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Please cite this paper as:

OECD (2015-04-09), "Public-private Partnerships in Biomedical Research and Health Innovation for Alzheimer's Disease and other Dementias", *OECD Science, Technology and Industry Policy Papers*, No. 20, OECD Publishing, Paris.
http://dx.doi.org/10.1787/5js36rc8wwbt-en



OECD Science, Technology and Industry Policy Papers No. 20

Public-private Partnerships in Biomedical Research and Health Innovation for Alzheimer's Disease and other Dementias

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DSTI/STP/BIO(2014)9/FINAL

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FOREWORD

The Organisation for Economic Co-operation and Development (OECD), through its Working Party on Biotechnology, undertook a project on "Healthy Ageing and Biomedical Innovation for Dementia and Alzheimer's disease". The project was conducted under Output Result 2.1 of the WPB Programme of Work and Budget 2013-14 and aimed to identify good practices to strengthen effective co-operation at a global level for the governance of biomedical technologies and health innovation in Alzheimer's disease and other dementias.

This report is in line with recommendations of the G8 Summit Declaration to strengthen collaboration for innovation and cross-sector partnerships focused on social impact investment, new care and prevention models, and academia/ industry partnerships. It had been informed by a literature review and information on public-private partnership case studies provided by members of the Working Party on Biotechnology.

The work on public-private partnerships was conducted in co-operation with the OECD Working Group on Innovation and Technology Policy (TIP).

The secretariat wishes to express thanks to Ms. Hana Kim (Seoul National University, Korea) for the substantial contribution to this report.

The Committee for Science and Technological Policy (CSTP) approved this report in February 2015 and recommended that it be made available to the general public. The report is published on the responsibility of the Secretary-General of the OECD.

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EXECUTIVE SUMMARY

The ageing of populations is coupled with an increase in dementia cases worldwide creating enormous medical, societal and economic challenges for governments and their public health systems. Epidemiological projections indicate that there will be a rapidly expanding number of cases of Alzheimer's disease and other dementias during the coming years. Alzheimer's is a complex, chronic neurodegenerative disease and represents the most common form of dementia. There is as yet no effective treatment for Alzheimer's disease. Stakeholders are joining forces to overcome medical scientific, regulatory, organisational and financial barriers in research and health innovation to accelerate the development of disease-modifying therapies and diagnostics for Alzheimer's disease and other dementias.

Despite significant discoveries in neuroscience and genetics and substantial financial investments, the number of new, innovative therapies based on biomedical technologies entering the market has been limited. Key barriers in research and health innovation for Alzheimer's disease mirror the major challenges stakeholders are facing in other complex diseases: 1) high investment costs and technical risks in research and clinical development; 2) lengthy processes from discovery research to regulatory approval; and 3) scattered knowledge and infrastructure. The situation for Alzheimer's disease is further complicated by an inadequate understanding of the disease pathology, a lack of validated diagnostic tools, and regulatory frameworks that may not meet the needs of a highly complex research environment.

To address this important topic, the OECD Working Party on Biotechnology (WPB) undertook a project on healthy ageing and the governance of biomedical research and health innovation. This report is the result of efforts to obtain evidence on how governments and other stakeholders can jointly support innovative approaches to address the key challenges of Alzheimer's disease and other dementias through multi-stakeholder collaborations. This report looks at the roles and options of stakeholders (governments, regulatory agencies, academia, small and mid-size biotech companies, the pharmaceutical industry, and patient organisations) in public-private partnerships for product development in Alzheimer's disease and other dementias.

There is a growing understanding amongst stakeholders that the pharmaceutical industry cannot be solely responsible for most of the drug discovery and development in disease areas characterised by complex pathologies, high resource-needs, and limited investment. Multi-stakeholder partnerships have been evolving to share resources, benefits and risks throughout the value chain of therapeutic development for medical needs paired with a strong public-health impact. Public-private partnerships are the most prominent example where governments, academia, patient organisations, and the private research community create an environment of open-science and resource sharing. Partners bring together the critical means to address grand challenges and leverage synergies from work across previously well-defined boundaries. Through this approach the role of academia and small and medium-sized biotech companies in health innovation is expanded from basic to translational and early clinical research. Pharmaceutical companies take advantage from working in a less constraint and more integrated environment together with otherwise competitive actors. The joint use of resources in neuroscience is considered as one of the main drivers of stakeholders to engage in public-private partnerships: academic research can offer a high degree of disruptive innovation to diversify therapeutic research; vice versa the private research industry can provide the technical, organisational, and financial

means to scale-up early research to proof of concept. For governments and regulatory agencies public-private partnerships can help make pharmaceutical research policy more responsive to the changing nature of technology, research practice, and to social and global challenges. Ultimately, the closer collaboration between governments, academia, and the private research community can enable a more efficient use of complementary strengths in order to generate and deploy innovation for health. In order to leverage the full potential of multi-stakeholder partnerships, the issues and needs, motivations, and objectives of each individual actor need to be addressed upfront and should be mirrored by adequate policy frameworks.

Public-private partnerships have the potential to reform existing drug development models through the implementation of non-linear, adaptive processes and a strengthening of collaborative approaches for the life-span management of therapies and diagnostics: starting from basic biomedical and translational research to product registration and post-marketing surveillance. This could lead to a higher quantity and quality of potential new drugs entering clinical trials – ultimately, reducing the attrition rate during clinical trials and limiting financial loss. In Alzheimer's disease, synergistic partnerships between policy makers, the research community and patient organisations mainly form in the precompetitive space of discovery and early clinical research. Due to the heterogeneity of stakeholders and the involvement of otherwise economically competitive pharmaceutical industries, this is a necessary but not ideal condition. Policies could help to expand the precompetitive space further down the value chain of product development and, thereby, increase trust between stakeholders and increase investment.

A close collaboration between public research institutions and the pharmaceutical industry is seen as a key success factor for the translation of innovation into product development strategies. On the one hand, academia has been advancing medical scientific knowledge and thereby delivering the majority of key enabling discoveries in the fundamental and mechanistic aspects of disease biology. On the other hand, the pharmaceutical industry has been the main driver of product development through transferring knowledge into innovative therapies and diagnostics. In public-private partnerships, difficulties between academia and the pharmaceutical industry arise from concerns about differences in their operational set-up, management, ownership and benefits. Both sectors can best engage in partnerships in which the goals and constraints of each entity are respected in order to avoid tension and to ensure efficient use of resources to bridge the translational gap. The importance of academic research as a source of innovation and scientific objectivity in public-private partnerships can be strengthened by long-term (public) funding opportunities and the placing of a neutral research-enabler at the interface between public and private stakeholders.

In public-private partnerships, academia benefits from having access to private research infrastructures and from being recognised as an important partner in health innovation. The efficiency of academia-industry partnerships is dependent on strong governance and project management structures of both public and private entities. The structured frameworks of public-private partnerships offer an adequate environment for more systematic and sustainable collaborations between the pharmaceutical industry and academia. This is expected to encourage discovery research and the use of emerging biomedical technologies in order to deliver innovative therapies in Alzheimer's disease.

The role of policy makers can be to develop and implement governance mechanisms that respect the diversity of stakeholders, their capabilities and goals. Placed at the interface between public and private researchers, governments and regulatory agencies can facilitate the use of complementary strengths and help to overcome scientific, organisational, regulatory and economic barriers. The

integration of public-private partnership models into national policy settings and into value-driven drug development models can help to pool the individual strengths, objectives and expectations from otherwise competing entities towards one common goal. This would help to ensure early communication, transparency, public trust and the respect of patients' needs.

In essence, public-private partnerships can facilitate a reform of traditional research and health innovation models towards more efficient innovation strategies. As a neutral environment, public-private partnerships can help to accelerate the development of effective therapies for Alzheimer's disease through supporting the mission of each stakeholder and incorporating the strengths, opportunities and needs of each individual stakeholder or stakeholder group. This can help to 1) strengthen discovery research and the delivery of quality drug candidates for translational and development programmes, 2) reduce failure during late-stage development, 3) manage costs and risks, 4) enable early communication between innovators and regulators, and 5) develop the global and national policy and regulatory frameworks that combine the needs of all stakeholders.

INTRODUCTION

The ageing of populations leads to an unprecedented need for health-related services and therapies for Alzheimer's disease and other dementias. With over half of all diagnosed cases, Alzheimer's disease represents the most common form of dementia (Prince, 2014). Dementia is a neurodegenerative condition, which impairs thinking, memory and coordinative functions. The World Health Organisation (2012) expects a tripling of dementia cases by 2050 (36 million people living with dementia in 2010, 115 million in 2050). With no effective therapy for Alzheimer's disease available, the socioeconomic costs will be enormous (USD 604 billion attributed to dementia globally in 2010 alone). Today's healthcare systems are insufficient to respond to the coming challenges and there is as yet no effective treatment for Alzheimer's disease (Feldman et al., 2014; Prince, 2013).

According to Scott (2014), the estimated total costs for the development of an effective (disease-modifying) therapy for Alzheimer's disease would be USD 5.7 billion – approximately five times the commonly cited costs (of approximately USD 1 billion) to develop a new, innovative drug (Bunnage, 2011; DiMasi, Hansen and Grabowski, 2003; Sternitzke, 2010). However, due to the use of different methods (for example, the inclusion of research costs not directly related to a specific drug), data sources, and research and development time periods, there are large variations in cost estimates for the delivery of a new drug (Adams and Brantner 2006; Morgan et al., 2011). An analysis conducted by Herper (2013) states maximum costs of approximately USD 10 billion per new drug approval. High investment costs and attrition rates during clinical development may have led to the relatively few clinical trials undertaken in Alzheimer's disease. It is worth noting that the number of potential drugs in Alzheimer's disease progressing to regulatory review is among the lowest found in any therapeutic area (Cummings, 2014). Given the costly and long drug development periods with disproportionately lower chances of successful market entry of new central nervous system (CNS) drugs the risks associated with CNS drug development are often weighed as being too great for many pharmaceutical companies. This is regardless of the continued need for treatment and an ever increasing market for effective CNS drugs (Kaitin, 2011).

It is evident that large investments in biomedical research and innovative conceptual frameworks are needed to address Alzheimer's disease in the context of the complex relationships that exist between science, technology, regulation and public policy. For example, in addition to other substantial funding mechanisms in dementia, the UK "Global Clinical Trials Fund" recently launched a new scheme to support clinical trials that have potential to be of benefit to dementia patients. The fund aims to make GBP 20 million available for early-stage trials over the next five years, supporting clinical research into new treatments for diseases like Alzheimer's. Canada has invested CAD 236 million over the past ten years in dementia-related research through the Canadian Institutes of Health Research. More specifically, the Canadian Consortium on Neurodegeneration in Aging (CCNA) has received funding of CAD 31.5 million over five years from the Government of Canada, through the Canadian Institutes of Health Research, and a group of 13 partners from the public and private sectors, including the Alzheimer Society of Canada and Fonds de Recherche du Québec – Santé. The CCNA researchers will also benefit from an additional CAD 24 million investment by a subset of the partners in Ontario and Quebec. Further, the Australian Federal Government decided in 2013 to invest AUD 559 million to support Australian health and medical researchers generating new health discoveries. And in the United States the NIH expects to spend USD 566 million on Alzheimer's disease in the fiscal year 2015.

The enormous scale of the pending crisis, unresolved biomedical questions and high investment risks have triggered the formation of non-profit organizations and collaborative research models between public and private stakeholders in biomedical research and health innovation (Snyder, 2014). Public-private partnerships offer a unifying environment that combines the expertise and strengths of all stakeholders across institutional and scientific disciplines. Questions have been raised about the major gaps in the understanding of Alzheimer's disease and which factors are holding back the development of effective medicines. Researchers have learnt important lessons from failures of therapeutic concepts in clinical trials, and are now testing new options, which take into consideration the multifactorial nature of Alzheimer's disease (Fitzgerald, 2014; Herrup, 2013). The following recommendations have been made in order to overcome persisting barriers in research and health innovation (Scott, 2014): 1) investing in diagnostic research for early detection and disease stratification; 2) streamlining enrolment of participants into clinical trials through candidate registries; 3) implementing qualified biomarkers in clinical trials; 4) strengthening of preclinical and translational research; and 5) establishing research networks and combining capabilities of stakeholders. In Alzheimer's disease, the aims and objectives of stakeholders are as diverse as the issues ahead. There is consensus that neither academia nor biotechnology companies, nor the pharmaceutical industry alone can solve the challenges and take ownership of the large risks. As a result, the number and diversity of public-private partnerships dedicated to the delivery of effective medicines for Alzheimer's disease has been increasing. This has led to a growing need for coordination, alignment, funding and the development of policy frameworks specific to disease areas (Ivinson et al., 2008; Stephenson, 2014).

During the G8 Dementia Summit in London on 11 December 2013, Health Ministers met to discuss how to shape an effective international response to dementia. Amongst other priorities, the "Dementia Summit Declaration"[1] asked Ministers to:

- Work together, share information about the research we fund, and identify strategic priority areas, including sharing initiatives for big data, for collaboration and cooperation;

- Develop a co-ordinated international research action plan which accounts for the current state of the science, identifies gaps and opportunities, and lays out a plan for working together to address them;

- Encourage open access, where possible to all publicly funded dementia research and to make the research data and results available for further research as quickly as possible, while protecting the privacy of individuals and respecting the political and legal frameworks of the countries in which the research is conducted;

- Take stock of our current national incentive structure for research, working in partnership with the Organisation for Economic Co-operation and Development (OECD), and consider what changes could be made to promote and accelerate discovery and research and its transformation into innovative and efficient care and services;

- Hold a series of high-level fora throughout 2014, in partnership with the OECD, WHO, the European Commission, the EU Joint Programme on Neurodegenerative Disease (JPND), and civil society, to develop cross sector partnerships and innovation.

Following the discussions held at the G8 Summit on Dementia in London, Canada and France co-hosted one of four Global Dementia Legacy Events in Ottawa (September 2014). This explored how to

take advantage of the synergies between industry and academia in order to release the power of discoveries. Through expert panel discussions, delegates established the way forward for the development of new approaches to partnerships and collaboration between industry and academia. Rona Ambrose, Canada's Minister of Health, announced a series of new initiatives and investments highlighting the commitment of the Government of Canada to tackling dementia. These included, for example, the launch of the Canadian Consortium on Neurodegeneration in Aging; a commitment to bring the successful Dementia Friends programme to Canada; a new partnership to support transformative dementia research; the release of the national dementia research and prevention plan; and the release of "Mapping Connections: An Understanding of Neurological Conditions in Canada". The legacy event in Ottawa aimed to 1) explore collaborative opportunities for research into novel diagnostic, pre-emptive and therapeutic approaches to dementia by bringing together academia and industry; 2) provide a better understanding of the impact of the paradigm shift in pharmaceutical research on the development of new drugs against dementia and find appropriate incentives to engage private research partners this field; 3) foster a collective approach to problem solving through the pooling of resources and the sharing of cohorts, data and best practices.

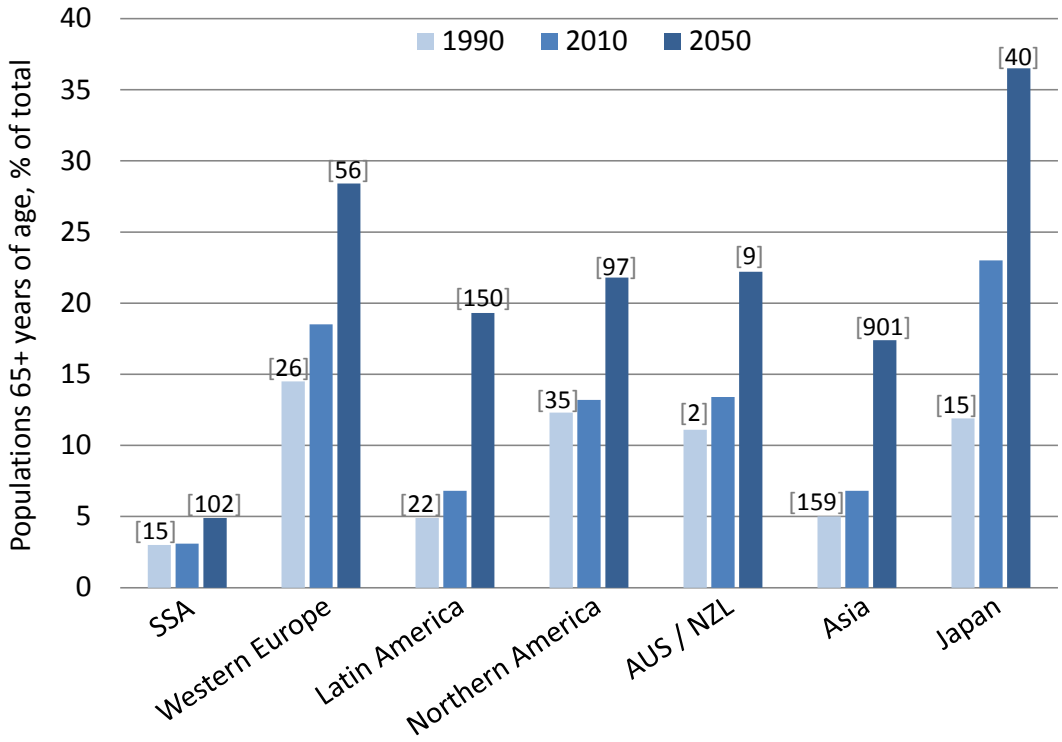
The report builds on previous work performed by the Working Party on Biotechnology on biomedical research and healthy ageing (OECD, 2013a; OECD, 2013b; OECD, 2014). It has been informed by case studies and a literature review; the report presents the key challenges and options for collaborative work between academia, the pharmaceutical industry, governments and regulatory agencies in research and health innovation. As a representative case for other forms of dementia, the report focuses on public-private partnerships in Alzheimer's disease and seeks to describe how the unique biomedical and organisational challenges are mirrored by the potential of emerging technologies, new drug development models, and evolving policy and regulatory frameworks. The report explores the options of public-private partnerships as a neutral space for stakeholders to accelerate the delivery of effective therapies and diagnostics for Alzheimer's disease.

BACKGROUND AND CONTEXT

Awareness of the complex nature of Alzheimer's disease, the limited resources allocated to research and the low efficacy of health innovation in this area have driven the ongoing reshaping of institutional structures and drug development models (Feldman, 2014; Ivinson, 2008). As indicated by the OECD (2010), new business models could become increasingly important in biotechnology as solutions to issues such as overcoming diseases and boosting food supply. In reality, a range of collaborative, cross-functional partnerships and business models have started to emerge (FitzGerald, 2010; Scott, 2014). These include collaborative and incubator models aimed at better information sharing, containment of research costs, and better management of the drug development approaches needed to tackle complex diseases. Key stakeholders, such as governments, regulators, academia, the pharmaceutical industry and non-profit organisations are forming disease-focused alliances that extend beyond previously well-defined boundaries. Despite their potentially competing interests in areas such as intellectual property and late stage development, multilateral partnerships have been formed around complementary strengths, joint interests and needs. The involvement of all stakeholders is critical in developing and sustaining the mechanisms that support the translation of innovative biomedical technologies into discovery and clinical research programmes.

The ageing of populations leads to an increased prevalence[2] of Alzheimer's disease and other forms of dementia. Dementia is a condition which manifests as a slowly progressing loss of cognitive functions, such as memory, language, problem solving and coordination. Alzheimer's disease is the most common form of dementia and accounts for 50-70% of dementia cases in the elderly (Feldman et al., 2014). Dementia is a syndrome that predominantly affects people 65 years and older – the estimated prevalence of dementia in this this age group is 6-7%. As shown in Figure 1, the proportion of people over the age of 65 will drastically increase during the next 35 years, coupled with a rise of dementia cases in all regions of the world, especially in Latin America and Asia. According to the World Health Organization (2012) the total number of people with dementia worldwide is estimated to increase from 35.6 million in 2010 to 115.4 million in 2050. Due to financial constraints and inadequate public health systems, resource limited countries will be strongly affected by Alzheimer's disease and other dementias in the coming years.

Figure 1. Populations 65 years of age and above in some countries and regions



Note: Sub-Saharan Africa (SSA), Australia/New Zealand (AUS/NZL). Figures in brackets are the absolute numbers of people 65+, millions. Source: OECD, based on www.unpopulation.org (accessed January 2015).

More than a century since Dr. Alois Alzheimer first described abnormal protein deposits in the brain of a patient (Maurer, Volk and Gerbaldo, 1997), initial hopes that Alzheimer's disease would be a pathologically clearly-defined neurochemical system degeneration cannot be confirmed (Plum, 1979; Huang and Muckle, 2012). On the contrary, research findings indicate a multifactorial and syndrome-like nature of Alzheimer's disease, which probably cannot be addressed by a single drug alone (Herrup, 2013; Maccinoni, 2009). Despite significant insights into the biochemical and molecular changes of disease progression, the available five drugs on the market do not address the underlying disease pathology and only temporarily help in modifying the symptoms (Cummings, 2014). A significant amount of resources in Alzheimer's research remain in the early discovery and translational phase across various scientific disciplines, such as neuroscience, genetics, immunology, and radiology – aiming to identify new targets and to develop disease-modifying therapies (Eldik, Koppal and Watterson, 2002; Feldman et al., 2014). This means to advance the understanding of disease mechanisms, to develop more predictive animal models of the disease, to qualify biomarkers, and to support translational research. A combination treatment might be needed to address the different factors which determine the complex disease pathology (Herrup, 2013).

Emerging biomedical technologies, such as genomics, antisense technology, stem cell technology, tissue engineering, and synthetic and systems biology can provide the necessary means to solve persisting issues in the development of innovative medicines (Andrieux and Couvreur, 2013; Choi et al., 2014; Reiman, 2014; Roy, 2014; Young, and Goldstein, 2012). However, the decreasing efficiency of drug development coupled with unresolved biomedical questions in chronic diseases (including Alzheimer's disease), complex technological infrastructure needs as well as lengthy and costly development processes have led to a rethinking of traditional models in which the pharmaceutical industry has the sole responsibility to perform the necessary research and transfer of potential drug from the laboratory to the bedside (Milken Institute, 2012; Chung, 2014; Lessl and Douglas, 2010). This process started more than 10 years ago, when large-scale mergers in the pharmaceutical industry were followed by a pronounced definition of stakeholder roles in the research and development process. The pharmaceutical industry has increasingly focused on selected disease areas, late-stage clinical development, manufacturing and marketing, whereas academia has strengthened its engagement in innovative discovery and translational research (Eldik, Koppal and Watterson, 2002). During this time, outsourcing of intermediate steps of the research and drug development process has further reinforced the definition of stakeholder roles. However, the all-in-one house development model of the pharmaceutical industry, which aimed to combine key biomedical research and clinical development capacities, has not been effective in all disease areas and is now questioned by stakeholders (Bunnage, 2011; Hudson, and Khazragui, 2013; Lindgardt, Reeves and Wallenstein, 2008; Mullard, 2011).

The key issues of current biomedical research and health innovation strategies comprise (Broich et al., 2012; Feldman et al., 2014; Scott, 2014): 1) high investment costs and technical risks in research and development; 2) lengthy processes from discovery research to regulatory approval; 3) intellectual property issues outside the precompetitive space; and 4) scattered knowledge and infrastructure. These issues have limited the success of drug development programmes in Alzheimer's disease and are now being addressed in partnerships between the research community, policy makers and the public (Snyder, 2014). Due to the lack of internal resources stakeholders are exploring integrated, collaborative models in order to increase the efficiency of research and health innovation (Feldman et al., 2014; Ivinson et al., 2008; Scott, 2014). The US President's Council of Advisors on Science and Technology[3] (PCAST) recommends to: "Double the output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and government working together to decrease clinical failure, clinical trial costs, time to market, and regulatory uncertainty" (PCAST, 2012). This will require the active involvement of all stakeholders across governments, regulatory agencies, the pharmaceutical industry and non-profit organisations (Feldman et al., 2014; Human Health and Services, 2014).

Public-private partnerships for product development mirror the multifactorial nature of Alzheimer's disease and combine the strengths of scientific disciplines and policy areas. The lead in forming these new partnerships has been taken by philanthropic organisations, governments and regulatory agencies. During recent years, the engagement of the pharmaceutical industry in health innovation for Alzheimer's disease has been limited – partly due to financial risks, set-backs in major clinical development projects and a lack of promising disease targets. Researchers in both public and industry settings share similar requirements for access to infrastructure, technical skills, bio-samples and information. Cross-sectoral alliances could facilitate access to dispersed sources of infrastructure (for example, research tools, compound libraries, biological samples, computer systems), intangible assets (for example, expertise, knowledge, intellectual property), and funding sources. Governments and regulatory agencies play a key role in public-private partnerships through the provision of context-

specific policies and regulatory frameworks in research and health innovation. They can develop a vision of what can be achieved and the needs of Alzheimer's patients.

In essence, the stakeholders in biomedical research and health innovation for Alzheimer's disease and other dementias are very diverse: their scientific expertise and objectives range from basic biomedical and discovery research to clinical development and regulatory review. It is recognised that the involvement of all stakeholders in policy development increases the quality and efficiency of governance models and that harmonised policies help to overcome barriers in the translation of emerging and converging technologies into applied research and clinical trials. Strongly networked researchers enhance the value of collaborations by aligning their activities where appropriate, thereby increasing the effectiveness of their efforts. Despite the organisational challenges involved, collaborative structures allow a broad spectrum of areas to be addressed and offer significant opportunities for the complementarity of expertise in basic research and therapeutic development. This report aims to discuss recent developments in public-private partnerships for biomedical research and health innovation in Alzheimer's disease and other dementias.

PUBLIC-PRIVATE PARTNERSHIPS IN RESEARCH AND HEALTH INNOVATION – AN OVERVIEW

Individual researchers and institutions continue to be the main recipients of National Institutes of Health (NIH) support, though funding of transdisciplinary research collaboration has continued to mature (Collins, 2014). The landscape of biomedical research and health innovation has been shaped by a strengthening of collaboration between stakeholders and sectors to address some of the inefficiencies of existing innovation models. Collaboration is often seen as a means of efficiently managing limited resources while building on the individual strengths of partners. As distinct from bilateral agreements with a narrow scope and rigid governance structures, Thomson, Perry and Miller (2009) defines collaboration as follows: "Collaboration is a process in which autonomous or semi-autonomous actors interact through formal and informal negotiation, jointly creating rules and structures governing their relationships and ways to act or decide on the issues that brought them together; it is a process involving shared norms and mutually beneficial interactions."

Previously limited in their scope, collaborations between, for example, academia and the private sector, or between large pharmaceutical companies, have evolved into multi-stakeholder partnerships aiming to better translate innovative research findings into product development. This necessitates the sharing of knowledge, infrastructure, costs, benefits and risks (Mullard, 2011). Defining the roles that stakeholders play in research and health innovation is an important step towards the development of effective policies.

This section presents an overview of the challenges and opportunities of public-private partnerships in biomedical research and health innovation for unmet medical needs. First, key drivers for collaboration along the value chain of discovery research, clinical development and regulatory review are discussed. The differences between public-private partnerships in public health and product development are presented. This section then focuses on the unique environment of Alzheimer's disease in which partnerships aim to establish new processes for clinical research, medicines regulation and data sharing (Feldman, 2014; Kozauer and Katz, 2013).

General aspects of public-private partnerships for product development

Public-private partnerships are alliances in which public and private entities work together and share resources and results to achieve mutually agreed objectives, which would have been out of range for each individual partner. Public-private partnerships are the most prominent example of multi-stakeholder collaborations that bring together the critical means from academia, governments, authorities, the pharmaceutical industry and patient organisations to drive the process of health innovation (Goldman, Compton and Mittleman, 2013; Vaudano, 2013). Their ultimate goal is to produce the maximum possible value, greater than the sum of what each partner alone could accomplish without collaboration. The growth in the number and complexity of public-private partnerships for product development (therapies, diagnostics) is an indication of their importance as collaborative research frameworks for Alzheimer's disease. As to Lessl and Douglas (2010) the number of structured, multi-dynamic partnerships between public and private entities (e.g. networks or competence clusters) has been increasing due to resource and information needs, and in order to address complex public health issues. There are prominent examples, in which governments, academia and private enterprises have been working together in order to manage larger projects, to solve complex

issues and to control risks. The rise in the number of public-private partnerships has been led by the aim to fill drug development pipelines, shorten timelines, a better management of costs, an increase of information sharing, broader scope and more inclusiveness. Depending on the research area and health context public-private partnerships either focus on clinical development, medicines access and rational use, or form around early discovery and translational research projects for product development. The advantage of the public-private partnership model in overcoming medical scientific, financial and operational barriers has been proven by prominent alliances in public health (see Box 1). Many of these have been created to address unmet medical needs where markets are limited (Buse and Walt, 2000; Witters, Marom and Steinert, 2012). The complex challenges of public health systems in resource limited countries require a broad scope of partnerships with a strong delivery focus (Campos, Norman and Jadad, 2011).

Scientists in academia and in the pharmaceutical industry share similar needs for information, tools and technical skills. Significant progress in biomedical research has accelerated the need for information sharing and cross-sectorial collaboration (Mitchell, 2008; Trochim, 2011). Researchers are increasingly following a "systems approach", which integrates knowledge, methods and perspectives from different disciplines and promotes rapid exchange and dissemination of information among virtual global expert networks. Stakeholders (academia, small and mid-size biotech companies, the pharmaceutical industry, governments and regulatory agencies) are exploring options to join forces in public-private partnerships across previously well-defined boundaries. Public-private partnerships have gained recognition across institutional barriers due to a shift in the view of how public and private sectors define their roles and what can be gained from working together. In order to make such partnerships successful, their objectives should be defined around a common ground with joint interests and where activities can be aligned between all partners. Additional challenges in cross-sectoral partnerships are cultural differences between private and public partners, managerial and financial issues, and conflicting goals and objectives.

The complexity of scientific challenges in unmet medical needs (e.g. neurodegenerative diseases), coupled to high attrition rates during clinical development and a growing economic pressure, has triggered a rethinking of traditional research and drug development models. Iterative, modular development processes and horizontal multi-stakeholder partnerships are now emerging, but might not be compatible with existing policies and traditional regulatory paradigms (Hudson and Khazragui, 2013; Stuart, Ozdemir and Ding, 2007). In parallel, the role that governments and regulatory agencies play has been changing from an observing and monitoring function to a fully integrated partnership throughout the value chain of product development. Their early involvement in the conduct of pre-clinical and translational research and planning of clinical trials is considered as an important measure to reduce the failure rate of clinical development and to support regulatory review and approval. Vice versa, the private sector has become an integral part of national programmes and government activities (Mitchell, 2008). During the last 15 years, public and private partners have been moving closer together and combining ideas in order to develop innovative and more inclusive strategies for unresolved health issues. Public-private partnerships can reduce the time it takes to move biomedical discoveries to clinical practice through a multi-disciplinary and collaborative approach, in which stakeholders share knowledge, competencies, resources and risks. By combining the individual strength into a common goal, partners benefit from both specialised knowledge and a broader scope (Moses and Martin, 2011).

Partnerships in research and health innovation can help to overcome barriers to financial investment and strategic risks. Collaborative product development permits individual partners to address complex biomedical and drug development issues, which would be too expensive for one entity

alone (Schacht, 2011). It has been estimated by Scott (2014) that the total research and development costs of a new, effective drug for Alzheimer's disease could be reduced from approximately USD 5.7 billion to USD 2 billion through a collaborative approach involving public and private stakeholders addressing the main barriers in research and health innovation. Agreements between purchaser (insurer, patients) and provider (innovator, manufacturer) in the form of risk-sharing schemes[4] are one way to control potential financial losses resulting from failure in research and development and to support investment in uncertain, high-risk disease areas. These risk-sharing schemes, which may attract the pharmaceutical industry back into the market, reflect a paradigm shift from the traditional, linear business model towards value-based agreements between stakeholders for the development and population-wide use of innovative medicines (Adamski et al., 2010). In order to measure the effectiveness and applicability of the various approaches, an in-depth understanding of the issues, opportunities and trade-offs of each is required. Pilot risk-sharing projects and surveys may provide the evidence needed to create generic implementation models and policies (Espín, 2011; Garrison et al., 2013).

According to Schacht (2011), public policies and legislative initiatives can support the commercialisation of new products within the context of public and private collaborations. As an example of how work in partnerships and information sharing can be enhanced by governments, the US Congress developed the Cooperative Research and Development Agreement (CRDA)[5] – a mechanism which aims to formalise agreements between government agencies and private entities. Using the CRDA as a technology transfer tool, public and private entities work together towards the commercialisation of innovative research findings. In particular, the CRDA aims to:

- Provide incentives that help speed the commercialisation of federally-developed technology;
- Protect any proprietary information brought to the CRADA effort by the partner;
- Allow all parties to the CRADA to keep research results emerging from the CRADA confidential and free from disclosure through the Freedom of Information Act for up to 5 years;
- Allow the government and the partner to share patents and patent licenses;
- Permit one partner to retain exclusive rights to a patent or patent license.

Box 1. Examples of Public-Private Partnerships in Health

- *The Mectizan Donation Programme (MDP) has been playing a crucial role in controlling onchocerciasis (river blindness) in resource-limited countries. It was established in 1987 as a mechanism through which the pharmaceutical company Merck donates the drug Mectizan (ivermectin). Today the programme consists of six independent public health partners, along with a liaison with the US Centres for Disease Control (CDC), the World Bank and the World Health Organisation (WHO). Its clear governance and management structure, strong linkages with other public health partnerships, and the positive external perception of the programme are important success factors (Peters, 2004). Link: www.mectizan.org*

- *The International AIDS Vaccine Initiative (IAVI) was founded by the World Bank, the United Nations Joint Programme on AIDS and non-profit organisations in 1996 to share risks, costs and opportunities of biomedical research to produce an effective vaccine against the human immunodeficiency virus (HIV). The IAVI is a globally integrated product development partnership managed by a professional project manager. It consists of academic, industry and government organisations aiming to develop safe, effective, accessible, and preventive HIV vaccines. Scientific, advocacy and community partnerships, coupled with more than 40 research projects ensure efficient use of knowledge and alignment between partners (Berkley, 2006). Link: www.iavi.org*

- *The Malaria Vaccine Initiative (MVI) is a global programme of the international non-profit organisation Programme for Appropriate Technology in Health (PATH). MVI was established in 1999 through a grant from the Bill & Melinda Gates Foundation with the overall goal of accelerating the development of malaria vaccines and catalysing timely access in endemic countries. As a public-private partnership (MVI, 2014), MVI works with partners in private industry (e.g. Crucell, GlaxoSmithKline Biologicals), government (e.g. National Institute of Health, Walter Reed Army Institute of Research) and academia (e.g. University of Maryland School of Medicine, Johns Hopkins University). Link: www.malariavaccine.org*

- *The Global Polio Eradication Initiative is a public-private partnership led by national governments and spearheaded by the World Health Organisation (WHO), Rotary International, the US Centres for Disease Control and Prevention (CDC) and the United Nations Children's Fund (UNICEF). Building on the successful polio vaccination campaign (initiated in 1988), the Global Polio Eradication Initiative was launched in 2008 as an intensified eradication effort involving the wide-scale use of new tools and tactics in each country, with renewed commitment by their leaders and donors. Key partners are: the Bill & Melinda Gates Foundation, United Nations Foundation, the World Bank, the European Commission, the International Red Cross, Aventis Pasteur and De Beers. Link: www.polioeradication.org*

- *The Global Health Innovative Technology (GHIT) Fund was recently founded as an interdisciplinary and multi-sectoral non-profit public-private partnerships between the Japanese government, the UN Development Programme, philanthropic organisations and the pharmaceutical industry. It aims to accelerate the development of innovative drugs and medical technologies to diagnose, prevent and treat high-prevalence infectious diseases worldwide. Results (knowledge and products) generated will be respected as public goods with royalty free licenses (Kurokawa, 2013). Link: www.ghitfund.org*

In response to the growing number of public-private partnerships for product development and an increased organisational need, coordinating structures have been evolving to achieve a higher efficiency and use of synergies. For example, the "European Advanced Translational Research Infrastructure in Medicine"[6] (EATRIS) was established in 2008 to support a faster and more efficient translation of basic research into innovative products through the provision of state-of-the-art expertise and capital-intensive facilities to academia and the industry. EATRIS provides coordination services to academia, small and medium-sized enterprises, and to the pharmaceutical industry for the translation of research findings from the laboratory to the bedside (Dongen et al., 2013).

Canada has put in place a number of programmes to support translational research. Notable amongst these are the "Networks of Centres of Excellence Program"[7] that includes the Business-Led Networks of Centres of Excellence (BL-NCEs) and the Centres of Excellence for Commercialization and Research (CECRs). BL-NCEs are large-scale non-profit collaborative networks led by industry that aim to increase private sector investment in Canadian research. The CECRs are non-profit corporations created around academic centres that match clusters of research expertise with compatible pockets of expertise in the business community. These consortiums include neuroscience, and offer effective partnership models for dementia initiatives.

The "Top Institutes Pharma"[8] (TI Pharma) represents another example of a research enabler, which offers governance and scientific management for complex projects at the interface between academia and industry. As a public-private partnership, TI Pharma links stakeholders to enable them to combine the knowledge present in science and industry. It aims to provide transparency and reliability to collaborating partners and to foster the realisation of joint research goals. TI Pharma is one of seven "Leading Technology Institutes" established as public-private partnerships in the Netherlands since 1997 in order to increase the innovative capacity and competitiveness of Dutch companies (OECD, 2004).

The Broad Spectrum Antimicrobials (BSA) Program of the US Department of Health and Human Services, Biomedical Advanced Research and Development Authority (BARDA)[9] provides complementary funding to companies to develop drugs. Due to the scarcity of new, effective antibiotics and a decrease in investment in research and development by the pharmaceutical industry, the rise of drug resistant bacterial infections is predicted to become a global crisis. Many companies have stopped research and development programmes in the area of antimicrobials due to the scientific challenges involved and lower potential returns on investment (May, 2014). BARDA has been establishing public-private partnerships with industry partners for the development of novel antimicrobials and anticipates a long term commitment to this market. For example, GSK will conduct non-clinical and clinical studies and generate data to address the unmet medical need for new antibiotics. With the mutual consent of GSK and BARDA, preclinical drug candidates may be included in order to expand the range of potential drugs included in clinical trials. According to Robin Robinson (Deputy Assistant Secretary, BARDA) "Medical countermeasure development is risky, lengthy, and costly with many inexperienced developers failing and larger pharmaceutical companies avoiding the sector completely. BARDA, as a key partner in the PHEMCE, serves as a bridge over a critical gap referred to as the "Valley of Death" in the development of innovative medical countermeasures through direct support, public-private partnerships, and technical core service assistance."[10]

The objectives of partnerships mirror the aims and needs of the individual partners, for example: filling knowledge gaps in biomedical research, identifying new targets and biomarkers, facilitating translational and clinical research, and developing effective medicines and diagnostic tools. In conclusion, the general characteristics of public-private partnerships for product development include:

- A strong focus on discovery research and translational science to address open questions in complex pathologies;
- Horizontal collaboration between diverse public and private entities;
- Sharing of information and resources in the precompetitive space of biomedical research and health innovation; and,

- Use of high level coordinating structures between stakeholders to enable research.

Public-private partnerships in the context of Alzheimer's disease

The challenges posed by ageing societies – particularly the impact of Alzheimer's disease and other dementias on patients, carers, society, and the economy – have been identified as global priorities. During his speech at the first Global Dementia Legacy Event in London[11], David Cameron, the UK Prime Minister, stated that "our global efforts in tackling dementia can be undermined by a lack of openness and collaboration". Biomedical research and health innovation for Alzheimer's disease represents a unique environment with a high diversity of stakeholders and public-private partnerships, requiring tailored approaches. The complexity of the open medical scientific questions around dementia, the growing burden of disease and the high level of investment risks have triggered an unprecedented collaboration between policymakers, the research community and non-profit organisations. Alzheimer's disease is a good example of how close collaboration between stakeholders can advance product development and help to modernise policy and regulatory frameworks (Carrillo et al., 2013). There is a tendency between stakeholders in neurodegenerative disease research to jointly develop non-competitive research strategies through a sharing of resources, opportunities and risks (Norris, 2014).

Public-private partnerships for product development are not new and the need for more collaboration in Alzheimer's disease research and development has been recognised earlier (Fillit et al, 2002). There are prominent examples in which the pharmaceutical industry has been collaborating with public institutions to address unmet medical needs. Many public-private partnerships in Alzheimer's disease have developed during the last 15 years – a time which has been highly productive in neurobiology and genome science (Collins, 2010; Glovin, 2010; Wheeler and Berkley, 2001). However, despite a few notable genomics-based medical breakthroughs in oncology, short-term effects of new technologies, such as genomics, combinatorial chemistry and high-throughput approaches, proved to be overestimated (Expanding the precompetitive space, 2011; FitzGerald, 2010; Goldman, 2013; Tralau-Stewart, 2009). The direct impact on the health of patients is still limited and promising findings in biomedical research are yet able to be translated into disease models and innovative therapies for Alzheimer's disease (Collins, 2010; Kozauer, 2013; Tralau-Stewart, 2009). In particular, the therapeutic potential of a certain class of medicines in Alzheimer's disease has been inadequate and the success of clinical trials addressing abnormal protein depositions in the brains of patients has been limited (Ballard et al., 2011; Fitzgerald, 2014).

Horizontal partnerships between the pharmaceutical industry, academics, and non-profit organisations best mirror the complexity of Alzheimer's disease (Corbett and Ballard, 2012). These are different from public-private partnerships for health which address unmet medical needs with limited market sizes (Buse and Walt, 2000; Croft, 2005; Peters and Phillips, 2004). A literature review and information obtained from case studies confirmed the strong emphasis on discovery research topics within public-private partnerships in Alzheimer's disease (see Table 1). Complementary to their primary objectives, many of the partnerships listed in Table 1 have additional focus areas that address significant challenges along the value chain of innovative medicines, for example:

- **Biomedical research**: The Accelerating Medicines Partnership, the Stellar Initiative, and the Alzheimer's Disease Neuroimaging Initiative address knowledge gaps in the disease pathology and aim to deliver innovative diagnostic and therapeutic concepts;

- **Clinical research**: In order to facilitate the translation of potential new drugs into therapies, the European Prevention of Alzheimer's Dementia Consortium, the UK Dementia Research Platform, and the Network of Centres of Excellence in Neurodegeneration aim to develop accessible patient cohorts, provide consensus data standards and harmonise clinical trial methodologies;

- **Patients**: Patients' needs and wellbeing are cornerstones of public-private partnerships in Alzheimer's disease. Often the strong research agenda is complemented with actions on patient-focused, socio-ethical issues, such as models of care, medicines access and patient empowerment (Access to Medicines India, Danubian Network for Dementia Education and Care);

- **Co-ordination and management**: Some public-private partnerships aim to strengthen the impact of stakeholders through dedicated collaborative, management and financing mechanisms (for example, the Network of Centres of Excellence in Neurodegeneration, the New Drugs Against Neurological Diseases Initiative, the Innovative Medicines Initiative, the EU Joint Programme – Neurodegenerative Disease Research);

- **Policy and regulatory frameworks**: The Coalition Against Major Diseases of the Critical Path Institute, highlights the need to modernise policy and regulatory frameworks and aims to increase the efficiency of drug development processes. It is appreciated that data standards, evidence based regulatory science, and collaborative approaches can de-risk drug development processes.

Two major trends in research and health innovation for Alzheimer's disease have been identified from this project on the governance of public-private partnerships in research and health innovation for Alzheimer's disease: first, a rethinking of the traditional, linear drug development model, and, second, the expansion of vertical collaborations to horizontal, multi-stakeholder partnerships. The multi-factorial nature of Alzheimer's disease has triggered a revision of existing pharmaceutical business models and regulatory frameworks (Lindgardt, Reeves and Wallenstein, 2008). Non-linear, modular and iterative drug development models combine a higher level of flexibility and context-specific approaches with the required regulatory oversight (FitzGerald, 2010). To this end, a shift of resources from late stage clinical trials to discovery research and proof-of-concept studies would be an option to enrich development pipelines with quality drug candidates (Paul et al., 2010; DiMasi et al., 2009; Munos, 2010).

High quality data and standardised information will be needed, for example, to support collaborative action to implement innovative research models; to develop more efficient approaches to the safety and efficacy assessment of new therapies; and to enable an integrative analysis of global population data. Information sharing could help to avoid duplication of work and would increase efficiency. However, global, cross-sectoral collaboration and the implementation of open source models in science require adequate infrastructure and governance. There is a consensus amongst stakeholders that standardised data collection and analysis methods can help assure quality and enable evidence-based decision making. One example of how researchers from different disease areas aim to work together can be found in a recent report on "Neurodegeneration: Exploring Commonalities Across Diseases" (Davis, and Stroud, 2013), which points out that studying genetic, biochemical and clinical overlaps across neurodegenerative diseases (disease commonalities) can complement a single disease focus. This requires the collection, collation and curation of data from different research groups on a

variety of diseases, and the report notes that a substantial number of multi-site federated data networks and regional collaborative consortia have emerged. Examples include the Ontario Brain Institute (OBI), the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Joint Programme on Neurodegenerative Diseases (JPND), and the US National Alzheimer's Coordinating Center (NACC). Key challenges, however, include: 1) ensuring compatibility, usability and security of shared information; 2) financing infrastructure and information sharing initiatives; 3) ensuring data privacy concerning, for example, bio-samples and patient information; and 4) developing policies and incentives to promote education and training of data analysts and bioinformatics experts.

In conclusion, there is consensus amongst stakeholders in medicines research and development that more can be achieved through working together than by the "all-in-house" approach of the pharmaceutical industry (Ares, 2013; Cressy, 2011; Feldman et al., 2014). Most of the collaborative agreements between academia, or biotechnology companies, with the pharmaceutical industry show strong vertical, donor/ recipient characteristics: two entities conduct many projects under one contract along the value chain of product development (Stuart, Ozdemir and Ding, 2007). In contrast, horizontal, multi-stakeholder public-private partnerships have a broader and more inclusive scope – offering better communication and pooling of information. These can be characterised best as an environment of mutual respect, joint use of resources, and sharing of rewards. Close communication, trust and transparency are important features of successful public-private partnerships in research and health innovation for Alzheimer's disease (Casey, 2007; Ramm, 2011; Witters, Marom and Steinert, 2012).

Table 1. Public-private partnerships in Alzheimer's and other neurodegenerative diseases

Public-private partnerships	Aims and objectives
Accelerating Medicines Partnership (AMP) *Established in 2014 and managed through the Foundation for the NIH (FNIH), the AMP brings together government, industry, and non-profit organisations. Focus areas are diabetes, lupus, Alzheimer's disease.* *www.nih.gov*	*The AMP aims to identify and validate the most promising biological targets of Alzheimer's disease for new diagnostic and drug development.* *The main objectives are to:* • *Identify biomarkers that can predict clinical outcomes by incorporating selected biomarkers into four NIH-funded clinical trials, which include industry support, designed to delay or prevent disease onset;* • *Conduct a large-scale analysis of human Alzheimer's patient brain tissue samples to validate biological targets previously shown to play key roles in disease progression. Identify molecular pathways involved in the disease to identify new potential therapeutic targets.*
Access to Medicines, India *Initiated in 2011, Eisai Pharmaceuticals India, Apollo Hospitals, HelpAge India make a contribution towards improving the quality of healthcare in emerging countries and regions by combining the resources of the multiple organisations in innovative ways.* *www.eisai.com*	*The Access to Medicines public-private partnership aims to create greater opportunity for early disease detection, diagnosis and access to quality medical care in Alzheimer's disease.* *The main objective is to:* • *Implement a programme to educate, screen, diagnose, treat and improve adherence among patients for Alzheimer's disease and depression.*

Alzheimer's Disease Neuroimaging Initiative (ADNI) *Established in 2004, the ADNI is an ongoing, longitudinal, multicentre study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease. It is funded by the National Institute on Aging/ NIH, pharmaceutical companies, and philanthropic organisations.* *www.adni-info.org*	*The ADNI aims to characterise clinical, genetic, imaging, and biochemical biomarkers of Alzheimer's disease.* *The main objectives are to:* • *Detect Alzheimer's disease at the earliest stage possible and to identify ways to track the disease through the use of biomarkers;* • *Support advances in Alzheimer's disease intervention, prevention and treatment through the application of new diagnostics;* • *Develop ADNI's data access policy and continuously improve and expand data sharing models.*
Critical Path Institute (C-Path) and Coalition Against Major Diseases (CAMD) *Established in 2005, the C-Path Institute is a non-profit, public-private partnership with the US Food and Drug Administration (FDA) created under the auspices of the FDA. The Coalition Against Major Diseases (CAMD) is a public-private-partnership under the C-Path Institute.* *www.c-path.org*	*C-Path Institute aims to accelerate the pace and reduce the costs of medical product development through the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the efficacy and safety of new therapies. The CAMD aims to create new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer's disease and Parkinson's disease.* *The main objectives are to:* • *Quantify biomarkers;* • *Develop consensus data standards;* • *Advance drug development tools for evaluating drug efficacy, conducting clinical trials, and streamlining the process of regulatory review;* • *Share precompetitive patient-level data;* • *Develop new tools to be submitted to the regulatory agencies.*
Danubian Network for Dementia Education and Care (DANDEC), Slovenia *The DANDEC project is carried out by 12 academic and private partners. It is implemented in six countries six countries along the Danube river: Bulgaria, Czech Republic, Germany, Romania, Slovenia and Ukraine.*	*The DANDEC project aims to generate a sustainable improvement of treatment and care for older people with dementia and their carers through information and communication technology (ICT) solutions.* *The main objectives are to:* • *Enhance public awareness and understanding of dementia;* • *Increase competence of physicians and other healthcare professionals;* • *Provide counseling and support for family carers;* • *Introduce ICT-based assistive, safety and monitoring systems in the home environment;* • *Establish a person-centered and coordinated case management.*

Dementia Consortium *Established in 2014, the Consortium unites the charity Alzheimer's Research UK with technology transfer experts MRC Technology and two pharmaceutical companies, Eisai and Lilly.* *www.dementiaconsortium.org*	*The Dementia Consortium represents a new model for translating medical charity research into treatments. It aims to expedite the development of new drugs for dementia by supporting research into novel targets for neurodegeneration. It brings together the voluntary, academic and private sectors in order to tackle the growing dementia problem. The Consortium seeks to end the ten-year wait for a new dementia treatment by closing the gap between fundamental academic research and the pharmaceutical industry's drug discovery programmes. It provides funding, expertise and resources to support new drug targets emerging from academic research that hold the promise of patient benefit.* *The main objectives are to:* • *Identify world-class early stage dementia research;* • *Support target validation and explore the tractability of the target for drug discovery;* • *Initiate collaborative drug discovery programmes on selected targets in parallel with the basic research;* • *Progress successful projects from laboratories towards the clinic, seeing new therapies delivered to patients and sharing in the financial returns.*
European Prevention of Alzheimer's Dementia Consortium (EPAD) *Established in 2015, EPAD will initially run for five years with an initial budget of Euro 64 million distributed across 35 public and private partners. The EPAD is part of the Innovative Medicines Initiative (IMI), a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations, EFPIA.* *www.synapse-pi.com/epad/*	*The EPAD consortium aims to develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm proof of concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations. This includes evaluating patients' reactions to a drug early in a clinical trial and modifying the trial according to these reactions.* *The project is divided into eight Work Packages: WP1 Scientific Challenges, WP2 Statistical/ Methodology Engine Room, WP3 Parent Cohorts and EPAD Register, WP4 EPAD Cohort and EPAD Trials, WP5 Project Management, WP6 Dissemination, WP7 Business Model and Sustainability and WP8 Ethical, Legal and Social Implications (ELSI) - with four Scientific Advisory Groups.*
EU Joint Programme – Neurodegenerative Disease Research (JPND) *Established in 2008, the JPND works through a collaborative approach ("Joint Programming") in which countries come together to define a common vision, a strategic research agenda and a management structure.* *www.neurodegenerationresearch.eu*	*The JPND aims to increase coordinated investment between participating countries in research aimed at finding causes, developing cures, and identifying appropriate ways to care for those with neurodegenerative diseases.* *The main objectives are to:* • *Improve the scientific understanding of the disease;* • *Improve the medical tools available to doctors to diagnose and treat;* • *Improve the social care and structures available so that patients can receive optimum care at all stages of their illness.*

Innovative Medicines Initiative *Established in 2008, the IMI is a public-private partnership between the European Union (represented by the European Commission), and the pharmaceutical industry (represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA)). After completion of the first phase of IMI (IMI1, 2008-2013) the programme will be continued as IMI 2 under "Horizon 2020" (2014-2020), the European Commission's framework programme for research and innovation. IMI 2 has been officially launched in July 2014 and will have a total budget of up to Euro 3.276 billion.* *www.imi.europa.eu*	*The IMI aims to support collaborative research projects and to build networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe through improving the drug development process. The research activities, supported by the IMI, are open to all research actors, provided that they are performed within Europe. IMI receives half of the funding from the EU and half from the pharmaceutical industry. The latter forms initial consortia, which then are broaden by public partners through IMI initiatives and external project proposals. In addition to research projects, IMI supports education and training projects. After completion of the first phase of the IMI in 2013, IMI 2 will place a greater emphasis on accelerating patient access to new treatments.* *The main objective is to:* • *Improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need;* • *Harness the know-how and expertise available across Europe's biopharmaceutical sector, by pooling competencies and resources from the public and the private domain.*
International Collaborative Research Strategy for Alzheimer's Disease (ICRSAD) *Established in 2009, ICRSAD has been set-up to strengthen Canadian research capacities by stimulating and leading innovative international research approaches. ICRSAD is led by the CIHR Institute of Aging and co-led by the Institute of Neurosciences, Mental Health and Addiction.* *www.cihr-irsc.gc.ca/e/43629.html*	*The ICRSAD aims to help provide Canadians with rapid access to the latest preventive, diagnostic and treatment approaches to Alzheimer's disease and related dementias. It is composed of two complementary components that take advantage of the recognised excellence of Canadian research in neuroscience and ageing: 1) an international component facilitating the participation of Canadian researchers in key international partnerships and allowing them to lead some of those international initiatives; 2) a national component to create the Canadian Consortium on Neurodegeneration in Aging (CCNA) as the hub for all aspects of research involving neurodegenerative diseases that affect cognition in ageing – including Alzheimer's disease.* *The main objectives are:* • *Primary Prevention – Prevent the disease from occurring through the identification of the mechanisms and/or conditions responsible for the neurodegenerative processes that lead to Alzheimer's disease and related dementias;* • *Secondary Prevention – Delaying/slowing the clinical progression of an already developing disease though better understanding of the mechanisms, diagnosis and early intervention;* • *Quality of life – Improve the quality of life of those living with the disease or who support those having the disease as well as to improve access to quality care and enabling the healthcare system to deal more efficiently with the rising number of individuals with dementia.*

Network of Centres of Excellence in Neurodegeneration (COEN), Spain *Established in 2010, COEN has been built around existing centres of scientific excellence with access to significant resources. It provides a fast and flexible mechanism for promoting trans-national research collaboration in Europe and Canada.* *www.coen.org/home.html*	*COEN aims to build a collaborative research activity in neurodegeneration research across borders, focusing on the critical mass and excellence. It also aims to provide a mechanism for industry to link to centres of excellence, and to develop novel and effective industry partnerships in precompetitive research.* *The main objectives are to:* • *Develop new disease models, the identification of biomarkers and the harmonisation of methodologies for clinical studies;* • *Catalyse collaborative research between centres with a critical mass of resources and expertise to drive a step change in neurodegeneration research.*
New drugs against neurological diseases (NEU²), Germany *Established in 2009 under the "BioPharma - Strategy Competition for the Medicine of the Future" initiative, NEU² brings together partners from academic, biotech and pharmaceutical sectors. It is coordinated by an independent project management company and original founder of NEU².* *www.neu-quadrat.de/start-en.html*	*NEU² aims to deliver novel treatments for multiple sclerosis and other neurological diseases.* *The main objectives are to:* • *Connect academic, biotech based and pharmaceutical expertise in the drug development process with the goal to efficiently generate new therapies to tackle multiple sclerosis;* • *Identify and test new paradigms underlying neurological diseases using novel molecular entities that have the can yield superior drugs;* • *Make funds available for pre-clinical research and clinical trials of potential multiple sclerosis drugs;* • *Expedite the repurposing of existing drugs to treat multiple sclerosis.*
Stellar Initiative, Belgium *Established in 2013, the Stellar Initiative is a collaboration between Janssen Research & Development, a division of Johnson & Johnson Innovation and three Belgian academic institutions and research centres (KU Leuven, University Hospitals Leuven and the Vlaams Instituut voor Biotechnologie). Under the Stellar Initiative, Jansen R&D collaborates with and supports academic institutions.* *www.stellar-project.be/index.html*	*The aim of the Stellar Initiative is to gain deeper insight into neurodegenerative diseases and accelerate delivery of breakthrough options to prevent, diagnose and treat them, ultimately helping patients to live better lives.* *The main objectives are to:* • *Gain deeper insight into neurodegenerative diseases;* • *Accelerate delivery of breakthrough options for prevention, diagnosis and treatment;* • *Help patients to live better lives.*

UK Dementia Research Platform (UKDP)

The Dementia Platform is a coordinated and integrated way of doing dementia research. By helping world-leading experts to work together to do better studies more quickly and at a lower cost, we will accelerate progress in dementia research. It is a public-private partnership between the Medical Research Council and Industry with an initial investment of GBP 53 million. Core activities are data sharing, research, and experimental studies.

www.dementiasplatform.uk

The UKDP aims to:

- *Find out: 1) Why brain cells stop working properly and what can prevent this; 2) How our genes and lifestyle interact to cause dementia; 3) What happens in the rest of the body that affects our risk of dementia.*
- *Develop new ways of: 1) Using brain scans to detect evidence of disease when it is early enough to do something about it; 2) Using blood markers to help scientists understand the disease; 3) Using sensitive tests to detect early changes in memory and thinking.*
- *Support dementia research more widely by: 1) Providing rich datasets to the research community; 2) Providing research tools and samples to scientists; 3) Providing a supportive environment for innovative research.*
- *Help people: 1) Get involved in dementia research; 2) Live well and make the most of their minds; 3) Understand what happens when we get dementia to help them help others.*

ROLES AND RESPONSIBILITIES IN PUBLIC-PRIVATE PARTNERSHIPS

This section describes the roles and responsibilities of the key stakeholders involved in public-private partnerships. It highlights the importance of identifying the capabilities and needs of each partner in order to define mutually-agreed roles and responsibilities within the boundaries of precompetitive space.

Defining the common ground

Stakeholders join public-private partnerships because of the potential benefits they expect to receive from participation. The most common incentives for working together comprise economic advantages, knowledge sharing, prestige, publicity and influence in the context of potential improvements in the health of populations. In addition to these stakeholder-specific, internal factors, important external pressures define the common ground: cost control, globalisation and reputation. A strong consideration has been given amongst stakeholders to integrative, collaborative models to support upstream research in Alzheimer's disease. Successful examples of public-private partnerships demonstrate the advantages of sharing responsibilities and concentrating on areas of expertise. Each member in a partnership provides its own culture, values, modes of operation, internal assets and skills. Although often competitors, participants in public-private partnerships recognise the benefits of working together when complementarities exist (Lessl, 2010; Moses, 2011; Milne, Malins, 2012). A study by Zycher (2010) examined the development histories of 32 drugs and drug classes, focusing in particular on the roles of the various stakeholders involved in their development. The study confirmed the existence of strong complementarities in terms of capabilities and objectives: the public research community has considerable expertise in basic biomedical research and disease biology, and the pharmaceutical industry has a stronger focus on discovery research, synthesis and compound testing (clinical research). It is therefore beneficial for academia and private researchers to build partnerships around areas of joint interest and needs, where stakeholders can agree on goals and objectives to enable efficient work and delivery of quality results.

The definition of common ground is closely linked with the description of "precompetitive space". Delineating the boundaries of "precompetitive space" is of particular importance in Alzheimer's disease, where public-private partnerships often contain both pharmaceutical competitors (hence Mullard's (2011) use of the term "pharma-pharma-public" alliances) and, as noted by Mattes (2014), many non-profit organisations and public research institutes that also typically compete with each over scarce resources. In order to avoid potential disagreement over issues such as intellectual property or competing marketing strategies, public-private partnerships therefore evolve predominantly in a "precompetitive space" that is limited to activities such as target validation and safety, pharmacological and proof-of-concept studies (Goldman, 2013).

From a scientific and proprietary point of view, the line between the precompetitive and competitive space can be drawn at the point of proof-of-concept clinical trials – the decisive step in which the therapeutic efficacy of a potential new drug is tested in patients. However, it should be noted that the research and development costs associated with discovery and early clinical research are small compared with the costs associated with the larger trials in Phase 2 and Phase 3 of clinical development. The adoption of an open science approach and the creation of a non-competitive space in clinical development could therefore have an appreciable impact on cost savings and overall efficiency

(Shaeffer, 2014). However, according to Olson (2011), proof-of-concept could even be part of the precompetitive space in which public-private partnerships are predominantly arranged. This would further broaden the scope of work and strengthen the health impact of public-private partnerships. There are concerns about ownership and who finances the ensuing, larger clinical trials (as the new drug could probably be seen as generic). Further work would be warranted to clarify the legal, ethical, economic and institutional implications of moving the boundary between the precompetitive and the competitive space in public-private partnerships.

Some stakeholders involved in the fight against Alzheimer's disease are embracing the concept of sharing risks and benefits. Four key factors characterising alliances involved in the struggle against Alzheimer's disease help define the common ground for more inclusive partnerships: first, clearly defined terms of references for the partnerships; second, an open science approach to information sharing; third, mutual responsibility; fourth, benefits for all partners.

The position of governments and regulatory agencies

Governments are expected to play many roles. Given the uncertainties and high financial risks involved in dementia drug development, the scientific community expects government to coordinate actions aimed, for example, at delivering research and drug development roadmaps; supporting research infrastructure development; promoting innovative science in collaborative structures; and developing appropriate policy and regulatory frameworks. However, traditional, hierarchical governance structures might not be optimal for embracing the notion of working together, or to address adequately the need for new communication structures, information sharing and specialisation. Structured network governance arrangements, in which experts and stakeholder groups are assigned responsibilities to deliver measurable outputs of high public value, might achieve better results in more complex environments (Goldsmith and Eggers, 2004). Governments are seeking to ensure efficiency through the use of appropriate governance frameworks, not least because of limited resources. Governance can be defined as a system of rules, norms, processes and institutions through which power and decision-making are exercised (Buse, 2000). Of the many organisational challenges arising from the diversity of stakeholders in alliances and partnerships tackling Alzheimer's disease, perhaps the greatest involve orienting and aligning partners towards a common goal. Possible governance measures to improve quality and efficiency in biomedical research and health innovation are: 1) inclusiveness and balanced representation of all stakeholders; 2) accountability of partners; 3) competence and appropriateness of action; 4) respect for due process; and 5) transparency.

Academic investigators play an important role in the early stages, effectively 'de-risking' projects for downstream commercial investment. New funding and risk-sharing mechanisms are being explored to support resource-intensive research in neurodegenerative diseases and to mitigate financial risks. Here government funding plays a significant role in early biomedical research within academia and within collaborative research networks at the interface of academia with the pharmaceutical industry (Sampat and Lichtenberg, 2011; Zycher, 2010).

The increasing globalisation and high complexity of research and health innovation have generated a need within governments and regulatory agencies for services in specific knowledge areas. These needs can be met through collaborations in which (private) partners offer the required medical scientific and managerial expertise. As a result governments are increasingly collaborating with private partners in areas of limited internal resources and experience. From an inter-governmental perspective, the United Nations (2008) characterises public-private partnerships as facilities and services, which aim

to finance, design, implement and operate public sector activities. In the face of budget deficits, the pharmaceutical industry can provide models, skills and management processes that have proven to be successful in the management of multi-stakeholder collaborations (Witters, Marom and Steinert, 2012). To fulfil their mandates, governments and regulatory agencies actively engage in public-private partnerships to, for example: 1) increase value for money of internal services through removing inefficiencies and improving quality (increase business credibility and authority); 2) foster research and drug development to improve public health; 3) manage costs; and 4) ensure policies and regulatory frameworks comply with the needs of the disease area and all stakeholders.

Significant public tasks and responsibilities cannot be outsourced to private partners and represent core competencies of governments and regulatory agencies, such as the development of legislation, policies and guidance. While academic and private research partners are focusing on the scientific issues and day-to-day management of public-private partnerships, governments and regulatory agencies fulfil a significant role in project oversight, transparency and public engagement. Due to the direct impact of product development partnerships in Alzheimer's disease on the health of patients and because of the possible diverging interests between public and private entities, these partnerships are under intense scrutiny by the wider public (Wheeler and Berkley, 2001). Governments and regulatory agencies create a link between the innovator (research community and manufacturer) and the patient through close communication, transparency and the generation of trust – characteristics that have been emphasised in successful multilateral collaborations. A concept of realism is important when discussing the scale of investments needed for the delivery of effective therapies for Alzheimer's disease. In view of the complex social and ethical implications of the disease public trust in biomedical research is important to ensure long-term support for partnerships and uptake of research findings. Governments can support public awareness of the relative costs, benefits and risks of the research activities and the public-private partnerships itself (OECD, 2012a). Public trust and understanding of public-private partnerships in Alzheimer's disease requires close communication with all stakeholders as well as involving the patients in defining the aims and objectives of partnerships.

In Alzheimer's disease regulatory processes may not match the complexity of the required study designs, clinical endpoints and involvement of volunteers in very early or non-symptomatic disease stages. Here governments and regulatory agencies fulfil a significant role in the development of integrated policies and regulatory frameworks, which reflect the unique needs of the disease. Collaborations between agencies and the research community can deliver the required strategic, ethical and legal guidance for investment into Alzheimer's research (Broich et al., 2012). In an area of uncertainty, it would be important to foster standardisation, integration and knowledge sharing between partners through an early dialogue. Considering the regulatory uncertainties of emerging biomedical technologies in research, clinical trials and diagnosis, partnerships also offer the right environment to discuss potential issues at an early stage (Goldman, Compton and Mittleman, 2013).

Stakeholders are working together to accelerate the transfer of innovations from the laboratory to the point-of-care. However, knowledge gaps in the biological understanding of the disease, inadequate regulatory procedures and fragmented infrastructures are significant contributors to the high failure rate of promising drugs. This holds especially true in the area of translational research – often referred to as the "valley of death" between pre-clinical research and in-human trials. There is a role for policymakers and regulators to reinforce strategic collaborations for discovery and translational research through new fund- and risk-sharing mechanisms, especially at an international level. However, the role governments play in partnerships for the delivery of drugs to patients is not limited to the support of biomedical research and the development of regulatory frameworks and approval processes. Governments and

regulatory agencies fulfil a key function at the interface of diverse public and corporate institutions throughout the whole life-cycle of a medical product, spanning intellectual property, quality control in manufacturing, market authorisation, market surveillance, health insurance, pharmacovigilance and care (Field, 2012). Their role as a facilitator of research and innovation is of special importance in research areas of limited commercial potential and high risks.

Recent experience in genomics has highlighted the challenges involved in translating innovations into research applications and therapies (Collins, 2011). Translating the growing knowledge base about genomes and emerging analytical techniques into new therapeutic options that address the molecular basis of a disease is proving difficult. In a situation of high investment risk for the pharmaceutical industry, government-funded public research institutions have played a leading role in efforts to close the translational research gap and accelerate the development of innovative therapeutic options (Field, 2012). As an example, the US National Centre for Advancing Translational Sciences (NCATS) was established by the National Institutes of Health in 2011 to transform the translational science process so that new treatments and cures for disease could be delivered to patients faster. In line with government investment in research and involvement in public-private partnerships, there has been an ongoing discussion about potential mechanisms for reclaiming some of this public investment from the profit streams of private entities successfully marketing products (Rand, 2010; Schacht, 2011; Zycher, 2010).

In public-private partnerships, both regulatory agencies and innovators can discuss potential research and development strategies in order to increase the prospects of potential new drugs during cost-intensive late-stage development. As an example, the US FDA has developed guidance for industry which aims to support the co-development of drugs for combination use[12]. The guidance provides advice on how to address certain scientific and regulatory issues that may arise during the co-development of new drugs for any indication to be used in combination to treat a disease. This guidance further strengthens the collaboration between otherwise competitive industrial partners and could be of major importance in Alzheimer's disease where a combination treatment might be needed. Here governments fulfil a crucial role in providing the frameworks and governance for the functioning of public-private partnerships (OECD, 2012a; Witter, 2012). Their success depends on clearly defined roles, responsibilities, and financing mechanisms. Good governance mechanisms provide the required norms, processes and roles through which activities in public-private partnerships are performed. The unique position of governments at the interface between global networks and local responsibilities enables the definition of legitimacy, accountability and transparency measures.

The integration of public-private partnership models into national settings is important to support the development of risk-sharing mechanisms and to set-up agreements on the use of results and rewards. In view of the many and diverse priorities and limited resources, governments can lead the definition of strategic goals. Governments can guide stakeholder discussions on investment priorities and ensure that decisions are made in support of the overall goal of the partnerships, separate from the objectives of individual actors. They can foster the implementation of private industry-owned quality control mechanisms to increase efficiency and mitigate risks. Within public-private partnerships, governments or independent research facilitators can oversee the management of risks. The development of medicines for Alzheimer's disease bears significant risks, which should be defined, identified and measured and transferred to the stakeholder best prepared to manage them.

The importance of working together with all stakeholders in biomedical research and health innovation is illustrated by the following statements:

- The European Medicines Agency (EMA):[13] "As a holistic approach, adaptive licensing requires the involvement of all stakeholders who have a role in determining patient access, including the EMA, the industry, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines and patient organisations."

- The Advisory Council on Alzheimer's Research, Care, and Services:[14] "The process of developing that scientific research plan and accompanying priorities should be viewed as a shared project of NIH, the Food and Drug Administration (FDA), and other relevant government agencies; the academic and corporate research community; industry; and NGO's".

- The 2013 update of the US National Plan to Address Alzheimer's disease, US Department of Health and Human Services:[15] "The scope of the problem of Alzheimer's disease is so great that public-private partnerships with a multitude of stakeholders will be essential to making progress. … The National Plan represents large-scale, coordinated efforts across the public and private sectors."

- The Advisory Council on Alzheimer's research comments on the US National Plan for Alzheimer's disease and related dementias and points out the importance of partnership models. In particular, the 2014 recommendations[16] advice to:

  - Include input from scientific experts from both academia and industry for the development and implementation of a roadmap to prevent and effectively treat Alzheimer's disease by 2025;

  - Work with experts from the research community and industry to 1) reform the clinical trial processes; 2) provide regulatory clarity with respect to the design, conduct, and analysis of Alzheimer's disease trials; 3) use scientifically sound regulatory mechanisms to help expedite the approval of effective therapies; 4) actively engage with public-private partnerships to qualify both endpoints and biomarkers to help facilitate the conduct of Alzheimer's disease trials; and 5) generate data standards that will help facilitate regulatory review; 6) engage with patient communities and advocacy groups to help inform the regulatory decision-making process;

  - Assure, in partnership with the private sector, that the development of health information technology includes tools for caregivers.

The position of the pharmaceutical industry

The pharmaceutical industry recognises the significant and urgent health burden that Alzheimer's disease represents and remains committed to developing new therapeutics for people living with this devastating disease. This commitment exists despite significant challenges associated with the design and implementation of clinical trials. These challenges include length and cost of trials in the context of limited data exclusivity, lack of qualified biomarkers and diagnostics, patient selection and enrolment, and definition of clinically meaningful endpoints. As the scientific understanding of Alzheimer's disease grows, research is moving to examine different pathways and earlier stages of disease where the opportunity for long-term benefit may be greatest. However, in these settings, the traditionally accepted

outcomes to measure benefit may not be appropriate. Integrated cross-disciplinary strategies are needed to identify potentially novel measures which may more appropriately capture the clinical benefit associated with different pathways and stages of disease, such as surrogates that measure impact on disease pathophysiology and progression. To continue to foster research in this area and accelerate the discovery of medicines that can slow or stop disease, collaboration and openness to novel approaches must be embraced by industry, academia, regulatory agencies, payers and patient organisations.

Since the "Decade of the Brain" (declared by the US Congress in 1990), progress in neuroscience has offered significant insights into the biological mechanisms underlying Alzheimer's disease (Morris et al., 2014; Reiman, 2014; Volkow, 2010). Close collaboration between stakeholders and a growing awareness of the social and economic burden of brain diseases has created a fruitful environment for neuroscientific research. This development has been driven by, for example, advances in genetics, stem cell and imaging technologies. Advances in molecular and cellular biology have accelerated basic and applied research, revealing new insights into key molecular and biochemical underpinnings of diseases (Collins, 2010; Reiman, 2014). However, the impact of an increased knowledge base and the emergence of sophisticated molecular research tools on the health of patients remains limited (Collins, 2010; Kozauer and Katz, 2013; Tralau-Stewart et al., 2009; Weinberg, 2010). The pharmaceutical industry is still falling short in terms of implementing emerging biomedical technologies (such as synthetic biology, genomics, tissue engineering, and cell therapy) into its processes. Experience has shown that it can take up to 25 years until scientific discoveries are formally recognised, assimilated into research and health innovation processes, and converted to patient benefit (Fortunato, 2014; Morris, Wooding, and Grant, 2011; Moses, and Martin, 2011). There is consensus that a collaborative approach is needed to accelerate the integration of new research findings into internationally accepted standards.

The pharmaceutical industry has been facing challenges of low drug development productivity, dwindling product pipelines and ever-increasing costs to deliver innovative treatments (Sternitzke, 2007; Vaudano, 2013; Woodstock, 2013). Not least because of the costs of up to USD 5.7 billion to develop an effective (disease-modifying) drug for Alzheimer's disease (Scott, 2014), the pharmaceutical industry has been cautious about large investments. Additional challenges the private research community has been facing are: 1) high failure rates of new drugs under development; 2) the time-lag of up to 14 years between filing a patent on a new compound during discovery research and achieving regulatory approval and marketing; 3) regulatory uncertainty about the safety and efficacy assessment of new therapeutic options; 4) a low number of potential revenue-generating drugs; and 5) declining profitability and economic growth prospects (Hudson, 2013; Paul et al., 2010; Shah, 2009; Sternitzke, 2010; Woodstock, 2013). Despite large investments in biomedical and disease research, the pharmaceutical industry still devotes most research and development funding to clinical research programmes (Stuart, 2007). In order to address these challenges and to bridge the innovation gap the pharmaceutical industry is now evolving into new, open science business models to increase the output of effective therapies while remaining competitive. As to Chesbrough (2005), open innovation represents a promising model in which companies pursue market strategies through collaborative and open exchange of information and ideas. In short: closed innovation is that which emerges from company internal innovation; open innovation springs from research and development sources external to the company. As an initial step to pursue open innovation strategies, the pharmaceutical industry is increasingly involved in collaborative partnerships, which share large pre-clinical data sets emerging from, for example, compound screening, genomics, and toxicity studies. The overarching aim of these data-sharing activities between pharmaceutical companies and academia is to increase the efficiency of pre-clinical and translational research through the use of global intellect, the avoidance of redundancy,

and, ultimately a faster translation of rapidly expanding biological data into knowledge and drug discovery pipelines (Roy, 2014).

The rapidly-expanding biomedical knowledge base and complex biomedical research tools have increased the specialisation in scientific research, drug development and regulation. Cross-disciplinary and inclusive research and business strategies are needed to close the innovation gap through accelerating the translation of medical scientific knowledge from the laboratory into the clinical setting (Collins, 2010; Hodges, 2014). As stated above, the pharmaceutical industry is increasingly replacing the "all-in-house" drug development model with adaptive and iterative approaches, which better match the requirements of cross-sectoral and interdisciplinary drug development programmes (Bunnage, 2011; Hudson and Khazragui, 2013; Lindgardt, Reeves, and Wallenstein, 2008). Public-private partnerships facilitate the absorption and implementation of ground-breaking biomedical knowledge into innovative diagnostic tools and therapies. In doing so, the pharmaceutical industry transfers precompetitive scientific knowledge and radical innovative ideas largely generated by academia into intellectually-protected medicines (Sternitzke, 2010). Ultimately, the strong know-how of the pharmaceutical industry in biomedical research and clinical development (innovation) is complemented by sources of emerging knowledge offered by academic and biotech partners. However, estimations of externally spent research funds by the pharmaceutical industry (e.g. investment into academic research) range between 1-3% of the total research and development investments (Boccanfuso, 2014).

Building on a broad range of service agreements and outsourcing strategies, the pharmaceutical industry offers in-depth experiences in collaborative models. Upstream of the value chain, it has been attractive for the pharmaceutical industry to fill internal knowledge or infrastructure gaps and to increase competitiveness through vertical collaborations with academia or small and medium-sized biotechnology companies. Public-private partnerships offer a more systematic and comprehensive approach to address the complex issues of Alzheimer's disease. As the different steps of research and health innovation are taking place across private and public institutions the new business models require closer collaboration with a broad range of partners. The joint use of resources between academic, biotech and industry partners helps to process increasingly complex information sources and to fill intellectual gaps. In addition, the clearer definition and rise of public-private partnerships have enabled the building of complex relationships between industry partners. Previously limited in their scope, one-to-one alliances between competitors have evolved into multi-stakeholder partnerships with a large range of cutting edge research collaborations and priority access to infrastructure and knowledge resources (Mullard, 2011).

The position of academia and small and medium-sized biotech companies

The tasks of the research community are diverse and comprise, for example: filling gaps in medical scientific knowledge in Alzheimer's disease, developing and validating new targets and biomarkers, strengthening translational research to bridge the gap between laboratory research and clinical development, and implementing adaptive and risk-based clinical trial designs. Academia and start-up biotech companies focus limited resources on research and discovery projects upstream of the value chain; they have contributed significantly to advancing the frontiers in biomedical science and disease biology. In the traditional research and health innovation model academia conducts much of the basic research that leads to the biochemical and molecular understanding of disease. According to Tralau-Stuart (2009), the number and scope of academic discovery research units has been growing. There has been a shift of compound and target screening activities from the pharmaceutical industry to academic research institutes and small and medium-sized biotech companies, which offer the

knowledge, resources and technical expertise in modern drug discovery (Blow, 2014). This development could be seen as a strengthening of public research institutes and biotech companies in early research, and as a consequence of the lack of adequate financial resources to sustain large clinical development programmes downstream of the innovation process. Despite their experiences as collaborative partners in biomedical research, academics have rarely been credited as major actors in drug development and often struggle to benefit from discoveries (Hume, 2014; Ivinson et al., 2008). Though universities/ medical schools might also be engaged in accessing large patient populations for clinical trials or host Phase I studies, the pharmaceutical industry alone has the capacity to perform large clinical trials and bring a potential new drug into the market.

To a large extent, the strengths of academic research institutions and the pharmaceutical industry are complementary: academia focuses on compound and target discovery, the development of *in-vitro* models, medical chemistry and genomics, and knowledge communication, whereas the pharmaceutical industry offers a strong expertise in clinical development, manufacturing, regulatory compliance and delivery. However, in the light of the stringent regulatory requirements, academia and industry partners may differently define the quality and quantity of information describing new discoveries (Ivinson et al., 2008). The linkage between academia and the pharmaceutical industry might also add further challenges with regard to information disclosure, ownership and ethical and legal questions about the sharing of biological samples. As to Roy (2014) the work of academia in newly evolving public-private partnerships is more focused, reproducible, and incorporates the principles of project management excellence in order to support the translation of biomedical discoveries into regulatory-compliant development processes.

The position of small and medium-sized biotech companies in public-private partnerships is different as they combine innovativeness with commercial interests. Their role can be best defined as technology broker (Stuart, Ozdemir and Ding, 2007): they directly interact with partners upstream and downstream of the research and development process. Not least because of the many formal and informal connections with academic research institutes, small and medium-sized biotech companies represent ideal partners in research alliances (Stuart, Ozdemir and Ding, 2007). However, because of their mostly limited spectrum of "owned" technologies and smaller research portfolios, small and medium-sized biotech companies are keen to protect their intellectual property and know-how. In addition, most biotech companies still lack the resources to translate a potential new drug from the laboratory into the market. In addition, as a result of the recent economic recession, the flow of venture capital into biotech start-up companies and university spinoffs has sharply declined (Boccanfuso, 2014; Roy, 2014). They benefit from participating in public-private partnerships through investments and increased recognition of their ability to deliver products. If a biotech company is well positioned at the interface between academic research and the pharmaceutical industry, the financial benefits can substantially outweigh investments.

The main reasons for the gap between early discovery research and pharmaceutical development outside public research institutions are: first, academic institutions are mainly driven by basic or applied biomedical research questions and often do not have the resources to optimise chemical structures and to perform pre-clinical testing; second, academic researchers define success in terms of the output of publications, which contradicts the intellectual property frameworks that govern the commercialisation and use of new drugs; third, academics lack the funds and the know-how to translate research findings into clinical practice. There is potential for closer collaboration between academia, small and medium-sized biotech companies and the pharmaceutical industry in order to generate and transfer innovative research findings from laboratories to the market. As noted by Collins (2010):

"…achieving the enormous promise of the myriad new drug targets emerging from genomic analysis of common and rare diseases requires new paradigms of public-private partnership. Academic investigators will have a much more important role in the early stages, effectively 'de-risking' projects for downstream commercial investment." One of the main objectives of current research strategies is the establishment of better, qualified animal models of Alzheimer's disease – a key component of innovative research and clinical trial strategies. The combination of academic creativity and industry know-how should provide fertile ground for research on Alzheimer's disease (Olson, 2012).

Accelerating the discovery and translation of effective therapeutic options in Alzheimer's disease requires strong partnerships, focused on clearly defined objectives pursued by well organised teams over extended periods (Lessl and Douglas, 2010; Olson, 2012). In particular, the growing impact of emerging and converging technologies in biomedical research and their evaluation as new tools in translational research and drug development will play an important role in strengthening academic/industry partnerships. Through engagement in public-private partnerships, academia benefits by: 1) gaining access to research infrastructure; 2) "field testing" innovative ideas and refining research strategies; 3) gaining improved access to funding; and 4) strengthening the link between university teaching and training curricula and "real world" research and development.

The position of patient organisations

Health innovation aims to develop therapies for the benefit of patients. Because patients are significantly affected by decisions concerning the approval of medicines, their needs must be respected in the decision-making process. Patients' rights and therapeutic needs are central when setting-up clinical research programmes, especially concerning the inclusion of patients at the very early stages of the disease or healthy volunteers with a genetic predisposition for Alzheimer's disease. Creating the conditions for translating promising therapeutic options into "first-in-human" studies is one of the biggest challenges in health innovation for Alzheimer's disease. Issues include: patient selection and stratification, the voluntary involvement of well-informed patients, and protection of privacy/ confidentiality to prevent unauthorised or inappropriate use of personal information.

It is important to enable informed decision-making by all stakeholders based on the best possible information available. To better understand disease progression and the clinical implications, and to better serve patients' needs, stakeholders should ensure close communication with patient organisations in collaborative models. Without their critical input, health innovation processes could miss valuable insights and underestimate risks. A public community informed about the nature of, for example, investment risks, treatment risks, and other uncertainties in research can increase acceptance of the risk elements involved along the route from the laboratory to clinical practice (OECD, 2012b).

Non-profit organisations play a crucial role at the interface between patients, governments and the research community. They are ideally placed both to channel information about patients' needs into research alliances and to ensure that the wider public is well-informed. Some also support patient empowerment, which is an important factor in health innovation for Alzheimer's disease. Effective cooperation in health innovation requires the participation of patient organisations in collaborative stakeholder alliances. Most patient organisations follow a non-profit approach and have flexible organisational structures. They often have a disease focus and are well placed to undertake patient and public outreach in these individual disease environments and can adapt to meet short-term needs when appropriate.

Governments often enter into agreements with non-profit/patient organisations to provide services such as the collection of information from the public. For example, in 2012 the US government, paid USD 137 billion to non-profit organisations for a range of services (Pettijohn et al., 2013a). Grants from the US government constituted one-third of the revenues of public charities in 2010 (Pettijohn, 2013b).

CHALLENGES OF PUBLIC-PRIVATE PARTNERSHIPS IN ALZHEIMER'S DISEASE

Public-private partnerships have become efficient tools in biomedical research and health innovation. In general, the heterogeneity of stakeholders and their expertise makes them complementary and can enable the research community to solve open questions about the biomedical underpinnings of Alzheimer's disease and help governments and regulatory agencies to develop adequate policies and regulatory frameworks. However, despite these advantages, the diversity of stakeholders has raised concerns about potential conflicts of interests, which can result in redundancy, opposing goals of partners, lack of inclusiveness, insufficient transparency and quality control issues. Diverging interests of stakeholders can negatively impact efficiency and require tailored innovation policies that address the specific requirements of public-private partnerships on a country level. Issues at the interface between academia and the pharmaceutical industry may arise from different work cultures, lack of ownership and delivery, inadequate rewards and compensation of indirect costs, and divergent contractual law and policies (Ray, 2014). Academics focus their interests on the biochemical and molecular underpinnings of diseases and define success through the quality and number of publications, and secured grant support. Key objectives of the pharmaceutical industry are the development of innovative therapies to increase the market share and economic rewards. In addition, companies are bound to stringent management and regulatory frameworks. Therefore, it remains challenging to involve large pharmaceutical companies in research projects which follow an open science approach.

The number and heterogeneity of stakeholders in Alzheimer's disease represent the biggest challenges to the efficiency and longevity of public-private partnerships. As to Lessl and Douglas (2010) the underlying organisational barriers for efficient academia-industry relationships are: miscommunication of needs and expertise, lack of operational flexibility and stringent hierarchal structures. In order to avoid tensions, public-private partnerships can focus objectives and resources on science, common goals, management and transparency as opposed to competitive, legal or economic aspects (Olson, 2011; Wheeler and Berkley, 2001). It is critical that, when the terms and references of public-private partnerships are discussed, common goals and areas of potential disagreement are clearly defined. There should be mutual agreement on roles, responsibilities and the use of benefits (for example, ownership of data, intellectual property, financial returns etc.). In addition, context-specific national policy frameworks for public-private partnerships in biomedical research and drug development can help to ensure efficiency and to manage organisational complexity and risks.

It should be noted that managing risks should not include the absolute avoidance of potential risks in research – innovation often comes from unexpected results in basic research, especially in academic environments. For example, in the field of emerging technologies in biomedical research, it is essential to identify and manage potential risks without discouraging innovative, cross-sectoral ways of thinking. Risks and uncertainty are inherent aspects of innovation, which can be effectively managed through, for example, strong governance, project management and risk mitigation structures, and the development of flexible, subject-specific regulatory environments.

Researchers in Alzheimer's disease are confronted with unresolved issues in disease pathology, low success in drug development, inadequate regulatory frameworks, and fragmented resources. The complexity of Alzheimer's disease and inconsistent research results have created an environment in which neither the private nor the public sector can manage investment costs alone. The suitability of the

traditional, closed research model in which the pharmaceutical industry alone pursues the development of innovative medicines takes all risks and benefits has been questioned (Hudson and Khazragui, 2013; Paul et al., 2010). In recent years the pharmaceutical industry has become increasingly willing to share knowledge and resources through, for example, the joint use of compound libraries and clinical databases. Within partnerships, large pharmaceutical companies exchange information and jointly use infrastructure which previously was considered as a confidential and strictly internal company asset. Open-source partnership models can accelerate the development of urgently required therapies for unmet medical needs (Judd, 2013a). One of the major challenges of open-source models is how to ensure the rewards and recognition for innovative ideas, investment costs and failure. Intellectual property rights represent the foundation of economic growth within the pharmaceutical industry and concerns have been raised about the future status of intellectual property rights (Munos, 2010; Saha, 2011). Sharing intellectual property rights in the competitive space of pharmaceutical development could run the risk of dis-incentivising private partners and, thus, reduce their interest in collaboration (FitzGerald, 2010; Judd, 2013b; Taubman, 2010). However, there are alternatives to the grant of patents for funding and supporting research and development and innovation, including direct government funding of research, tax policy, the creation of non-patent monopolies, mandates to fund research based upon a percentage of product sales, and innovation inducement prizes (World Intellectual Property Organization, 2014).

CONCLUDING REMARKS

The contradiction between the urgent need for effective medicines for Alzheimer's disease and the lengthy and costly processes involved in translational and clinical research has raised questions about the adequacy of existing policy and regulatory frameworks. The acceleration of biomedical research and health innovation in Alzheimer's disease is also dependent on the use of emerging and converging biomedical technologies for which the knowledge base and regulatory frameworks are still limited. Researchers are exploring innovative research strategies through, for example, systems biology, nano-technology, genomics, and adaptive clinical trial designs, which can help to fill the innovation gap. However, evolving strategies partly diverge from traditional drug development models and require tailored, context-specific policies and regulatory guidance with a long-term vision – these should be built on the knowledge, experiences, and needs of all stakeholders. A challenge remains how the translation of innovative ideas and technologies to effective treatments for patients can be accomplished and best managed; a significant gap persists between high investments and resource needs, and the generation of economic value for all stakeholders.

Key drivers for stakeholders to join collaborative partnerships in Alzheimer's disease and other dementias are: 1) the increasing burden of the disease and related medical, social and economic consequences; 2) the complexity of unresolved biomedical questions; 3) the need to share knowledge and infrastructure, in order to manage high investment costs and risks; 4) the need to reform regulatory frameworks through the strengthening of regulatory science and increased flexibility in clinical trials; and 5) the importance of respecting patients' needs. In essence, stakeholders join public-private partnerships to take advantage of the benefits from working together, realising economic advantages, fostering upstream research through open science approaches, gaining access to innovation and accelerating its translation into clinical applications, and strengthening the bonds with patients and the public.

The diversity of stakeholders (and their scientific expertise) in dementia research and health innovation is enormous. Their interests range from basic biomedical research and regulation to health economics and patient care. Aims and objectives overlap substantially; complementary strengths and resources offer opportunities to join forces through a closer collaboration in order to address complex medical, scientific, financial or organisational challenges. Governments and regulatory agencies in close collaboration with other stakeholders fulfil an important role to establish appropriate organisational structures and frameworks that support cross-sectoral collaboration (expanding the precompetitive space) and to deliver sustainable business models for the development of effective treatments for Alzheimer's disease and other dementias. They play a key role at the interface between the heterogeneous public and private research partners and ensure a focus on issues such as the rights and wellbeing of patients and the efficient use of funds.

Most public-private partnerships in Alzheimer's disease have been established over the last 15 years and focus on discovery research and sharing of resources (infrastructure, data, knowledge, and funds). The information obtained from the literature review and case studies has revealed that the complexity and scope of partnerships in biomedical research and health innovation have been changing – from industry-academia task-based collaborations to long-term, more inclusive collaborative networks for know-how interchange.

Public-private partnerships in Alzheimer's disease often have additional foci, which may include the design and facilitation of clinical trials, strengthening of operational excellence, the modernisation of policy and regulatory frameworks, and the sharing of investment risks and benefits. The broad spectrum of areas addressed and the high number of otherwise economically competing pharmaceutical industries joining public-private partnerships reflect the magnitude of the challenges in Alzheimer's disease. The horizontally-structured public-private partnerships in Alzheimer's disease and their focus on both research issues (basic, discovery and translational research) and governance issues (operational excellence, policy and regulatory frameworks) exhibit unique characteristics:

- A focus on unresolved biomedical questions upstream of research and health innovation;
- Clearly defined terms of reference for the partnerships;
- Mutual responsibility, and shared benefits and risks for stakeholders as appropriate;
- Involvement of many, otherwise competing public and private entities in cross-sectoral collaborations (pharma-pharma-public alliances);
- Direct involvement of non-profit/ patient organisations in goal setting and to align strategies with patients' needs;
- Broadening of the common ground through more inclusive partnerships and widening of the precompetitive space;
- The aim of reforming policy and regulatory frameworks to accelerate product development through new, non-linear drug development models.

Public-private partnerships offer significant advantages for stakeholders but, given their heterogeneity, diverging and competing interests, they may require new forms of coordination, which are increasingly offered by centres of excellence or research enablers. There is now considerable experience with issues related to the establishment of public-private partnerships in biomedical research and health innovation, and efficiency and effectiveness lessons can be learned from existing partnerships concerned with Alzheimer's disease. Professional management of partnerships is a prerequisite for the efficient use of limited resources and the generation of value out of collaborative efforts.

Public and private research entities, funding organisations and policy makers fulfil complementary roles in biomedical innovation and in the development of new therapies. In particular, researchers from both academia and the pharmaceutical industry share the same interest in providing treatments for unmet medical needs and require access to specialised talent and infrastructure. In order to leverage the full spectrum of advantages of public-private partnerships in Alzheimer's disease, the issues and needs, ideologies, and objectives of each individual stakeholder need to be addressed upfront. Policy frameworks that define the legal, economic and ethical implications of topics at the boundary between the precompetitive and competitive space (for example, topics such as intellectual property and defining mechanisms for joint proof-of-concept and late stage trials) can facilitate collaboration and help to manage financial and non-financial risks.

Stakeholders can work together to develop flexible and context-specific policies on risk governance. These can help to manage uncertainties over the life-cycle of medicinal products, thereby leveraging the inherent society gains of collaborative biomedical research and the development and use of emerging and converging technologies. Questions remain to be answered, including: What are the options to develop risk-regulation frameworks in a proportionate and balanced way to allow society to benefit from innovation? How to involve non-government actors in the development and implementation of risk-governance systems supporting the translation of scientific research into innovation and application?

Stakeholders have realised that more can be achieved by combining strengths and sharing rewards between academic and private research partners in health science and policy. A key success factor of partnerships is the value gained to each individual stakeholder relative to alternative investments. Policy options to harness and integrate the strengths of public-private partnerships for research and health innovation in Alzheimer's disease and other dementias include:

- Developing national governance frameworks for public-private partnerships with transnational outreach.

- Ensuring that public-private partnerships are affordable, respect value for money, are transparently treated in budget processes, and are monitored for quality and efficient use of resources.

- Empowering academia and small and medium-sized biotech companies as a key source of innovation and partner of the pharmaceutical industry. Providing the frameworks which support scientists at academia in field-testing innovative ideas and translating innovative ideas into products.

- Developing terms of reference for multiple industry-industry collaborations in public-private partnerships.

- Enabling information sharing and a systems approach in research and health innovation through the development of infrastructure, norms, standards, and policies across research areas and between stakeholders. Supporting open innovation models through the right frameworks at the interface between the precompetitive and the competitive space.

- Encouraging investment, joint thinking, and innovation through the development of novel funding structures, incentive models, risk-sharing and risk-managing schemes.

- Developing tailored research and drug development approaches for Alzheimer's disease and other dementias by adapting existing policy and regulatory frameworks to evolving, non-linear drug development models.

NOTES

1. www.gov.uk/government/publications/g8-dementia-summit-agreements

2. Prevalence is the proportion of those with the disease in a given population and is a broad measure, or a snapshot, of the impact of the disease at a given point in time (Prince, 2014).

3. www.whitehouse.gov/administration/eop/ostp/pcast

4. Performance-based risk-sharing arrangements (risk-sharing schemes) involve a plan by which the performance of the medicine is tracked in a defined patient population over a specified period of time and the amount or level of reimbursement is based on the health and cost outcome achieved.

5. www.usgs.gov/tech-transfer/what-crada.html

6. www.eatris.eu/about/SitePages/about.aspx

7. www.nce-rce.gc.ca/Programs-Programmes/NCE-RCE/Index_eng.asp

8. www.tipharma.com/

9. www.phe.gov/about/BARDA/Pages/default.aspx

10. www.hhs.gov/asl/testify/2014/02/t20140227e.html

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