be included in the projects, as the legal discussions can take months or years to solve issues.

2.3. Data protection challenges

The Neuronet WG highlighted a number of challenges linked to the General Data Protection Regulation (GDPR; EU 2016/679), which regulates the sharing of personal data for health research in the EU, and came into force in May 2018. Under the GDPR, research participants in PPP clinical studies must be provided with information about how their personal data is collected, used, disclosed, transferred and retained. This information must be kept up-to-date, with material changes to the nature of data processing that impact on research participants' legal rights and privacy risks to be communicated through appropriate privacy notifications. Deficiencies or unclear statements of consent forms used for research with human participants can result in publicly funded research data being unsuitable for sharing with other researchers (27). Apart from the right to be informed about how their data is used by researchers, participants also have the right to obtain a copy of their data and, under certain circumstances, can request for the transfer of the data in a portable format to an entity of their choice. Additionally, under the GDPR, research participants can influence whether, and/or to what extent, their existing (i.e., already collected) personal data can remain in use

for future research projects. More specifically, participants may request their data to be deleted, if applicable, or alternatively, exercise their right to object to processing. These and other rights afforded to participants under the GDPR translate into corresponding obligations for medical researchers, thus increasing researchers' overall legal compliance burden.

Although the GDPR was originally intended to simplify data sharing for societal benefit, certain provisions of the GDPR remain open for interpretation. Moreover, the GDPR does not provide specific guidance to clinical researchers (6, 28). Data sharing and reuse can fall under the provision of "further processing" under the GDPR, which imposes additional compliance requirements on researchers, with the situation further complicated by a lack of consensus over how articles and recitals relating to further processing should be interpreted (29). For example, although the GDPR deems further processing for scientific research purposes as a "compatible" form of data processing, currently there is no agreement on what this means in practical terms. In particular, a recent legal analysis by a group of privacy researchers has shown that "compatibility" of further processing should not be misconstrued to mean that further processing is necessarily permissible, or in GDPR terms, lawful (30).

Another major source of confusion within the clinical research community is the notion of consent as the legal basis for processing personal data under the GDPR. Consent, within the meaning of the GDPR, shares many similarities with the informed consent for participation in a medical study, a research ethics requirement. Nevertheless, the two types of consent are not the same, giving rise to somewhat counter-intuitive situations where although medical researchers routinely obtain informed consent from research participants, the participants' personal data is processed under a GDPR legal basis other than consent (e.g., performance of a task in the public interest; Article 6 (1)(e) GDPR). Moreover, when consent is the GDPR legal basis for processing personal data in the context of medical research, it is unclear to what extent a valid consent can cover future, yet-to-be-specified research uses of the data. Recital 33 GDPR allows participants to consent "to certain areas of scientific research when in keeping with recognized ethical standards for scientific research," thus seemingly obviating the need for study-specific consent. However, this interpretation has been expressly rejected by the Article 29 Working Party, the predecessor of the European Data Protection Board, the leading European authority tasked with interpreting provisions of the GDPR through its guidance documents (31). Several national data protection authorities, including, more recently, the Italian authority, have also reaffirmed that under the GDPR, a consent obtained at the time of data collection cannot be valid in relation to future unspecified research projects, thus necessitating a repeat consent (32). However, owing to the practical challenges associated with reconsenting research participants, this interpretation remains controversial within the medical research community, and has generated significant backlash in recent years (33, 34).

Finally, the GDPR, in particular Article 89(1) of the Regulation, broadly defines certain obligations, such as appropriate "technical and organizational measures" that must be complied with when processing personal data for scientific research purposes. However, the choice of, and compliance with technical and organizational measures to secure and pseudonymise data can be challenging for neurodegeneration PPPs, particularly when dealing with brain imaging and motion capture datasets where defacing and removal of other identifiers are required.

2.3.1. Addressing data protection challenges

The lack of clarity around data protection policies and practices is an important barrier to data sharing among researchers, and was discussed at length by the Neuronet WG on data sharing. To address data protection challenges, it is crucial to confirm whether the consent forms permit sharing of study data with other researchers for secondary research purposes. Researchers should carefully consider potential uses of their research data when designing confidentiality agreements and consent forms, including long-term use, storage and sharing of the data (33). To support retrospective biomedical research using existing clinical datasets, the AD Data Initiative (ADDI) has created a decision tree to help researchers evaluate consent forms, to determine whether they permit data sharing (35). If this decision tree reveals that the consent form forgoes the desired data sharing or uses, potential alternatives can be investigated in collaboration with legal/administrative colleagues. An additional, useful resource is the Open Brain Consent Project, which was launched in 2014 to provide reference consent forms for data sharing, and tools to support pseudonymisation, has developed consent templates for researchers wishing to share brain imaging data, including a GDPR-compliant data consent form (36).

Researchers should also be aware that participant consent is not the only source of restrictions for data sharing. There can be additional constraints resulting from the needs of funding agencies (e.g., data cannot be shared for commercial reasons), various national laws (e.g., a separate ethics approval is necessary before sharing), or fundamental GDPR-related restrictions (e.g., data cannot be shared with parties relying on a particular legal basis to process data; or cannot be shared with parties in third countries). These constraints should be collaboratively identified and evaluated at the project outset, using and building on mechanisms such as Data Protection Impact Assessments (DPIA), and involving all key PPP project stakeholders, including data protection officers (DPOs) of the participating organizations.

The IMI-funded Big Data@Heart project is creating a translational research platform on heart failure, acute coronary syndrome and atrial fibrillation, aiming to deliver scalable insights from RWD, clinical trials, cohort studies and patient registries. The BigData@Heart project combined data from a wide range of already-existing databases with advanced analytics to produce clinically relevant disease phenotypes (37). A number of learnings on how to address data protection and governance challenges were identified through this work. Networked or federated governance structures can reduce administrative burdens or delays that may arise with centralized governance structures. Excessive reliance on pre-specified local governance policies can hamper data sharing; early involvement of local data protection officers can add substantial value and efficiencies.

2.4. Psychological, social, and motivational challenges

Researchers have reported several psychological, social and motivational obstacles during data sharing. For example, in a survey

BOX 3: Recommendations on addressing data protection challenges to data sharing.

Data protection challenges

- Data protection rights afforded to research participants under the EU's General Data Protection Regulation (GDPR) can add a substantial burden of legal compliance for PPPs involving clinical research.
- A lack of specific guidance for clinical researchers, and the existence of Member State derogations in several important areas, has created a lack of clarity around consent parameters, lawful bases for data sharing, and technical and organizational measures to ensure patient privacy.

Recommendations

- Early evaluation of consent and clinical study documentation (from all sites, in the case of multi-site studies) by PPPs can help clarify the permitted use conditions for data and support the development of effective data sharing agreements.
- Researchers should consider the potential future uses of clinical datasets when designing confidentiality agreements, consent forms and other study documentation.
- From project outset, PPPs should analyze of all potential restrictions to data sharing (e.g., funding agencies specifying that data cannot be shared with commercial entities) in collaboration with project partners, building on mechanisms such as data protection impact assessments
- Early involvement of local data protection officers can help identify and overcome issues linked to local data governance policies in PPPs; similarly, federated governance structures can reduce administrative burdens that can arise with centralized data sharing platforms.

conducted to understand the importance of data being discoverable, the authors reported an average rating of 7.3 on a scale of 1–10 (38). However, the concept of individual reputation and rewards can generate an exaggerated sentiment of ownership and competitive 'loss' associated with sharing and can create barriers, sometimes implemented as over-complicated access processes, or declining requests to share (39, 40). For example, a 2018 British Medical Journal (BMJ) study analyzing compliance of RCT investigators with BMJ and PLoS Medicine data sharing policies were only able to obtain data from 46% of 37 RCTs, with researchers either not responding to requests, or citing concerns relating to the financial cost and time required for the effort of data sharing (41).

In PPP projects, trust, trustworthiness, credibility, and reliance on systems already in place are further, crucial drivers and determinants of data sharing. This is especially true in the case of research consortia, where by definition of some level of sharing and collaboration is implicit in the work plan. For example, research participants must accept the risk of their data being compromised, and trust that clinical researchers will act honestly and to the best of their abilities, to maximize benefit for their patients. Similarly, researchers sharing data must trust that the data recipients will not misuse their data, and provide appropriate credit and acknowledgement for data generation. Group behavior is also an important factor; for example, the inexistence of a critical mass of peers sharing data can create an environment where there is a general reluctance to share as well, even without any objective obstacles. Reservations toward being the "first to share" are not uncommon.

2.4.1. Addressing psychological/social challenges

Financial support for data sharing is not always provided by research funders, which also restrict financial support to the project duration. To address this issue, systems can be implemented to ensure that data sharing capabilities continue after the initial project, for example through continued funding from research funders, and/or sharing data through existing platforms such as the AD Workbench of ADDI or the Dementias Platform United Kingdom (DPUK) portal. This is an approach that has been successfully adopted by the IMI-EPAD project, which has provided open access to its longitudinal cohort study (LCS) datasets through the AD Workbench. These datasets include a wide range of cognitive, clinical, neuroimaging and biomarker variables from more than 2,000 participants in the LCS study.

Researchers could also take on the role of data stewards to receive credit for any reuse of their data, which could help incentivize continued involvement in data sharing and address motivational issues. In an ideal world, research systems should also ensure that researchers who share data are acknowledged and rewarded for doing so. For instance, a metric that measures the volume of data shared by researchers following findable, accessible, interoperable, and reusable (FAIR) principles (42) could be introduced, or funders could provide awards for researchers (as role models) for sharing their data. Ensuring appropriate recognition through the use of metrics and awards such as these could lead to "snowball" effects in terms of disposition to sharing, if they are used widely, consistently and in a highly-visible way.

COVID emphasized the importance, value, and feasibility of data sharing between research community stakeholders and organizations. Today, while there is a significantly higher level of preparedness and willingness to share data with researchers and policymakers to advance science, interpersonal relationships and parameters relating to trust still have the potential to impede data sharing. Trust and trustworthiness are therefore important considerations to address, for example by providing proof of the reliability of the research entity that is interested in the data, and by providing accessible, easy-to-understand information on how the processes, policies, procedures, and technologies work.

2.5. Technical challenges

Although there has been rapid development in technologies to capture, manage, discover, standardize, visualize, analyze, and exploit data, technical challenges remain one of the key limiting factors impeding data sharing. A major problem is the fragmentation of the data landscape within PPP projects, which hinders interoperability and encourages new research projects to produce even more *de novo* innovations. The associated datasets are impacted by the numerous solutions that are not maintained or developed as a result. Every time a project tries to meet its unique needs while adhering to budget and time constraints, it must "reinvent the wheel," which results in a sizable number of rudimentary solutions.

To maximize benefits from IMI-funded research projects, data should be available to external researchers, ideally in a format that is easily findable, accessible and reusable. These considerations extend

BOX 4: Recommendations on addressing psychological and social challenges to data sharing.

Psychological and social challenges

- The concept of individual reputation and reward, which is particularly prevalent in academic institutions, can generate an exaggerated sense of ownership and competitive "loss" when sharing data.
- Financial and technical costs of data sharing can act as additional disincentives, impacting motivation to share.

Recommendations

- Data DOIs, citations and metrics for data sharing and re-use can help incentivize data sharing, providing a mechanism for recognition and reward; similarly, researchers could act as data stewards to receive credit for any reuse of their data.
- PPPs could reduce the financial and technical costs associated with data sharing, and increase the visibility of their data sharing efforts, by using existing infrastructures for data sharing (e.g., the AD Workbench of the Alzheimer's Disease Data Initiative).

to the metadata, which should help provide information as to the context of data collection, limitations of their applicability and interpretation notes, parameters that can hugely affect data reusability. However, curating data before analysis and sharing can require considerable effort, particularly when working with data from multi-site clinical studies or RWD, in different languages (both machine and human). For example, data harmonization involves ensuring the standardization of diverse datasets, removing errors and inconsistencies, and aligning on assumptions, syntactic and semantic interoperability. Several data harmonization methods can be used (each of them involves three operations: extract, transform and load), however, the processes are generally resource-intensive, particularly as the fidelity of the harmonization needs to be verified to enable further analyses. In addition, datasets need to be well-characterized (i.e., completeness, consistency and coverage) and the assumptions underlying the data need to be taken into account, ideally through collaborative processing with individuals who have domain expertise.

Other technical challenges arise for semi-structured and unstructured data, which require additional work, such as natural language processing. The choice of data sharing infrastructure also confers particular challenges; centralized infrastructures have advantages in terms of clarity of who is responsible for managing and organizing data, following in some cases an "honest broker" paradigm where trust and clear terms and conditions become key underpinning factors. However, they also have disadvantages in terms of implying the transfer of data to another location, which can be affected by problems of legal, ethical, governance and psychological nature and therefore requires an appropriate governance model. Federated infrastructures, where data is kept at source, with the data custodian as final arbiter on its use, have the advantage of more straightforward compliance with local legal and ethical rules and regulations. However, there are also disadvantages in terms of diluted responsibility, reliability and persistence of data, audit trail and also regarding the establishment and operation of unified access mechanisms for potential data users.

2.5.1. Addressing technical challenges

Although there has been a significant push toward "open" solutions and "open" data in recent years, as well as the creation of numerous online repositories and catalogs, the adoption and reuse of tools and data heavily depend on appropriate provenance, context, and application domains. Support systems for data sharing need to provide details about the type of data being shared, where it came from, why it was collected, etc., all of which can significantly impact future analysis and interpretation. For this data, producers need to annotate, record, and provide as useful, effective, and actionable metadata as possible. Despite advancements in semantic web technologies, human input into the provision of such metadata remains crucial in many areas and requires enormous, frequently underappreciated efforts. To support these efforts, new ways to interact with data are being developed, such as machine learning tools to annotate metadata, as well as computational pipelines for improved visualization, analysis and comprehension of data. Here, the Neuronet WG identified several enablers for data sharing, which address the technical challenges outlined above.

2.5.1.1. Addressing technical challenges: making data findable, accessible, interoperable, and reusable

Making data FAIR can supercharge how data are used. The IMI2 project FAIRplus was launched in 2019, to increase the FAIRification of valuable clinical datasets (43). Aiming to develop processes and guidelines on how to make data sets FAIRer, FAIRplus has created two tools for researchers to use: a FAIR Capability Maturity Model Integration (CMMI) and the FAIR cookbook. The FAIR cookbook which is hosted by ELIXIR (a European, distributed Research Infrastructure for life science data) collates protocols (termed "recipes") for making data FAIR, targeted at researchers and data stewards. The FAIRplus CMMI incorporates these protocols, identifying different stages on the journey toward FAIRification of data and specifying protocols that can be used at different stages (from single-use datasets to standardized datasets and up to fully managed data assets, which are fully FAIR). To make data accessible in the long run, FAIRplus is applying its knowledge to the ELIXIR IMI data catalog at the University of Luxembourg (44), which will act as a searchable metadata repository of IMI data.

To support a metadata-driven catalog for FAIR data, it is crucial to identify all existing data that might have come from and are available from PPP projects and to share high-level information about such datasets. Numerous cataloging projects have been created as part of IMI neurodegeneration projects [e.g., EMIF Catalog, ROADMAP Data Cube, European Health Data & Evidence Network (EHDEN) data portal, EPND Catalog, AETIONOMY AData(Viewer)]. The ELIXIR-LU/eTRIKS Data Catalog, which is being created for major research initiatives like IMI and H2020 and is more expansive than the ND field, centralizes metadata of active and completed projects (45). Federated catalogs such as these allow users to discover the existence of data without accessing it, making them very helpful for facilitating requests for access to the desired data sets.

2.5.1.2. Addressing technical challenges: harmonization

Data harmonization can be technically challenging, but is a strong enabler of data sharing, supporting FAIRification of data. The use of a

BOX 5: Recommendations on addressing technical challenges to data sharing.

Technical challenges

- The data sharing landscape within and between PPPs can be fragmented, with data stored in proprietary formats, in inaccessible locations, or with insufficient annotations, posing particular challenges for FAIRification of data.
- Processes such as data curation and harmonization, which facilitate data sharing, are resource-intensive; particular technical challenges may arise when sharing semi-structured and unstructured data, which may require, e.g., natural language processing.

Recommendations

- Mapping data to a widely-used common data model (e.g., OMOP) can support interoperability and facilitate data sharing in PPPs, while also enabling the use of standardized analytics across diverse datasets.
- Sharing harmonization processes, scripts and tools between PPP partners and with the wider research community can reduce the technical burden on individual researchers, build capacity, and break down silos.
- Open-source tools such as the FAIR cookbook can support FAIRification of datasets, providing protocols for assigning unique, persistent data identifiers, data transfer protocols, guidance on terminologies and ontologies for interoperability, and exemplars of data licences to permit data reuse.
- Using searchable, federated catalogs can be a resource-effective way to render PPP metadata findable, facilitating access requests and supporting data collaborations/sharing.

common data model (CDM) to support harmonization and interoperability, for instance within a standardized, modular and extensible collection of data schemas, has gained considerable ground in recent times. Harmonization of vocabularies is integral to this process, especially within CDMs such as OMOP (Observational Medical Outcomes Partnership). The FDA's Sentinel within a shared health data network (SHDN), the OMOP CDM within a federated or distributed network, or the Patient Centered Outcomes Research Institute (PCORI) CDM, are examples of such approaches, facilitating collaboration and harmonization of diverse data for analytics, in particular and for example, via a standardized analytics stack from OHDSI (Observational Health Data Sciences & Informatics) initiative, utilizing the OMOP CDM. OMOP is also at the centre of the EHDEN project, and, more recently, the DARWIN EU initiative of the EMA. Other established data standards to faciliate the sharing of structured data are also available, such as the CDISC SDTM and ADaM for clinical data, and SEND for preclinical data.

Within the IMI2 Big Data for Better Outcomes (BD4BO) initiative, individual projects, such as HARMONY (for hematological cancers), are mapping to the OMOP CDM, in this case via a pooled (centralized) SHDN, with Prostate Cancer Diagnosis and Treatment Enhancement Through the Power of Big Data in Europe (PIONEER) in prostate cancer working on mapping to the OMOP CDM via elements of a pooled SHDN and a federated SHDN, a hybrid model, or in the case of EHDEN a federated or distributed SHDN. The EHDEN project is unique in utilizing project-certified SMEs to undertake the extract, transform, load (ETL) with Data Partners, while working symbiotically with OHDSI on methodological, tools and use case development.

To support data harmonization, the EHDEN project identified a number of specific recommendations. Fundamentally, there needs to be a common understanding of the focus and standardized querying required for the common research proposed in a collaboration. In addition, the ETL process can be used to generate deeper insight into individual datasets while harmonizing, and is an excellent opportunity to have a feedback loop to the source for verification and improvements. During an ETL process, e.g., to the OMOP CDM, there should be a clear process for working between those knowledgeable of the source data and those responsible for the ETL, and clear verification and evaluation steps. Semi- or fully-automated steps and tools, with output reports during sequential steps and at the end of the ETL phase are important. Of note, with RWD on neurodegenerative diseases there will likely be a subset of variables harmonized, perhaps for specific queries, or for an ongoing program of research. Aligning on what will be harmonized is of paramount importance. Verification and evaluation of the fidelity between source data and harmonized data is good practice, in part with appropriate tools (integral to the OMOP CDM ETL process), but also in conducting validation studies, for instance by re-running protocols previously run in source data in the harmonized data. Utilizing standardized analytical tools assists with the preceding recommendation, and also assists with error detection with regards to whether an issue is with the source/harmonized data or the analysis, in particular with, e.g., higher dimensional data. Sharing the harmonization/ETL process, scripts, tools, and methods across the collaboration helps ensure complementarity of approach, even with a centralized ETL, while also educating relevant parties on the inherent steps and outputs. Harmonizing may be a one-off process, for instance with historical or static datasets, quite often with ND-RWD. With more dynamic datasets, the frequency of updates will need to be agreed upon, depending on the scope and scale of those datasets, and the ETL approach (e.g., to a CDM) could be semi or fully automated.

2.6. Learnings from data sharing in IMI neurodegeneration projects: real-world data, imaging datasets, and digital biomarkers

The previous section details the most prevalent challenges faced by neurodegenerative research PPPs, spanning organizational issues linked to the unique structure of these cross-sectoral, collaborative initiatives, to technical issues that affect the storage, structure and annotation of individual datasets. Equally, the learnings and recommendations that we outline are intended to be broadly applicable across different disease areas and research contexts. In this section, we focus on specific types of data that may be generated and shared by neurodegeneration PPPs: neuroimaging datasets, digital biomarker data, and clinical data that is routinely collected during healthcare delivery, also known as real-world

data (RWD). Based on practical experiences from four IMI projects working with these datasets, we highlight particular challenges and learnings for sharing these datasets, identifying intersections with the five areas addressed in the previous section.

2.6.1. Addressing sociotechnical concerns when working with RWD in neurodegenerative disorders: EMIF and EHDEN

The utilization of RWD for insight and evidence generation in a normative, observational setting outside of a clinical trial is not new, but has seen a remarkable expansion in recent years. The use of RWD is disease agnostic: the capture of clinical and associated data from diverse sources (phenotypic, genotypic or both) may bring new insights into our biology, right through to real-world outcomes of therapeutic interventions on disease progression. However, working with, sharing and reusing RWD comes with a number of sociotechnical challenges. It involves technical requirements to find, curate, and analyze data that is appropriate for the task. Likewise, it requires a sociological framework of governance, ethics, policy, and law to ensure that patients and citizens are adequately protected, and that data are available for research purposes.

The EMIF and EHDEN projects share the aim of scaling up the RWD ecosystem across Europe, to enhance the generation of reproducible and reliable evidence through large-scale, federated analyses of health data. EMIF, which was funded by the IMI between 2013 and 2018, developed a platform for electronic health records (EHR) and cohort-derived data, allowing users to find and explore these data sources. EMIF was divided into the platform development (EMIF-PLAT), metabolic focus (EMIF-MET) and in Alzheimer's disease (EMIF-AD). EHDEN has leveraged elements of the EMIF catalog for its platform, and is also working to harmonize EHRs from millions of people to the OMOP CDM, in collaboration with institutions, data sources and data custodians across Europe. To date, EHDEN has created a network of over 187 data partners from twenty-nine different countries, which are mapping their data to the OMOP CDM in a federated network; in total, approximately 850 million EHRs are represented in this network, creating a hugely valuable resource for health data discovery, analysis and research.

With the experience gained from working on EMIF and EHDEN, the following recommendations have been put forward to address sociotechnical issues that may arise when working with RWD:

1. *Ethical guidance:* To enable relevant and compliant research within the framework of social norms, anyone working with RWD should acquire ethical guidance or employ an ethics advisory board. Any research utilizing RWD must strike a balance between risk and benefit for the individual, a cohort, and society as a whole.
2. *Compliance with regulations:* Legal advice must be obtained to ensure alignment with, for example, the GDPR, the Data Governance Act, derogated member state interpretations and regulations, and local institutional requirements.
3. *Transparency and federation:* The intended data use and research goal must be transparent to all parties, following local and regional permission requirements and governance standards, before the release of positive or negative findings. Federated systems have the distinct advantage of allowing for data custodians to apply their local governance frameworks, rules and regulations. Sharing only aggregated data through standardized tools minimizes privacy concerns. In addition, IT systems should be in place to avoid digital security threats and allow data to be accessed and shared safely.
4. *Public involvement:* Depending on the nature of the research, it may be possible to integrate meaningful patient and public involvement to provide guidance and direction on using RWD within the parameters of legitimate research and also account for social norms and diversity in its representation.
5. *Codes of conduct:* Instead of using several different techniques, overarching code(s) of conduct (e.g., the EMIF Code of Practice) can help ensure the consistent application of methods that adhere to ethical and data protection criteria across projects that use RWD. There are many guidelines available in Europe that promote the use of RWD in general and can be used to research practices concerning the nuances of working specifically with RWD.

The recommendations outlined illustrate how EMIF and EHDEN have met many of the *organizational, legal*, and *data protection* challenges detailed in the first half of this review, highlighting transparency and federation as an enabler for sharing RWD when supported by clear codes of conduct to support compliance with supranational, national and local regulations and laws.

2.6.2. Sharing data from remote measurement technologies: remote assessment of disease and relapse – Alzheimer's disease

Smart devices collect a wide variety of data from the wearer, such as daily activity patterns and levels, calories burned, sleep patterns and weight. Increased health awareness and greater use of smart devices have opened the door to using these RMT to evaluate patient outcomes, both to support the day-to-day management of health and as tools for clinical research. However, the collection, use and sharing of data collected via RMT entail particular technical, legal and ethical challenges.

RADAR-AD (Remote Assessment of Disease and Relapse - Alzheimer's Disease) was launched by the IMI in January 2019 and will finish in June 2023. RADAR-AD aims to develop a digital platform that draws on a smartphone, wearable and home-based digital technologies to track subtle changes in the cognitive and functional abilities of people with AD. RADAR-AD is performing clinical studies that aim to assess different remote monitoring technologies and how the data that are generated using these technologies reflect the activities of daily living in people at different stages of AD. These data are being managed, stored and shared via the open-source RADAR-BASE platform, which was created during the RADAR-CNS project.

Data sharing and interoperability are firmly embedded in both RADAR projects. The framework supporting this data sharing (i.e., the type of data to be shared and access governing data sharing) was been established in line with IMI2 IP policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners are committed to sharing all data (clinical, biosensor etc.) available to, or generated by the RADAR program among all members of a RADAR topic, and across topics, as required. In addition to data, RADAR constituents also share domain practices and expertise developed concerning data management

procedures, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures. It is expected that any system built within the RADAR program adheres to well-accepted data standards, where applicable, to ensure compatibility and interoperability with other systems both within the RADAR program and more widely. The developed solutions, irrespective of whether leveraging the foreseen facilitating common platform infrastructure or built independently from it, should, in any case, allow for cross-analysis, data stream sharing and aggregated visualization across all RADAR-AD solutions, as well as in combination with pre-existing solutions such as those being elaborated under RADAR-CNS.

With the experience gained from working on RADAR-AD, the following recommendations have been put forward:

1. *Data management planning:* Development of a data management plan before patient enrollment can help guide the management and sharing of patient and caregiver-generated RMT data according to FAIR principles, and should provide information about how study data will be handled during the project lifetime, the types of data that are being collected and shared, the standards and ethical policies for study data, and parameters for storage and retention of data during, and after the project.
2. *Data standards:* Any system developed for data curation, storage or management should adhere to widely known data standards, if applicable, to ensure compatibility and interoperability with other systems inside and beyond the RADAR initiative.
3. *Enabling collaboration:* Improving the process of acquiring access to datasets, which is usually time-consuming due to legal and ethical issues, can facilitate better research by promoting collaboration and multifaceted work.
4. *Sustainability and scalability:* The solutions developed should support cross-analysis, data stream sharing, and aggregate visualization across all RADAR-AD solutions and in combination with existing solutions such as those being elaborated under RADAR-CNS, regardless of whether they leverage the foreseen facilitating common platform infrastructure or are built independently of it.

The recommendations outlined illustrate how RADAR-AD has met *organizational, data protection*, and *technical* challenges relevant to sharing of data collected from remote measurement technologies including wearables and home-based digital technologies. Embedding interoperability and FAIRification through careful data management planning, application of well-established data standards, and use of modular, open-source platforms such as RADAR-BASE can support analysis across datasets, data sharing, and aggregate visualization.

2.6.3. Working with imaging datasets: amyloid imaging to prevent Alzheimer's disease

Alzheimer's disease pathogenesis is characterized by the accumulation of amyloid-beta (Aβ) plaques, which is considered the first detectable change in the brain of a process that takes decades before the onset of the cognitive decline. In this context, amyloid positron emission tomography (PET) imaging has shown to be capable of capturing the continued accumulation of amyloid burden beyond the plateau observed in cerebrospinal fluid, and therefore it is an excellent tool that provides information about the topographical distribution and the burden of amyloid accumulation in the brain.

Although amyloid PET imaging holds great promise in a detailed characterization of the natural history of AD and its early stages, this technique must be accompanied by a well-phenotype description of the individuals. Despite the availability of longitudinal data sets on AD, such as ADNI, there was a need for large-scale (semi) quantitative amyloid PET data collected in the early population, where the pathological signal is often subtle. Therefore, the AMYPAD Prognostic and Natural History Study (PNHS) was established to build on existing cohorts, reducing the burden of *de novo* participants (46).

The AMYPAD PNHS data collection is a combination of prospective and historical data from twenty European sites in 8 different countries. These sites have provided information through eleven parent cohorts (PC) (47).

The "organizational" challenge was one of the first difficulties faced in the early stages of the project. AMYPAD PNHS was defined as an additional layer for existing PCs, providing financial support to perform an amyloid PET scan. As expected, this design was a source of organizational difficulties to define the "legal" framework governing the research data and ensuring that "data protection" aspects were well covered. A data transfer agreement template was used across PCs to facilitate and speed up the legal discussion. Additionally, regular updates and open discussions were maintained with all the PIs and members of the consortium on the different aspects of the project, to build trust in the project and overcome any psychological barriers. This communication channel was supported by allocating resources within the sponsor team to include the roles of project manager, research coordinator, and data manager. The support of this "sponsor team" was crucial to overcoming the challenges faced during the project, for example during the COVID period.

The participation of the different PI and their PCs facilitated the process of making the data available during the life of the AMYPAD project, as defined by the IMI grant. In contrast, challenges were more prominent to define the aspects surrounding data sharing after the IMI period, and most of the concerns presented above in this manuscript were manifested, such as data access request process, access rights or usage limitations.

To face this challenge, the AMYPAD PNHS dataset was defined with a sufficient degree of granularity to account for different research scenarios and the restrictions established by the PCs. Specifically:

1. *Data minimisation:* The variables included in the data set were grouped into concepts (i.e., common ideas or measurements) and domains (i.e., groups of concepts that share common characteristics). This allows the researcher to navigate the information available and enables access only to the subset of information needed to address the research question.
2. *Data protection:* The variables were further classified as *source* (i.e., original data shared by the PC), *raw* (i.e., minimally processed data, such as years of education, body measures or score in neuropsychological tests), *harmonized* (i.e., processed data harmonized across centers, such as x-scores or categories), and *derivative* (i.e., metrics obtained from neuroimaging processing methods). This division provided the project with three scenarios for data access requests: (1) *source* data will not

be shared by AMYPAD PNHS, and the researcher needs to request access directly to the PC; (2) *raw* data will be shared only under direct approval by the PC; (3) sharing *harmonized* and *derived* data will require only the approval by an internal AMYPAD committee, while the PC will be kept informed.

3. *Data sharing platform*: To ensure the preservation of the data after the finalization of the IMI period, the AMYPAD PNHS established a 5-year partnership with the ADDI. Researchers interested in using the AMYPAD PNHS data will be able to request access to imaging and clinical data for scientific research and/or educational activities using the AD workbench platform.
4. *Use of standards*: Due to the variety of sources and data formats present across the PCs, the data curation process in PNHS has dealt with multiple challenges. Among those, the most notable was the use of different data models, measurements, and cognitive questionnaires by the PC. Therefore, it was decided to perform a comprehensive process of data curation based on the work of the Data Curation Network,[1] which developed a standardized set of Check, Understand, Request, Augment, Transform, Evaluate, and Document (CURATED) steps. This integration process, and the strategies used for data transformation and harmonization, will be documented in a manuscript that will serve to understand the rationale followed during the study and, hopefully, will give guidance to future researchers that faced similar projects.
5. *Harmonized protocols:* The acquisition of amyloid PET data across different sites (e.g., a variety of PET and MRI scanners and acquisition protocols) presented a challenge to harmonizing the results obtained during image analysis. To tackle this, a specific Work Package was devoted to defining a protocol to harmonize the quantification of the amyloid PET imaging, a task performed in close collaboration with the EANM Research GmbH (EARL) initiative, from the European Association of Nuclear Medicine (EANM).
6. *Harmonized data:* finally, clinical research data will be shared using two different data models: first, using a flat-file model defined during the integration process in AMYPAD PNHS and, second, using the OMOP CDM that will allow the analysis of the data in combination with other databases that use the same common format. For neuroimaging data, the images will be shared using the directory structure, file naming, and metadata convention proposed by the Brain Imaging Data Structure [BIDS; (48)].

The recommendations outlined illustrate how AMYPAD has met *organizational, data protection*, and *technical* challenges that may arise when sharing and reusing brain imaging data, for example in defining legal frameworks, achieving GDPR compliance, and determining data access rights and processes. As highlighted in the previous sections on real-world data and data from remote measurement technologies, development of harmonized protocols, use of data standards, and defined data models can help address these issues; in addition, outlining potential scenarios for data access requests allowed AMYPAD to establish robust processes to enable data sharing.

3. Discussion and conclusion

Although the value of sharing data is widely acknowledged in the ND research community, multifaceted challenges remain, with public-private partnerships facing particular organizational, legal, data protection, social/psychological, and technical hurdles. Strategies to overcome specific hurdles may not improve data sharing if related barriers are not addressed comprehensively, or if the underlying systemic issues are not resolved. The goal of this policy and practice review was to provide a broad overview of common issues and dimensions related to data sharing and effective reuse, from the perspectives of experts working in IMI projects on neurodegenerative diseases. Our analysis highlighted a number of barriers inherent to large-scale, cross-sectoral and transnational research projects, starting with the complex hierarchy of relationships between partners, which impacts data sharing at several levels. With organizations that range in size from small groups of people to multi-national companies with thousands of employees spread across different divisions, there can be a lack of clarity and transparency in the roles and responsibilities of key actors in data sharing processes. As well as raising particular issues around data ownership, access rights, intellectual property and usage limitations, the involvement of both public and private partners means that multi-layered, multi-party agreements are often required, which are particularly complex to negotiate and comply with when the transactional roles of individual partners are not clearly defined.

Challenges caused by a lack of clarity on roles and responsibilities are further compounded by the lack of specific guidance on the governance of highly-sensitive clinical research data generated by PPPs. Regulations such as the GDPR are viewed by some as a double-edged sword, creating stringent rules for data protection, but not providing precise guidance on key requirements such as consent parameters and technical and organizational measures for pseudonymisation. This imposes a substantial burden of legal and ethical compliance on researchers and PPP partners, adding an extra layer of complexity that can hinder the establishment of essential contracts such as data transfer agreements. Indeed, some IMI projects reported negotiation periods lasting a year or more, with multiple rounds of review involving several legal teams. As a result, data governance - an essential requirement for effective data sharing - can become a highly-charged issue fraught with perceived risks, negatively impacting the motivation of researchers to share data.

Our review also identified systemic barriers to data sharing in PPP projects, which can create an unfavorable environment for fruitful collaboration and innovation. 141 of the 270 organizations partnering in IMI neurodegeneration projects are academic institutions. Academic metrics for impact, reputation and reward are primarily centered on the individual, measuring research parameters such as scientific publications and grant income. This can generate an exaggerated sense of data "ownership" and competitive loss when sharing data in and from PPPs, a sense that is further amplified by the legal and ethical burdens discussed in the previous paragraph. As a result, researchers understandably report that they are more prepared to trust existing collaborators, or high-profile researchers and institutions, which can create research silos that limit wider data

1 https://datacurationnetwork.org/

sharing and collaboration. Indeed, silo-ing is a major issue at several levels: Neuronet WG members reported challenges due to organizational and collaborative silos, as described above, but also due to technical silos, where data discovery and sharing is restricted due to the use of proprietory formats and annotations, or inaccessible locations behind institutional firewalls. Curating data before analysis and sharing can require considerable effort, particularly when working with data from multi-site clinical studies, neuroimaging datasets, or RWD. Consequently, projects may resort to "in-house" data standards, processing pipelines and curation methodologies that may negatively impact semantic interoperability and harmonization, further limiting the potential for data sharing.

The Neuronet WG on data sharing was created to share lessons learned, discuss common challenges and needs, and identify priorities and opportunities for synergy and collaboration across projects. As such, we identified several enablers for data sharing in PPP projects, which can help overcome the challenges and barriers described above (also summarized in text Boxes 1–5).

Transparency was highlighted as an important facilitator at several levels. At the organizational level, transparent data governance processes with clear allocation of roles and responsibilities among PPP partners can accelerate data sharing, facilitating the establishment of agreements and contracts. In addition, using searchable, federated catalogs can be a resource-effective way to render PPP metadata findable, facilitating access requests and supporting data collaborations. Transparency should also extend to communicating about data sharing processes with key stakeholders, including research participants and the general public along with PPP partners and the wider neurodegeneration research community. As well as meeting ethical and legal requirements for informed consent and consent to data use, this can increase the visibility of, and public trust in, data sharing. Working Group members noted that this could also help bring about systemic changes in how data sharing is viewed, recognized and rewarded in academia. Increasing the visibility of data sharing, and emphasizing the moral imperative to share data from ND research studies, could lend further support to the adoption of metrics for data sharing. Metrics could include data access requests or publications that cite the use of shared data, facilitated by identifiers such as data DOIs (such as those assigned by Elsevier's "Mendeley Data" platform) that allow data to be cited and shared in a visible way. Complemented by existing metrics such as publications, impact factors and grant income, adoption of these metrics by academic systems would boost collaboration and further enhance awareness and recognition of data sharing.

A second common theme when discussing facilitators for data sharing was standardization. The establishment and use of templates for cross-consortium agreements, where feasible, was identified as a way to accelerate legal and administrative processes for all involved parties, particularly when templates incorporate pre-existing clauses required by institutions or companies. Efficiencies could also be gained by harmonizing data and metadata, by mapping to widely-used common data models such as OMOP (as exemplified by the EHDEN project), preceded where necessary by comprehensive data curation using standardized steps (e.g., the CURATED approach used by AMYPAD). Integration of curation processes, and aligned strategies for data transformation and harmonization, were identified as important enablers of interoperability. Sharing of these processes, scripts and tools between PPP partners and other researchers can also help build capacity in the wider community, reducing the technical burden on individual researchers, breaking down silos, and reducing redundancy. For example, open-source tools such as the FAIR cookbook (developed by the FAIRplus project) can enable FAIRification of datasets, while avoiding "reinventing the wheel" for each successive PPP project. Similarly, using existing, federated platforms for sharing data (such as ADDI's AD Workbench) can ease access to datasets and increase interoperability, while providing free computing power for analysis and re-use. However the principle of standardization should not be limited to legal agreements, technical tools and platforms. Experiences from IMI projects including EMIF and EHDEN emphasized the value of developing ethical guidelines and codes of conduct for PPPs, which help researchers to navigate some of the ethical complexities that may arise when sharing or reusing data.

The value of involving patients in all aspects of research - from development, to design and delivery – is now widely recognized (49, 50). While patients are usually not directly involved in data sharing, as the ultimate beneficiaries of research, and as data subjects, there is an ethical imperative to ensure patients' needs and preferences are respected. Working Group members agreed that patient and public involvement (PPI) can provide valuable guidance and directions on sharing and re-using patient data in research. Involving patients in the design of protocols, agreements and processes can also increase public trust in data sharing. An equally important enabler for data sharing is the early consultation of key stakeholders in data sharing processes, such as data protection officers, legal signatories, database managers and clinical research coordinators. Involving these individuals from the PPP proposal stage onwards can help anticipate potential challenges, and identify ways to overcome them. For example, early involvement of local data protection officers can identify issues linked to local data governance policies, and consultations with clinical research coordinators can help clarify the perimitted use conditions for data.

Although our analysis has identified a number of practical enablers, a mindset shift in the research community is still required to advance data sharing more effectively. In particular, the community needs to reconsider who should be responsible for data management after the end of PPP projects. Technical, financial and administrative costs of data sharing can be prohibitive once project funding periods have ended. Could funding agencies therefore take on the role of data managers? At least at first glance, some advantages can be derived from this: state- or community-of-states-led initiatives are less subject to end-date risks. The interests are clearly on the side of the most frequent and effective use of the collected data (and less on the side of potentially existing self-interests of those who have collected the data), and the repository could thus also reach a critical size, which could lead to a self-perpetuating process concerning data collection and data analysis networks. Finally, there is growing awareness that federated networks can potentially bypass legal, organizational and sociotechnical issues linked to ownership of data, enabling research and innovation without compromising privacy or security. As Europe moves toward more digitized and well-connected health and research systems between Member States, creating data spaces under a common governance framework, is it time to think about data collaboration, rather than data sharing?

Author contributions

AB drafted and edited the manuscript. RB, MH-A, AO, AJB, NH, WM, KE, CH, PV, DC, and DV-G provided their perspectives as members of the Neuronet WG and data sharing experts in IMI neurodegeneration projects, developing the manuscript content. LS and CD coordinated the Neuronet project, together with all authors. All authors provided critical comments on manuscript drafts and approved the final manuscript.

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Conflict of interest

NH is an employee of Janssen Pharmaceutica NV and owns stock in Johnson & Johnson, but no product-related aspects. LS is an employee of Janssen Pharmaceutica NV. RB was employed by Aridhia Informatics Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AD	Alzheimer's disease
ADDI	AD Data Initiative
AMYPAD	Amyloid Imaging to Prevent Alzheimer's Disease
CDM	Common data model
CMMI	Capability Maturity Model Integration^
CURATED	Check, Understand, Request, Augment, Transform, Evaluate, and Document
DPIA	Data Protection Impact Assessments
DUA	Data use agreements
EFPIA	European Federation of Pharmaceutical Industries and Association
EHDEN	European Health Data & Evidence Network
EHR	Electronic health records
EMIF	European Medical Information Framework
EPAD	European Prevention of Alzheimer's Dementia
ETL	Extract, transform, load
EU	European Union
FAIR	Findable, accessible, interoperable, and reusable
GDPR	General Data Protection Regulation
IMI	Innovative Medicines Initiative
IP	Intellectual property
JU	Joint Undertaking
LCS	Longitudinal cohort study
ND	Neurodegenerative disorders
OHDSI	Observational Health Data Sciences & Informatics
OMOP	Observational Medical Outcomes Partnership
PC	Parent cohorts
PET	Positron emission tomography
PI	Principal investigators
PNHS	Prognostic and Natural History Study
PPP	Public-private partnerships
RMT	Remote measurement technologies
RWD	Real-world data
SHDN	Shared health data network
SME	Small and medium-sized enterprises
WG	Working group

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EDITED BY
Jonathan P. Dyke,
Cornell University, United States

REVIEWED BY
Kieran Breen,
St. Andrew's Healthcare, United Kingdom

*CORRESPONDENCE
Linus Jönsson
✉ linus.jonsson@ki.se

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Precision medicine in neurodegeneration: the IHI-PROMINENT project

Ashley Tate[1], Marc Suárez-Calvet[2,3,4,5], Mats Ekelund[6], Sven Eriksson[6], Maria Eriksdotter[1,7], Wiesje M. Van Der Flier[8,9], Jean Georges[10], Miia Kivipelto[1,7], Milica G. Kramberger[1,11], Peter Lindgren[12], Juan Domingo Gispert López[2,3,13,14], Jyrki Lötjönen[15], Sofie Persson[12], Sandra Pla[16], Alina Solomon[1,17], Lennart Thurfjell[15], Anders Wimo[1], Bengt Winblad[1] and Linus Jönsson[1]*on behalf of the PROMINENT consortium

[1]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden, [2]Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain, [3]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain, [4]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain, [5]Servei de Neurologia, Hospital del Mar, Barcelona, Spain, [6]BioArctic AB, Stockholm, Sweden, [7]Karolinska University Hospital, Theme Inflammation and Aging, Stockholm, Sweden, [8]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC, location VUmc, Amsterdam, Netherlands, [9]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, Netherlands, [10]Alzheimer Europe, Luxembourg, Luxembourg, [11]University Medical Center Ljubljana and Medical Faculty, University of Ljubljana, Ljubljana, Slovenia, [12]IHE, The Swedish Institute for Health Economics, Lund, Sweden, [13]Universitat Pompeu Fabra, Barcelona, Spain, [14]Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid, Spain, [15]Combinostics Oy, Tampere, Finland, [16]Synapse Research Management Partners SL, Madrid, Spain, [17]Institute of Clinical Medicine and Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

Neurodegenerative diseases are one of the most important contributors to morbidity and mortality in the elderly. In Europe, over 14 million people are currently living with dementia, at a cost of over 400 billion EUR annually. Recent advances in diagnostics and approval for new pharmaceutical treatments for Alzheimer's disease (AD), the most common etiology of dementia, heralds the beginning of precision medicine in this field. However, their implementation will challenge an already over-burdened healthcare systems. There is a need for innovative digital solutions that can drive the related clinical pathways and optimize and personalize care delivery. Public-private partnerships are ideal vehicles to tackle these challenges. Here we describe the Innovative Health Initiative (IHI) public-private partnership project PROMINENT that has been initiated by connecting leading dementia researchers, medical professionals, dementia patients and their care partners with the latest innovative health technologies using a precision medicine based digital platform. The project builds upon the knowledge and already implemented digital tools from several collaborative initiatives that address new models for early detection, diagnosis, and monitoring of AD and other neurodegenerative disorders. The project aims to provide support to improvement efforts to each aspect of the care pathway including diagnosis, prognosis, treatment, and data collection for real world evidence and cost effectiveness studies. Ultimately the PROMINENT project is expected to lead to cost-effective care and improved health outcomes.

KEYWORDS

Alzheimer's disease, dementia, precision medicine, biomarkers, clinical decision support

1. Introduction

1.1. Aim

The aim of this project is to create a platform for precision medicine in the diagnosis and treatment of neurodegenerative disease and comorbidities. This digital platform will integrate multi-modal diagnostic data to generate personalized prediction of patient relevant outcomes as well as evidence-based recommendations for clinical management. The platform will also support the implementation of new diagnostic and therapeutic innovations and provide required evidence on safety, efficacy, and cost-effectiveness for relevant stakeholders.

Expected key impacts of the project include:

1. increased precision in diagnosis, prognosis, and management of patients with (suspected) neurodegenerative disorders and comorbidities,
2. optimal introduction and use of new health technologies, such as disease-modifying therapies (DMT), leading to improved patient outcomes, and
3. empowerment of patients and caregivers by through person-centric health care decisions, leading to improved adherence and reduced inequalities in access to care

1.2. The PROMINENT consortium

PROMINENT represents the first project funded by the Innovative Health Initiative (IHI), an extension of the Innovative Medicine Initiative. With the ultimate aim of fostering the translation of health research and innovation into tangible progress for patients and society, the IHI is a collaboration between the European Union and industry associations representing the healthcare sector: COCIR (medical imaging, radiotherapy, health ICT and electromedical industries); EFPIA, including Vaccines Europe (pharmaceutical industry and vaccine industry); EuropaBio (biotechnology industry); and MedTech Europe (medical technology industry). The IHI funds collaborative, innovative, and interdisciplinary projects which have a patient-centered approach. The first call for proposals for projects related to innovation in cancer, neurodegenerative diseases, and health data was issued on June 2022. PROMINENT was notified of their award of grant funding in November, 2022.

The PROMINENT consortium is comprised of 13 universities, research institutes, hospitals, companies, and patient groups, with teams highly specialized in medical technology development and dementia care and research. Together, we have harnessed our already existing digital health tools, prediction models, comprehensive data sources, and expertise to push the dementia care to new frontiers. Our ambition is firmly based in our currently running projects, and while our expectations are high the steps forward are merely incremental from previously awarded grants and projects.

1.3. Background

AD is a neurodegenerative disease, and the etiology behind 50–70% of all cases of dementia (1). The prevalence of symptomatic AD (prodromal, i.e., pre-dementia, AD or AD dementia) in Europe has been estimated at 22.1 million, while the estimated number of cognitively unimpaired persons with abnormal AD biomarkers is as high as 53.2 million (2). Due to an ageing population, dementia prevalence is expected to nearly double over the coming three decades, bringing enormous challenges for health and social care systems (3).

There is rapid development in the diagnosis and treatment of AD and other neurodegenerative disorders (4), across plasma-based biomarkers (5), pharmacological treatments and non-pharmacological prevention strategies (6). Thus, avenues are emerging for earlier and more accurate detection and diagnosis, however the implementation of these advancements is challenging. There is opportunity to improve on current care practices, which often include late, unspecific diagnosis and mainly palliative care provision, in favor of precise diagnostics and early treatment – a transformation similar to what has been seen in oncology over past decades (1). However, ensuring appropriate use and access to novel diagnostics and treatment is problematic, primarily due to lack of resources and available expertise. Limited capacity in the primary care settings and, occasionally, in specialist memory clinics can also lead to the prioritization of use in younger patients without significant comorbidities.

Implementing new technologies and latest treatments, such as emerging disease-modifying drugs lecanemab and donanemab, in routine care will be challenging, and the availability of specialists in neurology and geriatrics is a constraining factor in many European countries (7). Given the high prevalence of subjective cognitive decline (SCD), effective selection mechanisms are needed to identify those who are likely to have underlying AD pathology in a primary care or community setting. Therefore, there is a need for a clinical decision support system that can assist specialists as well as non-specialists with the interpretation of complex, multi-modal diagnostic data and provide accurate diagnostic and prognostic predictions derived from reference populations.

2. The PROMINENT digital platform

2.1. Overview

The digital platform that will be developed in PROMINENT is visualized in Figure 1. At the core of the platform are prediction models trained on large, representative datasets, capable of producing predictions of the correct diagnosis, future course of disease and care needs based on a wide range of factors including demographics, clinical history, cognitive tests, diagnostic imaging, fluid biomarkers and genetics. These predictions are combined with data on performance and cost of diagnostic tests, to produce optimized diagnostic algorithms. The platform will also incorporate updated guidelines on the use of relevant therapies, which will be leveraged to produce individualized eligibility assessments.

The platform will give personalized, timely and accurate information about the current disease state, prognosis, and potential benefits and risks with novel therapies. The primary target user group for the platform is clinicians engaged in the care of patients with neurodegenerative disorders. Based on available information on the individual patients being examined, the platform will provide guidance to clinicians on the likelihood of differential diagnoses, the likely future prognosis, and recommended next steps in the diagnostic

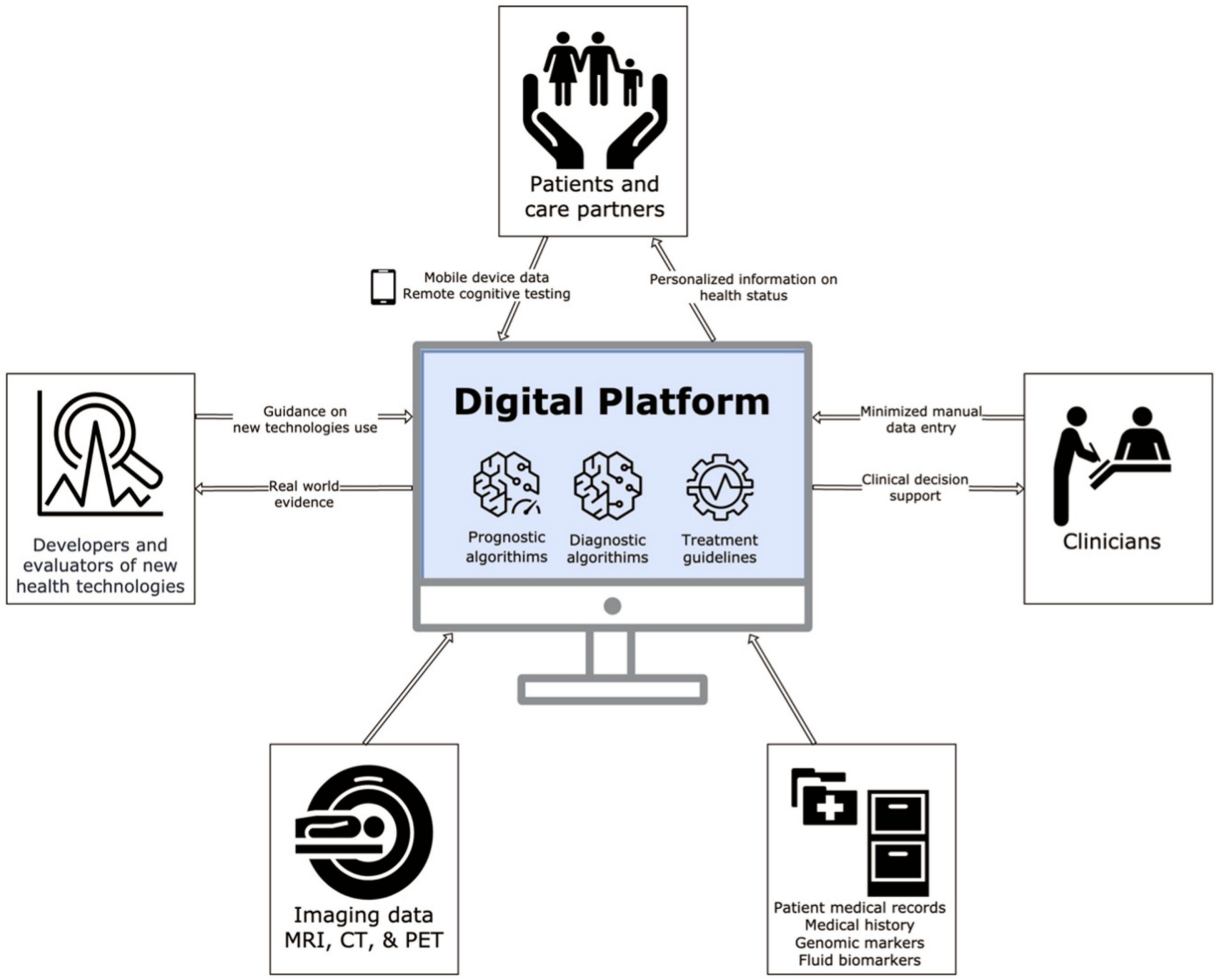

FIGURE 1
This figure shows what information is fed into and obtained from the digital platform, indicated by the arrow direction. The digital platform itself relies on an underpinning of prognostic and diagnostic algorithms and treatment guidelines. Adapted with permission from Combinostics.

process. The system will also summarize available information about the potential benefit and risk of disease-modifying therapy, tailored to the individual patient, and provide an assessment of the eligibility for treatment.

Patient and caregiver engagement will be promoted through individualized, lay-language information about diagnosis, prognosis and treatment recommendations. The system will provide longitudinal predictions of the likely course of disease in terms of cognitive decline and major events of relevance to patients and care partners such as loss of independence in key functions, institutionalization, and mortality (8). Visualizing this information in a manner that is understandable and meaningful is paramount, so patients and care partners will be closely engaged in the design of the system and outputs. These materials will be developed in dialog with patient and caregiver representatives. Such information materials may greatly improve communication provided by the physician and provide a concrete document patients and care partners can take with them from the visit. The materials will be developed in close collaboration/co-design with care partners and patients, enabled by public engagement mechanisms developed by Alzheimer Europe. We will also explore the feasibility of including evidence-based recommendations for patients and care partners relating to non-pharmacological prevention, availability of support services and similar relevant information, based on current disease status and individualized risk predictions.

Further, by prospectively capturing data on patients treated with disease-modifying therapies, the system is expected to produce valuable information for the assessment of the response to therapy, adverse events experienced, and the overall value and cost-effectiveness delivered by these therapies. This will enable health economic evaluation of diagnostic and therapeutic strategies, and implementation decision rules to guide cost-effective use of novel technologies.

2.2. Developing the digital platform

The PROMINENT digital platform will be developed from an existing, commercially available system for AI-based diagnostic imaging analysis and CDSS: Combinostics cNeuro. This system is already commercially available and used in hospital settings across Europe and the United States. cNeuro is a cloud-based tool including two components: cMRI and cDSI. cMRI is an AI-based tool for quantification of MRI-brain images and is mainly used in dementia

and multiple sclerosis (9). Findings are summarized in PDF-reports that contain information about atrophy and lesions, which assists radiologists in making more detailed and consistent reports in shorter time.

The second component, the Disease State Index or cDSI, assists clinicians with the differential diagnosis of patients with suspected dementia. cDSI combines imaging information (output from cMRI) with other manually entered patient data such as demographics, CSF-biomarkers, and cognitive test scores. Then, the patient's data profiles are compared to a database with data from previously diagnosed patients with a known outcome. cDSI provides information about differential diagnostics and prediction of progression, i.e., the disease state index. cNeuro has been validated using both retrospective and prospective data. In a comprehensive prospective study with 800 patients, the tool was found to increase clinicians' confidence in making early diagnostic decisions (10). A screenshot of the tool is shown in Supplementary Figure 1.

The existing systems will be developed into an open, interoperable platform (Figure 1) capable of interacting with a wide range of other systems to acquire data and deliver outputs. Key advancements of the PROMINENT digital platform compared to existing systems will include:

- Interoperability with EHR and other systems, reducing or eliminating the need for manual data entry, improving functionality and usability.
- Enhanced imaging analysis capabilities, including ARIA E/H detection.
- Interactivity with patients and care partners, including development of a web solution and/or mobile app for remote assessment of cognition and other functions, and individualized outputs from the platform designed to facilitate communication and shared decision making.
- Prediction models validated in routine care patient populations, accounting for comorbidities and incorporating novel blood-based biomarkers in addition to other predictors
- Clinical decision support including recommendations of optimal, cost-effective diagnostic pathways, the probability of diagnostic accuracy, and costs of individual test components.
- A tool for guiding clinicians on the optimal use of novel interventions such as DMT for AD and generating real-world evidence (RWE) on the actual usage, safety, effectiveness, and cost-effectiveness of these technologies in routine care.

2.3. Prediction models and diagnostic algorithms

In PROMINENT we aim to consolidate (rather than replicate) the vast body of research into prediction models for AD diagnosis and prognosis. This work will focus on predictions within symptomatic populations (SCD, mild cognitive impairment [MCI], or dementia), as this is currently the clinically most relevant population for diagnosis and potential treatment with DMT (11). We will first conduct an updated systematic review of different categories of multimodal prediction models and select models of potential clinical usefulness. We plan to specifically examine models related to differential dementia disease diagnosis and time until disease progression. Next, we will implement and expand on selected models using machine learning where the models are trained with the diverse datasets available to the consortium. Table 1 presents an overview of the outcomes that will be targeted in the modeling, and the range of predictors that will be included. Additional outcomes may be included based on consultation with patients, caregivers, and medical professionals through surveys.

Importantly, we will explore the impact of comorbidities on diagnostic and prognostic accuracy. Specific focus will also be placed on integrating data from blood-based biomarkers into prediction models and diagnostic algorithms. This includes (1) predicting the likely outcome of the blood-based biomarker given a set of known patient characteristics, (2) predicting the results of downstream diagnostic investigations in patients who test positive vs. negative on the blood-based biomarker, (3) including the result of the biomarker test in predictive models of future disease progression and clinical events.

Based on these prediction models, diagnostic algorithms will be developed that in a stepwise fashion estimate the expected outcomes of the next potential diagnostic test, and identifies the sequence of tests that produces the optimal overall diagnostic performance and cost.

TABLE 1 Outcomes and tentative predictors categories for prediction modelling.

Outcomes	Classes of predictors
Underlying etiology ■ Differential diagnosis: probability that the patient currently has one of several neurodegenerative and neurovascular disorders, or does not have any neurodegenerative disorder. Standard of truth will be the reference diagnosis at end of follow-up based on clinical and biomarker criteria.	■ Co-morbidity profile ■ Cognitive function ■ Blood biomarkers (p-tau, NfL, GFAP) ■ CSF biomarkers (amyloid, tau, p-tau) ■ Diagnostic imaging (MRI, PET) ■ Genetic markers (e.g., APOE) ■ Demographics ■ Concomitant medication ■ Socioeconomic factors
Future health outcomes ■ Probability of disease progression in terms of disease state: subjective cognitive impairment (SCD) to mild cognitive impairment (MCI) to dementia, over time ■ Longitudinal decline in cognitive function scores (e.g., MMSE, MoCA, neuropsychological test batteries) and other clinical scales (ADL, NPI) ■ Institutionalization and other changes in care setting and provision of support services ■ Hospitalizations, health care resource utilization, and costs ■ Mortality	

Finally, we will validate the models in data reflecting routine clinical practice in unselected populations across different care settings and evaluate performance outside of the datasets used for developing the models.

2.4. Datasets for prediction model development and validation

The consortium possesses eight large datasets (registries and cohorts) with a combined total sample of over 128,000 participants that cover the full spectrum of AD from preclinical stages, through to dementia and end-of-life institutional care. Supplementary Table 1 provides a description of the included datasets. As the datasets represents currently on-going studies, the PROMINENT consortium will benefit from existing knowledge from each of the data holders on the strengths and weaknesses of each dataset. Moreover, the collaboration ensures that scientific efforts within each register and data source will be harmonized.

Further, the PROMINENT consortium will seek to collaborate with other projects across European and national initiatives, such as (but not limited to) MOPEAD (12), PRODEMOS (13), EUROFINGER (14), ROADMAP (15), NEURONET (16), PREDEM (17), EPND (18), and ABOARD (19), as well as the recently announced IHI projects AD-RIDDLE and PREDICTOM.

2.5. Security considerations

When developing the predictive models, we aim to minimize the transfer of data through the use of federated architecture. The system will not disclose patient level information nor will the models output any patient identifying information. An independent ethics advisor will be appointed to monitor any issues that may arise.

3. Evaluation and validation of the digital platform

Two prospective studies will soon begin to (1) *evaluate* how well the decision support system provides relevant, actionable information to clinicians, patients, and care partners, and (2) generate *validation* data on the accuracy of the diagnostic and prognostic estimate of the system, compared with clinical reference standards and actual outcomes.

The evaluation study will be conducted by digital surveys to patients and care partners, before and after using the system. Structured interviews will be conducted with clinicians, patients, and care partners at each site to obtain detailed feedback, identify issues and opportunities for improving the system and user experience.

The validation study will be conducted as a prospective, single-arm study where the intervention (CDSS) is received by all participants. Study participants will include patients attending regular initial visits for a suspected cognitive disorder at participating specialist clinics. Inclusion criteria will be broad to reflect the patient population seen under routine care conditions. Subjects who contributed to data used in the training of the predictive algorithms will not be included.

The primary endpoint is the diagnostic accuracy of the CDSS, and will be measured by comparing the system's output with the clinical diagnosis at baseline and after 24 months of follow-up, as rated by an independent panel of specialists. The accuracy of predictions of disease progression will similarly be assessed by comparing system predictions with actual disease progression (e.g., change in MMSE scores from baseline) at 24 months of follow-up. When possible, data will be collected directly through the CDSS. Confidence in diagnosis will be assessed through visual analog scales administered by questionnaire to clinicians before and after accessing the system. The targeted sample size is 125–150 patients per site, for a total sample size of around 800 patients. The instrument used for assessment of cognitive status (MMSE or MoCA), will be determined through local practices as well as licensing conditions for the instrument to ensure data availability.

4. Applying the platform to support introduction of new technologies

At the time of writing, the recent approval of lecanemab and positive trial results for donanemab spell an exciting advancement for the treatment of dementia. However, the process of integrating the treatments into the healthcare system is complex. Thus, there is an increased need for support across the clinical implementation process. The PROMINENT digital platform can make important contributions by enabling generation of RWE and evaluation of new interventions as well as their pricing and reimbursement.

Starting within the clinic, the platform can identify eligible participants, calculate risks and benefits, and provide recommendations on how to initiate treatment at the individual level. The system will do so through comparing patient characteristics with eligibility criteria and evidence from clinical trials or other studies. In this way, the platform will impact treatment strategy and triaging. Once treatment is initiated, the system will provide a framework for consistent follow-up of treatment effectiveness and monitoring of side-effects, in line with what is needed to generate RWE data and health technology assessments (HTA). The main task of reimbursement agencies and HTA bodies is to ensure appropriate, safe, and cost-effective use of innovative therapies.

The generated data from the digital platform will contain de-identified patient-level data that is summarized, and then aggregated across health care providers. Based on this aggregated data, pre-defined analyses and reports are generated that answer key questions about the uptake, usage, impact, and outcomes with the new technology of interest. The focus will be on metrics of interest and relevance for reimbursement agencies and HTA bodies, to allow clinicians to fulfill requirements on follow-up and data collection with minimum administrative burden.

By generating RWE data, the platform will assist pharmaceutical companies in developing new interventions for neurodegenerative disorders by likely reducing the cost and burden of stand-alone phase IV clinical studies and increase the accessibility of healthcare databases. Thus, the successful implementation of the RWE module may contribute to speedier (re)assessment and follow-up by agencies benefiting both patients and innovators.

We will develop a set of specifications for the HTA module based on input from agencies. A standardized analysis protocol will be developed to obtain the metrics of interest relating to safety, efficacy, and cost-effectiveness. The protocol will serve as a template for the implementation of specific technologies and will be developed in

consultation with clinicians, health technology assessment bodies, patients, and care partners.

5. Project limitations and potential obstacles

Based on the current study design there are a few limitations and obstacles that we must take into consideration. First, the harmonization of the different data sources represent a key hurdle, as available data types differ across each source. Next, there could be some difficulties in implementation of the digital platform for countries which do not make extensive use of EHR, thus limiting the accuracy in comparison to countries with complete EHR coverage. Finally, the PROMINENT digital platform will primarily be targeted to memory clinics, although we hope to extend its use to primary care in the future.

6. Potential impact of PROMINENT

6.1. Broader impact

6.1.1. Understanding comorbidities

Patients seen in routine care with a suspected cognitive disorder often have comorbid illnesses, such as cardiovascular disorders, type 2 diabetes, and psychiatric disorders (20). Comorbidities can have a decisive influence on neurodegenerative disease diagnostic investigations and the interpretation of their results, e.g., reduced renal function can influence cut-off values on plasma biomarkers which changes the interpretation of test results (21). Additionally, the presence of comorbidities can also impact the initiation of treatment. The appropriate use recommendations for aducanumab, the first therapy to obtain regulatory approval in the United States, do not recommend treatment for patients with comorbid neurological or psychiatric conditions, or any poorly controlled or severe medical illness until the condition is 'managed and stable' (22). This guidance is nonspecific with a limited evidence base since patients with significant comorbidities were excluded from the clinical trials of this therapy. Despite the clear impact of comorbidities on health outcomes, research has been hampered in part due to small study sizes. The development and utilization of the PROMINENT digital platform can provide important contributions to this field through the utilization of our data.

6.1.2. Overarching impact

The PROMINENT digital platform aims to make improvements on each aspect of the healthcare system, as well as to facilitate the cohesion of patients, care partners, clinicians, reimbursement agencies, and HTA organizations. This collaborative effort represents the incremental refinement of a digital platform already available for use in a clinical setting. Patients will directly benefit from the information provided by the platform on disease status, prognosis, and potential risks and benefits of novel therapies. Moreover, the already built in data collection feature will save clinicians time and reduce the administrative strain, while also benefiting reimbursement agencies and HTA organizations. Although, the primary target of the platform is Alzheimer's disease (AD) and other dementia disorders, scalability is possible to other neurodegenerative diseases and beyond. While ambitious, it is our hope that this project represents a tangible first step toward a paradigm shift in the care of neurodegenerative disorders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

PROMINENT Consortium members

Karolinska Institutet, Stockholm, Sweden; Combinostics Oy, Tampere, Finland; Synapse Research Management Partners SL, Barcelona, Spain; Alzheimer Europe, Luxembourg, Luxembourg; Region Stockholm, Sweden; BioArctic AB, Stockholm, Sweden; Klinikum der universitaet zu Koeln, Cologne, Germany; IHE Institutet för Hälsoekonomi AB, Lund, Sweden; Barcelonaβeta Brain Research Center; Pasqual Maragall Foundation. Barcelona, Spain; CHU Hopitaux de Bordeaux, Bordeaux, France; University Medical Center, Lubljana, Slovenia; ITA-Suomen Ylipisto, Kuopio, Finland; Stichting VUMC, Amsterdam, the Netherlands.

Author contributions

LJ and AT drafted the first version of the manuscript. All authors reviewed the manuscript and approved the final version.

Conflict of interest

ME and SE were employed by BioArctic AB. JL and LT were employed by Combinostics Oy.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1175922/full#supplementary-material

SUPPLEMENTARY FIGURE 1

The figure shows the cDSI tool with the list of biomarkers available for the patient (left), the classification panel (middle), and a comparison of the patient's disease state (yellow line) versus the distributions of AD and FTD cases (right). The tool shows that the patients data profile fits best to the distribution of previous AD cases, with FTD being the second most likely diagnosis.

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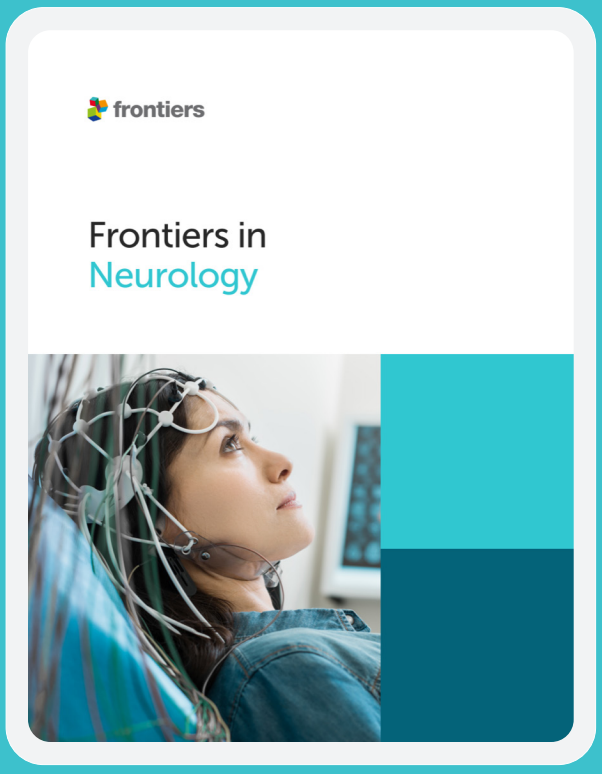

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