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OECD Science, Technology and Industry Policy Papers No. 22

Enhancing Translational Research and Clinical Development for Alzheimer's Disease and other Dementias

OECD

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.

The OECD workshop "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and other Dementias: The Way Forward", 11-12 November, Lausanne, Switzerland, provided an international forum for all stakeholders to drive forward a change in the global paradigm in biomedical research and health innovation for Alzheimer's disease and other dementias. The workshop was organised under the auspices of the OECD Working Party on Biotechnology (WPB) and was hosted by the Government of Switzerland and supported by the Global CEO Initiative on Alzheimer's Disease (CEOi) and Alzheimer's Disease International (ADI). It produced an important dialogue between governments, regulatory authorities, the pharmaceutical industry, academia, and patient organisations regarding the challenges we face as we all work together in the shared effort to develop a disease-modifying treatment for Alzheimer's disease by 2025.

Discussions at the workshop have shown that progress on key issues is being made, thanks to a willingness of stakeholders to join forces and work together towards a future cure. In line with recommendations of the G8 Dementia Summit Declaration to strengthen collaboration for innovation and cross-sector partnerships this report considers the challenges and options to promote and accelerate research in dementia and its transformation into innovative therapies and diagnostics.

Participants in the meeting expressed very positive reactions to the tone of the meeting, which highlighted the shared challenge of Alzheimer's and the need for a shared solution across stakeholder communities. There was a consensus on the need for continuing dialogue among stakeholders, including a positive interest in similar workshops in future years. Consideration of how best to continue the dialogue and possible future action was put to the co-organisers of the Lausanne workshop.

The Committee for Science and Technological Policy (CSTP) approved this report in March 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

Accelerating innovation for Alzheimer's disease and other dementias is a key challenge. Over the past few years, the OECD has conducted work in a number of areas related to innovation in biomedical research and health innovation for healthy ageing. The workshop aimed to provide an international forum for all stakeholders to drive forward a change in the global paradigm in biomedical research and health innovation for Alzheimer's disease and other dementias. The main findings and conclusions of the workshop were the following:

- **Patient and public engagement** – We need to balance between traditional/ low-risk approaches and new strategies with some uncertainties. Position papers and draft guidance that reflect the opinions and needs of patients and the public (especially of caregivers and payers) would help regulators to bridge the gap between the development-push from pharmaceutical research and the demand-pull by patients. Dr. Janet Woodcock invited the submission of such guidance from patient-centred perspectives, noting its utility with respect to other therapeutic areas of high unmet need. EMA representatives expressed similar support as part of their ongoing processes for increased input regarding their development of guidance in this area. A better alignment of clinical outcome measures with patients' expressed needs, including patient-reported outcomes (PRO), could translate into a higher success rate of clinical trials and improved uptake of future therapies. However, it remains an operational challenge to build clinical trials around patient-reported outcome measures and to ensure data comparability and regulatory, quantitative assessment. There is a need for more, high quality data from global clinical trials that consider the potential genetic variability in populations. Collaborations among public- and private-sector stakeholders in proof-of-concept trials are now beginning, and much is expected of them. These and other novel approaches to encourage collaboration and further the public interest in knowledge creation and diffusion, therefore merit greater attention. Government policies could help to deepen the involvement of patients and the wider public through a strengthening of public trust, transparency, and oversight in broad diagnostic campaigns, global patient registries, and clinical trial platforms.

- **Driving the paradigm shift –** Significant progress has been achieved in the diagnosis of Alzheimer's disease and other dementias – both on a genetic/ molecular and biochemical basis. This has led to the paradigm shift of research in established dementia to people with prodromal and mild-stage disease. However, in these settings, the traditionally accepted outcome measures for safety and efficacy may not be appropriate. Integrated cross-disciplinary strategies are needed to identify potentially novel processes that 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.

- **Prevention and symptomatic treatment –** The development of disease-modifying therapies that alter disease progression or ultimately provide a cure is the main goal in Alzheimer's disease clinical research. However, preventive measures and therapeutic routes to improve the living conditions of symptomatic patients should not be neglected. Treatments with a sustained symptomatic effect can have a significant impact on people living with neurodegenerative diseases and should be developed in parallel. There is a need for better understanding the impact

of lifestyle, food and nutrition on healthy ageing and the development of Alzheimer's and other neurodegenerative diseases.

- **Regulatory processes –** There is consensus amongst stakeholders that more must be done to ensure that patients will be provided with new and innovative medicines. A more convergent and synchronised regulatory environment would strongly increase the efficiency of translational and clinical research programmes. There are opportunities to accelerate and streamline the operational conduct of multinational clinical trials through more efficient and harmonised national regulations. It will be important to incorporate the learnings from currently ongoing prevention trials into regulatory science and approval processes in order to change the regulatory paradigm based on the best available science. Regulatory agencies across the globe are key partners in the fight against Alzheimer's disease and providing more resources to regulatory agencies for scientifically sound decision making would help to speed-up the process without putting patients' health at risk.

- **Translational research and clinical trial conduct –** The translation of pre-clinical evidence into human trials remains a rate-limiting barrier to drug development. Researchers and regulators aim to balance the incomplete pre-clinical knowledge base with the urgent need for more, high quality data from human testing. The likelihood of successfully developing new, more effective treatments increases with the research community's fundamental understanding of Alzheimer's pathologies – and with the successful application of this knowledge to, for example: developing disease models; investigating the clinical validity of drug targets; characterising the performance characteristics of biomarkers for enrichment and predicting treatment effect; and improving clinical trial designs. Clinical trials can contribute much to the creation of this knowledge, and a great deal of sorely needed insight can come only from clinical trials of potentially disease-modifying therapies. Novel approaches to encourage greater dissemination of knowledge from clinical trials therefore merit consideration. Options should be discussed for an earlier entry into trials allowing the collection of valuable pharmacokinetic and pharmacodynamic information from patients. This would help to refine adaptive clinical trials and enable early failure.

- **Open science and smart data –** Open science has an enormous potential for the generation and sharing of smart data to accelerate progress in developing new treatments for dementia – thereby avoiding wasteful duplication of effort. Regulatory clinical trials are the most reliable and useful process to account for the variety of Alzheimer's pathologies within populations and to deliver the required uniformity of data. Combining efforts of building a Global Clinical Trials Platform with a future Central Clinical Database in Alzheimer's disease would offer the required international outreach and leverage synergies from a joint use of infrastructure, better aligned national regulatory and policy frameworks, and the implementation of incentives for all stakeholders. New funding mechanisms and incentive structures should be developed along the data life cycle, supporting data creation, management, analysis, storage, access and long-term use. Importantly, policies and processes must safeguard the rights, aims, and interests of all stakeholders. Future work on open science and smart data should be built around: 1) information governance (the creation of the right frameworks for use and exchange of information, e.g. Bermuda principles for Alzheimer's disease and other dementias); 2) data management (e.g. global dementia research inventories); and 3) patient and public engagement (e.g. enrichment of data by patient-centred outcome information).

- **Cross-sector learning –** Much can be learnt from the multitude of existing evidence in neighbouring medical fields, for example in other neurodegenerative diseases and psychiatry, that can offer both evidence-based policy support and the acceleration of clinical trials in Alzheimer's disease. Evidence from clinical trials and patient management can be used to further optimise

research and to define relevant outcome measures for more predictability of responsiveness. We need more cross-sector collaborations, reminiscent of HIV/AIDS meetings in the 1980s, in order to find a cure or prevention.

- **Research incentives and risk-sharing –** Drug development for Alzheimer's disease remains a high-risk endeavour. Because of the limited (financial) resources being devoted to research, there is a growing need for governments, funders and the pharmaceutical industry to co-ordinate research investments in a systematic way. Governments, in close collaboration with other stakeholders, can help to explore new funding vehicles and risk-sharing mechanisms to support resource-intensive research in neurodegenerative diseases and to mitigate financial risks. Increased investment and shared funding structures in translational and early clinical research could help to de-risk processes and attract researchers into an area which has been traditionally characterised by high attrition rates and financial loss. A global Alzheimer's research fund could provide the necessary resources and planning security to translate innovation into the clinical setting. In particular, there is a need for indicative baseline figures about public and private investment into Alzheimer's and dementia research and drug development. Performance indicators may be required to evaluate the efficiency of research and health innovation processes and investment systems, and to assess the quality of results delivered.

- **Medicines access and the payers' perspective –** Optimisation of patient access and respect for stakeholder needs (e.g. return of investment) along the life cycle of a future disease-modifying therapy for Alzheimer's disease requires a broad, cross-stakeholder discussion. Coverage and payment decisions are based primarily on available medical evidence and relative costs of existing therapies. To date, for Alzheimer's disease there is a paucity of discussion about the future use and pricing of a potential disease-modifying therapy. Special attention should be paid to the implementation of payer considerations, affordability, and access into regulatory decision making. In order to adequately plan for access and rational use, governments, pharmaceutical industry, payers, patient organisations, and regulators will need to develop and discuss access arrangements, pricing and reimbursement structures, and risk-sharing mechanisms.

INTRODUCTION

This report presents the main lessons and policy insights that emerge from the Workshop "Enhancing Translational Research and Clinical Development in Alzheimer's Disease and other Dementias: The Way Forward" (Lausanne, Switzerland, 11-12 November 2014). The workshop focused on: *1)* the identification of knowledge gaps in the development of disease-modifying treatments in Alzheimer's disease and other dementias; *2)* the implementation of innovative processes in product development and regulatory models, including the scope for flexible regulatory processes, enhanced clinical trial designs and a strengthened diagnostic environment; and *3)* collaborative research models and open science, which respect individual needs, challenges and options of all stakeholders.

Societies are confronted with health and economic challenges of an ageing population and the increased prevalence of Alzheimer's disease and other dementias. The number of people living with dementia worldwide today is estimated at 44 million, set to almost double by 2030 and more than triple by 2050 with a shift in burden to low and middle income countries. OECD countries account for nearly half the global cases of dementia today and have a particular responsibility in accelerating the translation of biomedical research into innovative therapies and diagnostics for healthy ageing. As a result the worldwide annual cost of dementia care is expected to increase to USD 1 trillion by 2030 (Alzheimer's Disease International, 2014; World Health Organization, 2012). In her welcome message Dr. Tania Dussey-Cavassini (Vice-Director General of Swiss Federal Office of Public Health, Ambassador for Global Health, Switzerland) highlighted the rapidly increasing number of dementia cases worldwide – with all its societal and medical consequences. In Switzerland alone 110.000 people are estimated to be living with dementia; approximately 6% (0.5 million) of the population are directly or indirectly affected by the dementia epidemic (Swiss Federal Office of Public Health, 2014). This has led to the development of the Swiss National Dementia Strategy 2014-2017. One of the goals of the strategy is to ensure the transfer of research findings into practice, and to support the dialogue between researchers, clinicians, and caretakers with appropriate instruments.

There is, as yet, no treatment for Alzheimer's disease, the main form of dementia. Currently available medicines only address the symptoms of Alzheimer's disease and do not provide any means to prevent, slow progression, or cure the disease. Providing a cure for Alzheimer's disease is a long-term goal of global dementia policy, however, collaborative strategies are equally critical in basic diagnostic research and for the development of more effective symptomatic treatments. There is consensus that the earliest pathological changes in the brain of patients take place long before first clinical symptoms appear – offering an opportunity for therapeutic intervention. Shifting therapeutic research from established dementia to pre-clinical stages requires adequate diagnostic tools, new trial designs, and more flexible regulatory processes. A joint engagement amongst all stakeholders is needed in order to strengthen innovative research and to accelerate its translation into clinical practice.

While numerous molecular and cellular events contributing to Alzheimer's have been revealed, the understanding of the pathological processes and feasible targets for therapeutic intervention is still limited. Translational research and drug development for central nervous system (CNS) disorders like schizophrenia, Huntington's disease, Parkinson's disease, Alzheimer's disease and other dementias is particularly complex due to inadequate disease models for pre-clinical testing, issues in identifying and reaching therapeutic targets inside the brain, narrow safety margins of potential therapies, high (diagnostic) infrastructure needs, and relatively lengthy clinical trials. Though researchers are significantly advancing our understanding of the aetiology and mechanisms of Alzheimer's disease and other dementias, and more putative therapeutics are being developed, stakeholders have failed so far to put emerging knowledge into therapeutic practice. Regulatory and policy issues in Alzheimer's disease are closely linked with persistent

knowledge gaps in biomedical science and fragmentation of resources. Key policy questions in Alzheimer's disease and other dementias are: How to accelerate innovation while balancing early access to promising therapies with medical scientific uncertainties? How to develop an innovation-friendly regulatory and policy framework around data privacy, access and standardisation? How to de-risk research and development in order to re-attract public and private funders? Ultimately, more holistic and sustainable innovation models should be built around the medical scientific and societal needs of Alzheimer's disease and other dementias.

In response to the dementia epidemic the World Dementia Council (WDC) was established at the invitation of the UK government following the G8 Dementia Summit in December 2013. The WDC follows a collaborative approach with all stakeholders along the value chain of biomedical research, health innovation, and care. It aims to stimulate innovation, development and the commercialisation of disease-modifying therapies and care for people with dementia. The Council has established a framework to enable and incentivise the eco-system around dementia and a plan to achieve its goals. Key focus areas of the WDC to develop a broad based platform for Alzheimer's disease are: *1)* integrated development (optimising the path of medicines from research through to market by reducing barriers and encouraging regulatory flexibility); *2)* finance and incentives (looking to increase investment in dementia research and drug development); *3)* open science (so that knowledge and information can be shared more widely in a collective global effort to find a cure); *4)* prevention (addressing risk factors for Alzheimer's); *5)* care (bring new technologies to care in order to rise the quality and efficiency of care and care delivery). Joint action would be needed by governments, regulators, academia and small and medium-sized biotech companies, the private industry, and patient organisations in order to deliver the first disease-modifying therapy for Alzheimer's disease by 2025. Dr. Dennis Gillings (CBE, World Dementia Envoy) pointed out that "Innovation is shaped through conversation and the conversation at the workshop continues stakeholders down the right path of stopping Alzheimer's by 2025. We are aiming to develop an environment of open science, which should stimulate more innovation. We must bring together the best people, share the best evidence, develop the best approaches, and marshal all the resources to defeat this disease. But if we don't address the barriers in accelerating translation of innovation to therapies for patients we will not reach our goal."

"Neurodegenerative diseases and in particular Alzheimer's disease, which have become a major challenge for research and development and public health, are the focus of the Lausanne workshop" stated Dr. Isabella Beretta, Chair of the OECD Working Party on Biotechnology and representative of the Swiss State Secretariat of Education, Research and Innovation. At the workshop experts convened to discuss the barriers and options to the development of disease-modifying treatments and diagnostics for Alzheimer's disease and other dementias. This includes the need for stronger involvement of biomarker research in drug development processes, to adopt more innovative clinical trial designs, and to encourage flexible regulatory processes. This report recognises the medical, scientific, policy, regulatory, and operational issues around the question of what can be done to support biomedical research and health innovation for the delivery of the required diagnostics and disease-modifying treatments for Alzheimer's disease and other dementias.

DRIVING THE GLOBAL PARADIGM SHIFT IN ALZHEIMER'S DISEASE RESEARCH AND HEALTH INNOVATION

Box 1. Key Messages

- *"Biomarker research in Alzheimer's has fuelled our understanding of the disease pathology and has been driving the paradigm shift we are observing now. The current concept allows for a diagnosis and potential treatment of Alzheimer's disease before and even without manifestation of dementia." (Prof. Dr. Philip Scheltens)*
- *"Alzheimer's is a very serious disease of the brain and should be treated just as cancer, HIV or other life threatening diseases. However, our ability to react scientifically is limited by two main factors: time and financial resources. We need to leverage the systems in place (policies, research, and financial resources) to accelerate the processes to deliver the science and medicines we need." (Prof. Dr. Randall Bateman)*
- *"We still do not fully understand the underlying pathologies of Alzheimer's disease in order to permit the selection of the right targets and to develop the treatments which are urgently needed to address the Alzheimer's epidemic." (Dr. Janet Woodcock)*
- *"There is broad agreement that Alzheimer's disease should be seen as a continuum of different disease stages and that any interventions should start before onset of symptoms. However, the question to be answered is how early is early enough to effectively alter the disease progress." (Dr. Karl Broich)*
- *"I do not see a fundamental discrepancy in the regulatory scientific questions around Alzheimer's disease between the EMA and the FDA. However, in order to drive the development of new medicines for Alzheimer's we should focus on the national jurisdictions where we have to translate our interpretation of larger, international regulatory frameworks." (Dr. Guido Rasi)*
- *"Funding in Alzheimer's disease has increased in parallel to the WDC legacy events. However, a couple of billion USD annually may be needed to support the goal to develop a disease-modifying treatment by 2025 – we are not yet there and there is a lot of progress to make." (Dr. Dennis Gillings)*
- *"Alzheimer's disease, from an economic perspective, offers an enormous market with a potentially high return of investment – this is inherently different from markets in, for example, infectious tropical diseases or orphan diseases. However, if we look into the potential use of off-patent (re-purposing) drugs the incentives for high-investment drug development programmes in Alzheimer's are rather limited." (Dr. Troy Scott)*

Given the scale of the dementia epidemic and due to the lack of effective treatments and diagnostics, governments and their agencies, the public and private research community and patient organisations need to strengthen efforts to develop disease-modifying treatments for Alzheimer's disease. The translation of progress in the scientific basis of Alzheimer's disease and other dementias into recent and future clinical and regulatory approaches represents a key driver of realising the paradigm shift. Current evidence suggests a long preclinical phase of Alzheimer's disease, which provides a critical opportunity for therapeutic intervention, and which needs to be considered by both the research community and policy makers. These changes require new trial designs, assessment tools and regulatory processes to monitor disease progression and to evaluate therapeutic efficacy in patients with preclinical Alzheimer's disease. A joint engagement amongst all stakeholders is needed in order to strengthen innovative research strategies and to accelerate its translation into clinical practice. In this regard Dr. Dennis Gillings argued that in order to accelerate translational research for dementia medicines we should aim for regulatory agencies working together and looking for ways to use existing laws and regulations collaboratively and collectively.

Medicine regulation defines the frameworks and approval processes for the delivery of safe and effective diagnostics, preventive medicines and treatments. Regulatory agencies are a key, independent partner for innovators in drug development for Alzheimer's disease. The unique needs of the disease, persistent knowledge gaps and failure in the delivery of disease-modifying drugs have shaped regulatory processes and governance models for product development. There is now consensus that treatment options should also be evaluated at earlier stages of Alzheimer's disease in an attempt to change the course of the disease. Populations of early disease and even pre-symptomatic patients are being included in clinical development programmes. This paradigm shift has implications on clinical trials designs, patient selection, the choice of outcome measures, and biomarkers which will be considered in a revision of the current Alzheimer's disease guidance. As laid out by Dr. Karl Broich and Dr. Manuel Haas, this paradigm shift was recognized by the European Medicines Agency (EMA) in the draft concept paper on the need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias (EMA/CHMP/617734/2013), released for public consultation in October 2013. EMA fully appreciates the scale of the disease, its impact on society and even more importantly on the life of the individuals affected and their caregivers. European regulators strive to contribute to accelerating innovation for Alzheimer's disease and its translation into innovative therapies. They help applicants in their research and development by issuing guidance, scientific advice and opinions on the acceptability of using biomarkers or a distinct methodology in clinical trials. In these qualification opinions biomarkers are accepted for identification and selection of patients at the pre-dementia stage as well as stages of mild to moderate Alzheimer's disease. Recently a qualification opinion for a novel model of disease progression and trial evaluation in mild and moderate Alzheimer's disease was adopted. The use of scientific advice and of this qualification procedure for new approaches and study designs is highly recommended and allows EMA to provide regulatory flexibility and support innovation in this therapeutic area.

Regulators are naturally conscious of the international challenge of Alzheimer's and the need to facilitate and accelerate global development of new medicines. As a result, EMA makes ample use of the mechanisms in place for international collaboration and through confidentiality agreements with other regulatory agencies and multi-lateral organisations (e.g. ICH, OECD, WHO). The EMA will continue to work with its partners to reach a maximum level of global regulatory efficiency. Following a collaborative approach, EMA has organised a multi-stakeholder workshop on 24-25 November 2014. This workshop was designed as an integral part of the revision of the EMA guideline and aims to take the most up-to-date scientific developments in understanding and treating Alzheimer's disease into consideration, as well as the positions of experts in the field. A discussion paper (EMA/CHMP/539931/2014) was recently released to support and focus the discussion of the workshop, outlining the current thinking of the European regulators on the scientific and regulatory challenges and avenues for the development and approval of treatments for Alzheimer's disease.

Dr. Janet Woodcock presented the perspectives of the US Food and Drug Administration (FDA) on the possible measures to overcome roadblocks to accelerate the development of effective therapies and diagnostic tools for Alzheimer's disease. There are different hypothesis as to why we have failed so far, however, the underlying issue may be that we are still lacking the tools to deal with the epidemic. We need a better understanding of the disease pathologies in order to increase the success rate of clinical trials and to avoid companies shifting their portfolios to other, potentially more attractive disease areas. The FDA has issued a draft guidance "Developing Drugs for the Treatment of Early Stage Disease"[1] which shows current thinking of the FDA on research and drug development in the early disease course; it recognises the need for cognitive and functional diagnostic criteria. The draft also suggests that FDA could use the accelerated approval mechanism in early, pre-symptomatic disease with prevention of decline in sensitive cognitive measures as an intermediate endpoint. How could Alzheimer's disease biomarkers be more rapidly developed ('validated')? At an industrial scale and for regulatory purposes, it is critical to understand the performance characteristics of these markers in each individual application area, for example to: 1) enrich clinical trials with the population the drug is targeted for; 2) refine and standardise

assays and diagnostic imaging techniques; 3) evaluate the performance of an investigational drug in impacting clinical outcomes along the therapeutic intervention. The research efforts behind the development of biomarkers in Alzheimer's disease require substantial efforts to recruit large numbers of people from different areas in the world (to account for possible regional variation), with different genetic predispositions, and in all disease stages. Dr. Woodcock pointed out that biomarker assays and data collection methods need to be standardised – this is where the pharmaceutical industry has its strengths, and where academia needs to improve.

The scientific basis for a paradigm shift - new insights and future opportunities

Box 2. Key Messages

- *"Much has been learnt from family members with autosomal-dominant Alzheimer's disease (ADAD). Here the cascade of events begins with amyloid-beta deposition about 20 years before the very first symptom onset. The metabolism of the brain changes about 10 years before, leading to structural changes of the brain about 5 years before symptoms become apparent. Thus, if we want to intervene in this process we have to diagnose and treat much earlier than we thought before." (Prof. Dr. Randall Bateman)*

- *"Dementia is not a normal part of ageing – it is a disease. And this disease should be modified and hopefully cured. Currently there is nothing for disease modification other than prevention through, for example, lipid and glucose control, exercise, brain activity, and inflammation control. If it is good for the heart, it is good for the brain." (Dr. Dennis Gillings)*

- *"I strongly believe that we need to fight the disease at the origin. However, because of the inherent differences in the pathologies of Alzheimer's we cannot apply the same concept to all 44 million patients out there. We need to work on sub-groups; we need biomarkers and targeted treatments for the individual abnormal proteins." (Prof. Dr. Philip Scheltens)*

- *"It is hard to understand how a drug which efficiently improves patients' symptoms on a long-term basis should not be viewed as having a "disease-modifying" effect." (Prof. Dr. Martin Rossor); "In my opinion, it does not matter how the doctor feels, but it is critical how the patient feels. We can look into other disease areas where we have time-to-progression outcomes. The FDA believes that any kind of impact on clinical symptomatology is viewed as a benefit for the patient." (Dr. Janet Woodcock)*

There has not been a new Alzheimer's treatment on the market in over a decade. A recent publication cited a near 100% failure rate in Alzheimer's drug development from 2002-2012. Overall, drug development in CNS has had a single digit success rate. At the same time, given the high attrition rate of drug development for Alzheimer's disease, stakeholders have been analysing the reasons behind failure, for example: wrong pathophysiological and translational models, lack of appropriate animal models, inappropriate trial design, drugs using an ineffective method of action, drugs not engaging their target, and intervention too late in disease progression. Understanding the molecular and biochemical underpinnings of Alzheimer's disease is of significant importance to fill drug development pipelines and to enable evidence based decision making in medicines regulation. Recent advances in neuroscience have provided significant insights into the biochemical and molecular underpinnings of Alzheimer's disease and neurological disorders, but there remains much to be discovered. Medical, scientific and clinical evidence indicates that therapeutic intervention in Alzheimer's disease should start before the manifestation of symptoms. Stakeholders aim to develop and implement the necessary tools and processes to accelerate the translation of discovery research and clinical evidence into effective diagnostics and therapies which address pre-symptomatic pathologies of Alzheimer's disease. This paradigm-shift – preventing the disease onset or its progression in pre-symptomatic stages versus treating the disease after symptoms appear or addressing symptoms themselves – creates further challenges in translational and clinical research in populations where there are no cognitive or functional symptoms.

In order to manage financial risks and efficiently use limited resources, clinical programmes are designed to allow an early verification of the therapeutic hypothesis through iterative processes in translational studies. The question remains to be answered whether the multifactorial nature of Alzheimer's disease can be addressed through the traditional model of a single-target therapy or whether it requires combination approaches with associated regulatory adjustments. In his presentation Prof. Dr. Philip Scheltens described how progress in Alzheimer's diagnosis has been driving a paradigm shift in dementia research and health innovation. The diagnosis of Alzheimer's disease has moved from exclusion to inclusion over the last 30 years, by using clinical, biomarker, imaging and genetic methods. Since the description by Dr. Alois Alzheimer in 1906 until the nineteen-eighties, Alzheimer's disease was considered to be a rare form of early onset dementia. Ensuing work from scientists in the US and EU showed that the characteristic pathologic changes as shown by Dr. Alois Alzheimer were present in most of the demented patients of any age. This called for treatment of dementia as a disease, and the first clinical criteria that allowed for a diagnosis of Alzheimer's disease appeared in 1984. These clinical criteria were subsequently used for all the clinical and therapeutic research until 2007 when a concept change was introduced which used biological markers to diagnose Alzheimer's in pre-clinical populations or populations with mild cognitive impairment. Research on biomarkers, notably magnetic resonance imaging (MRI) and cerebrospinal fluid[2] (CSF) and more recently positron emission tomography (PET) amyloid brain scan, greatly influenced and inspired the "International Working Group on Criteria for Alzheimer's disease", led by Bruno Dubois and Philip Scheltens, to formulate the concept of diagnosing Alzheimer's disease based on pathology (Dubois et al., 2007; Dubois et al., 2010; Dubois et al., 2014). Since the concept change, Alzheimer's diagnosis has become much more (pathology) specific, and clinical trials are now designed using biomarkers as inclusion or entry criterion. CSF beta-amyloid$_{42}$ is the earliest marker providing the earliest biological signal of Alzheimer's disease. This has implications for biomedical research, drug development and clinical practice; it also has inspired the research community to further investigate potential biomarkers in other neurodegenerative causes of dementia. However, Prof. Dr. Philip Scheltens pointed out that amyloid imaging is expensive and not universally available. The above illustrates how the field has moved from phenotype-centred assessment to protein-type diagnostics in Alzheimer's disease. A consequence may be that research will be focused on the more pure forms of disease, notably, the type of disease that displays a single protein pathology, e.g. amyloid, or tau, or progranulin. Other example of this approach is research strategies focusing on monogenetic forms of Alzheimer's disease and Down's syndrome. This provides clarity and narrows down the broader field of dementia and large populations of elderly that have mixed diseases – a necessary step in the process of discovering an effective therapy that may subsequently be administered to the later onset forms of disease. Consequently, one may also conclude that we have studied Alzheimer's disease in the past as one clinical entity, based on clinical definitions and criteria – strategy, which has not been successful in drug discovery and which needs to be rigorously changed in order to increase the likelihood of success on the road to therapy.

Prof. Dr. Randall Bateman showed that research in the clinical, pathological, biochemical, and molecular characteristics of autosomal-dominant Alzheimer's disease (ADAD) has led to a concept change in the development of diagnostic and therapeutic targets – what we now call disease-modifying therapeutic approaches. However, growing evidence in Alzheimer's disease research shows that most drugs that failed in clinical trials did not reach their targets in the brain. Thus, we may have not addressed the right stage of the disease and may have treated too little – this does not necessarily mean that the underlying disease hypothesis is incorrect. Therefore, to increase the success rate of translational research and clinical trials, researchers need to prove target engagement of potential new drugs in the central nervous system (CNS).

Prof. Dr. Andrea Pfeifer stressed that the lack of any new approved therapies for Alzheimer's disease since 2003 and failure of all 11 recent Phase 3 studies of investigational disease-modifying therapies is a cause for great concern. The pathogenesis of Alzheimer's disease is complex, leading to multiple potential new targets for therapy, such as neurotransmitter enhancement, anti-inflammatory, antioxidant and neurotrophic agents. With increasing understanding of neurogenesis and neuroplasticity, and developments

in the stem cell field, there is even the growing prospect of being able to reverse some of the changes of the disease in the future. Despite several failures in the beta-amyloid field the recent positive results on cognition with both monoclonal antibodies solanezumab and crenezumab in mild Alzheimer's disease patients make this a promising therapeutic target if applied early in the disease (see Figure 1 and Figure 2).

Figure 1. Crenezumab ABBY Phase 2 Change in ADAS-cog 12 in mild patients (MMSE 22-26)

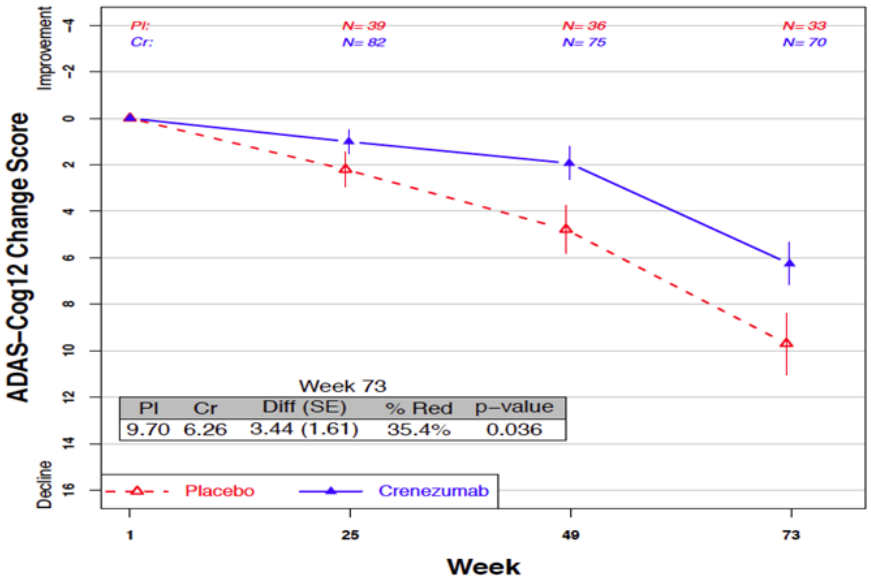
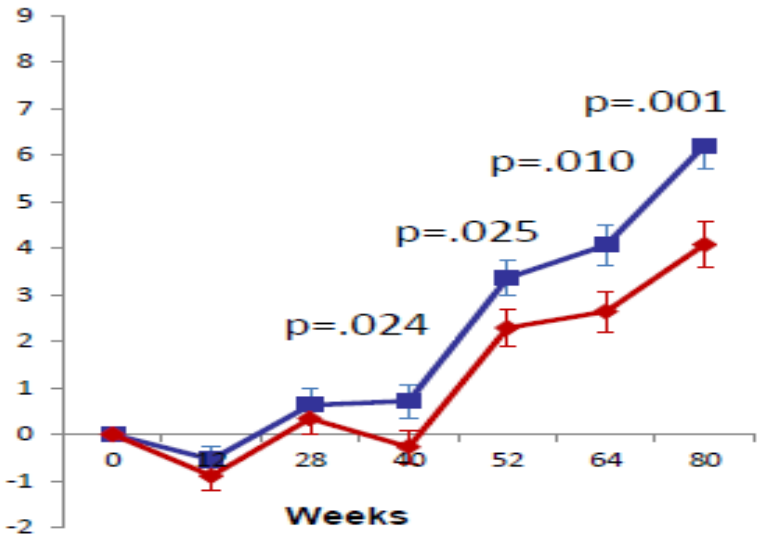


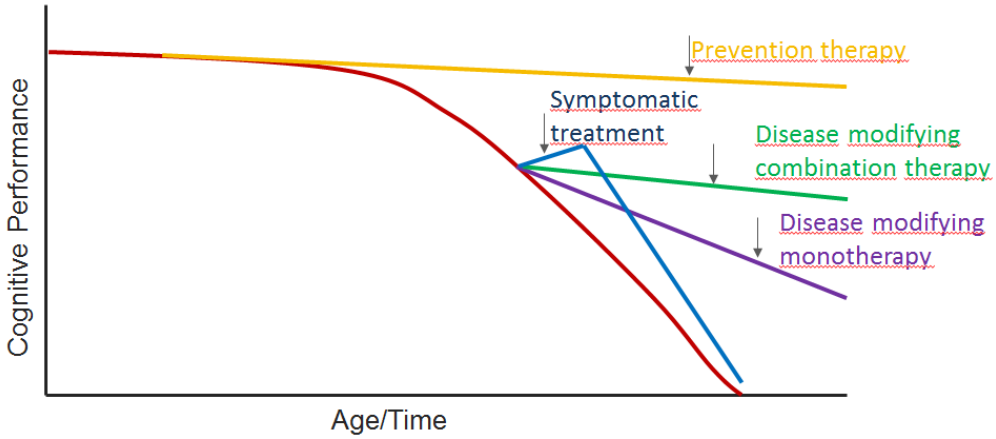
Figure 2. Solanezumab Expedition 1 and 2 Phase 3 - pooled change in ADAS-cog 14 in mild patients (MMSE 20-26)



Several exciting initiatives based on public-private partnerships are ongoing to test the potential of such approaches in patients with genetic risk factors associated with excessive amyloid deposition, such as the API ADAD study[3] of crenezumab in pre-symptomatic Colombian carriers of the Paisa PS1 mutation, the DIAN study[4] of solanezumab, gantenerumab and a BACE-inhibitor in dominantly inherited Alzheimer's disease, the A4 trial of solanezumab in healthy elderly people with imaging or CSF amyloid positivity, the API ApoE4 study of CAD106 and a BACE-inhibitor in pre-symptomatic ApoE4

homozygotes and the planned study of an anti-amyloid vaccine in people with Down syndrome. There is increasing scientific evidence to support tau as a therapeutic target, strengthened by new data from PET imaging agents targeting this aspect of the pathology. For example, recent Tau-PET results suggesting that spread of tau from the limbic system to the neocortex is associated with increasing cognitive decline, with increased levels of tau detected even in early stages of the disease.

Figure 3. Slowing of cognitive decline by therapeutics and prevention.



Combination approaches will be increasingly important in maximising the effects that can be obtained with agents targeting different aspects of the pathology (see Figure 3). Regulatory support for such approaches will be needed to guide the co-development of different investigational agents. Continued development of surrogate markers as well as efforts to address the issue of insensitivity of functional as compared to cognitive endpoints not only in prodromal Alzheimer's disease but also in early dementia are important.

Progress in Alzheimer's disease diagnostics – the potential of biomarkers in early stage disease

Box 3. Key Messages

- *"The absence of qualified biomarkers is one of the biggest impediments for Alzheimer's research. At the moment we cannot identify dementias early enough to arrest the pathology. New diagnostic techniques are emerging, but they are at the same time very expensive and will have an impact on the cost of clinical research and future treatment." (Dr. Dennis Gillings)*

- *"Recent evidence from clinical trial populations shows that up to 25% of trial subjects do not show the pathology the drug is targeted at. That is a huge undermining of the ability of the trial to show if the drug works. Biomarkers can be used to address this problem and to enrich clinical trial populations" (Prof. Dr. Randall Bateman)*

- *"In order to be used under accelerated approval schemes of the FDA, biomarkers would need to prove that these are reasonably likely to predict clinical benefit. I think we are not there yet in Alzheimer's disease. However, the FDA is willing to use a variety of cognitive tests for accelerated approval if the sponsor can show a prevention of deterioration compared to a control group." (Dr. Janet Woodcock)*

- *"Differences between regulators in the definition of disease stages and use of biomarkers for the enrichment of clinical trials can have an impact on the composition of study populations and results of clinical trials." (Dr. Karl Broich)*

- *"In order to facilitate a broader use of biomarkers in Alzheimer's trials, the EMA is asking for more standardisation and validation of biomarker data for the different disease stages" (Dr. Karl Broich). The EMA strongly encourages the voluntary use of scientific advice for the biomarker qualification. Through this procedure the EMA has qualified four biomarkers for the enrichment of clinical trials in other disease areas." (Dr. Manuel Haas)*

- *"Validation is a word that should not be used because it too vague in the context of biomarkers. What we need now are diagnostic criteria to identify people with a high probability of disease progression in order to enrich clinical trials. However the data which are currently available do not allow any conclusive decision." (Dr. Janet Woodcock)*

- *"We are facing operational challenges in using CSF-based biomarkers. It will not be possible to perform a lumbar puncture on every patient during a treatment course. We need to advance the technologies in Alzheimer's diagnosis." (Dr. Janet Woodcock)*

- *"The functional outcome cannot be only predicted on the basis of scale scores and brain modifications. Alzheimer's just like psychosis should be considered as whole body disorder for which some at-risk peripheral biomarkers can be identified." (Dr. Philippe Nuss, Professor, Department of Psychiatry and Medical Psychology Saint-Antoine Hospital, Paris)*

- *"Inadequate standardisation of data remains a key challenge in the development of biomarkers." (Dr. Diane Stephenson)*

Prof. Dr. Randall Bateman presented "Progress in Alzheimer's disease diagnostics – validation and use of cognitive endpoints and surrogate markers". Despite the vast number of patients (more than 30 million worldwide – with 5 million in the US alone) and related annual global costs of care of more than USD 200 billion, there is still no cure (or disease-modifying treatment) currently available for Alzheimer's disease. Prof. Dr. Bateman also referred to the limited (financial) resources in Alzheimer's disease research and pointed out that still about 90% of research grants in this important area are rejected and not funded. The multifactorial nature of Alzheimer's disease and its slow, chronic progression requires collaboration between diverse research disciplines in lengthy translational and clinical research projects. Additional substantial governmental resources are urgently needed in order to prevent the epidemic of Alzheimer's disease from causing immeasurable suffering, loss of life, and economic collapse of medical systems.

To date most trials have targeted mild to moderate stages of Alzheimer's disease. Until a drug demonstrates, individually, clinically substantial benefit, confirmation of the targets of Alzheimer's disease remains uncertain. Clinical trials of investigational disease-modifying treatments have to date failed to meet their primary outcomes, and most potential new drugs have not demonstrated significant (>25-50%) engagement of their target in the brains of patients. Prof. Dr. Bateman mentioned that 'too little' engagement of the targets raise the possibility that drugs to date have not tested full target engagement and may provide limited improvement in clinical outcome. Given the high attrition rate of clinical trials in neuroscience, and Alzheimer's disease in particular, there is a need to increase the number and quality of investigational drugs entering human clinical trials. In addition, evidence suggests that the percentage of patients in clinical trials who show the pathology the drug is targeted for is much lower than we have aimed for. This strongly undermines our ability to better understand the pathologies and to verify the efficacy of a potential new drug. In this context Prof. Dr. Philip Scheltens pointed out that biomarkers need to be tested and qualified as a surrogate for the individual Alzheimer's pathologies, disease progression, and cognitive status. The research community and regulators aim to advance biomarker technologies as non-invasive tools that can be used to monitor the effect of treatments on patients. However, to date, the success of developing non-invasive or blood-based biomarkers has been limited – research on that matter is in a very early stage.

The success of developing specific and sensitive diagnostic tools for Alzheimer's disease is closely linked with the understanding of the biochemical and molecular pathological processes preceding disease manifestation and symptoms. However, as Dr. Dennis Gillings pointed out, "the current research along the disease stages is not sufficient for the development of disease-modifying treatments". Rare forms of dominantly inherited Alzheimer's disease, which can be identified through genetic testing, are highly informative as these offer valuable insight into disease onset and development. Given that the clinical, cognitive, brain structure, metabolism and pathologies of inherited Alzheimer's disease are similar to sporadic forms, researchers can compare and extrapolate information to more common/sporadic manifestations of the disease. In 2008, a global study, the "Dominantly Inherited Alzheimer's Network" (DIAN) was established to inform about dominantly inherited Alzheimer's disease utilizing a comprehensive panel of clinical, cognitive, imaging, and biomarker assessments. The "Dominantly Inherited Alzheimer Network Trials Unit" (DIAN-TU) is a novel Alzheimer's disease trial platform to test multiple drugs in parallel for prevention and adaptively transitioning to confirmatory cognitive endpoint trials. Prof. Dr. Bateman highlighted that prevention of disease is likely to be an effective strategy to combat the dementia epidemic. The first Alzheimer's disease prevention trials have been launched by the DIAN-TU in 2012. Prevention efforts targeting amyloid-beta, including the A4 prevention trial enrolling participants with pre-dementia amyloidosis and the API prevention trial in a large kindred with dominantly inherited Alzheimer's disease have begun as have prevention efforts including other targets (TOMM40). Future trials are planned which will enrol those with increased genetic risk (ApoE4 carriers) of developing Alzheimer's disease.

Dr. Janet Woodcock addressed the question whether a biomarker could be an outcome measure (surrogate endpoint) in clinical trials. Here it would be critical to understand the performance characteristics of the biomarker in the different disease stages, under treatment conditions, and how it correlates with disease progression. A discussion should be started about what evidence would be needed to develop ('qualify') biomarkers for use as surrogate endpoints. This is in line with Mark Hope's statement that the existing endpoints in dementia research are subjective and do not have the sensitivity to be used in prodromal or early disease stages of Alzheimer's.

Opportunities to accelerate translational research and clinical trials

Box 4. Key Messages

- *"There is not enough financial investment in Alzheimer's disease research and drug development; and probably not enough incentives. We need more financial creativity to support the translation of innovative research into clinical use." (Dr. Dennis Gillings)*
- *"By speeding up the drug development process by one year potentially 8 million more people with dementia will have access to a new treatment" (Mr. Marc Wortmann)*
- *"To speed up the development of disease-modifying treatments for Alzheimer's disease we have to increase the efficacy of translational research and clinical trials through decreasing the cycle time it takes to find out if a potential new drug works or not. The limitation here is not the science, but the speed of how we can test in the clinics." (Prof. Dr. Randall Bateman)*
- *"In order to speed-up the development of innovative therapies for Alzheimer's disease we need to balance flexibility of our research with regulatory guidance, advice, and direction." (Mr. Mark Hope)*
- *"At the EMA, adaptive licensing (conditional and accelerated approval) mechanisms will be a model for potential new therapies in Alzheimer's disease similar to the FDA. However, this has other implications on the market exclusivity, intellectual property rights, and return of investment by the pharmaceutical industry."*

(Dr. Karl Broich)

- *"There is no single regulatory bullet to the problem of Alzheimer's disease. However, there are a number of mechanisms in place which can be used, including conditional approval and adaptive licensing if we have the data. Also, the EMA embraces a concept of an early, multi-stakeholder dialogue in order to accelerate the approval of drugs; we appreciate that a sequential dialogue is not efficient enough. Parallel European Medicines Agency / Health Technology Assessment bodies' scientific advice during the medicines development process is a good example of how this can be organised." (Dr. Manuel Haas)*

- *"Harmonized regulatory guidance on aspects such as conditional approval and adaptive licensing approaches should be further developed to allow early access of patients to therapies when robust initial efficacy and safety are observed." (Prof. Dr. Andrea Pfeifer)*

- *"We work to increase alignment between the EMA and other regulatory agencies. However, we cannot necessarily be fully harmonised and aim to achieve a situation where our requirements are not different to a point that these impede development in a global environment." (Dr. Manuel Haas)*

- *"We have a global problem of 44 million people suffering from dementia. We have a global industry trying to develop new medicines for the patients. And we have local regulatory requirements. What are the barriers to achieve a common scientific advice and common agreement with regulators on global clinical trial designs?" (Dr. George Vradenburg)*

- *"If you really want to move fast and do translational research and development effectively, then you need an industrial scale effort in clinical trial infrastructure. There is no shortage of patients out there, but there is a lack of funding and resources to get things done." (Dr. Janet Woodcock)*

- *"In order to achieve a higher efficiency in trial conduct, we need first, a higher degree of certainty (enrolling the right patients, assessing the right endpoints), and second, a higher degree of utility (validated biomarkers, real clinical impact measures, and predictability for future progress). This would lead to faster and more efficient learning to enter pivotal trials with lower risks and more efficient confirming for a higher probability of achieving patient access to effective therapies." (Dr. Luc Truyen)*

- *"There is an urgent need for a quantitative pharmacodynamic measure of drug effect to allow for an early failure of drugs in development. This would certainly help to attract funders into the field because they do not have to risk large funds in late stage efficacy trials of a drug for which researchers have very limited understanding of whether it works or not." (Dr. Janet Woodcock)*

- *"Hope for the future is evident in emerging technologies to not only assist with diagnosis and monitoring of patients but possibly to serve as a personalised medicine platform to faster assess effects of therapies." (Dr. Diane Stephenson)*

Dr. Diane Stephenson laid out that innovation is clearly evident in the current Alzheimer's disease landscape and novel discoveries and technological breakthroughs serve as catalysts that fosters progress and optimism. Recent examples include a three-dimensional human neural cell culture model of Alzheimer's disease in a dish (Choi et al., 2014) and non-invasive biomarker discoveries such as plasma lipidomics and neurotrack technologies for early diagnosis (Trushina et al., 2013; Zola et al., 2013). Yet, most of such novel discoveries do not reach the point of having impact on the many people suffering from Alzheimer's disease.

Successful discovery and regulatory acceptance of new biomarkers and other innovative tools is a time-consuming and costly process, with some parallels to the costly challenges in developing new drugs for approval. The required paths are not well recognized by many stakeholders and to-date such initiatives have frequently been owned by individual stakeholders. Experience in Alzheimer's disease research suggests that there are very high risks in continuing along the path that has been common practice to date. The challenges faced are that many biomarker discoveries do not replicate, repeated failures are costly and

validation is key (yet not owned by the scientific community or industry collectively), and the competitive landscape and intellectual property issues pose hurdles to sharing of information useful for faster learning. It was suggested that public-private partnerships, particularly with regulatory engagement, can accelerate a viable path for the future.

The Critical Path Institute (C-Path), a non-profit organisation with the mission of delivering on FDA's Critical Path Initiative, was formed 10 years ago. C-Path leads a total of eight precompetitive consortia covering a broad range of diverse disease areas and platforms; however, all share in common the goals of development of consensus data standards and precompetitive data sharing to develop tools that will accelerate and streamline drug development. The Coalition Against Major Diseases (CAMD) aims to advance drug development tools for Alzheimer's and Parkinson's diseases. CAMD aims to tackle multiple challenges facing Alzheimer's disease drug developers by obtaining regulatory decisions that will benefit the field as a whole. CAMD's successes include: *1)* development of Alzheimer's disease CDISC consensus data standards (including biomarker standards developed in conjunction with ADNI); *2)* development of a unified clinical trial database consisting of placebo data from 24 trials pooled, integrated and available to qualified external researchers; *3)* regulatory endorsement (EMA and FDA) of an Alzheimer's disease clinical trial simulation tool for the purposes of aiding with clinical trial design; and *4)* qualification of Alzheimer's disease neuroimaging biomarker for patient enrichment with EMA. At present CAMD is targeting qualification of a new composite outcome measure for early-stage Alzheimer's disease clinical trials. Notably EMA and FDA have communicated their intent to proceed with this project in parallel given the current unmet needs in this area. New regulatory paths are being developed by C-Path, such as a letter of support (LoS) recently endorsed by FDA and EMA for safety biomarkers. It's hoped that such biomarker decisions in Alzheimer's disease will de-risk the utilization of defined biomarkers in ongoing and prospective Alzheimer's disease clinical trials.

CAMD's progress is critically dependent on access to data as well as resources, both of which pose challenges in the current environment. At present, CAMD lacks Alzheimer's disease biomarker data from industry sponsored trials in the early Alzheimer's patient population, a key gap that will be critical to successfully achieving biomarker qualification with FDA. Likewise, refinement of the Alzheimer's disease clinical trial simulation tool in the predementia stages of Alzheimer's disease will require more data including biomarker data.

Dr. Diane Stephenson concluded by offering possible recommendations to foster the translation of innovation into research and clinical practice: *1)* a more universal employment of data standards; *2)* reconsideration of incentives and reward systems for innovative discoveries; *3)* disclosure of biomarker validation data from legacy trials; and, *4)* endorsement of the roadmap for biomarker requirements prior to implementation in clinical trials (McGhee et al., 2014). In this context Dr. Janet Woodcock commented that standardised cognitive batteries in pre-symptomatic disease would be needed in order to truly accelerate clinical research programmes and to allow cross-regional comparison of potential outcome measures (both pharmacodynamic and trial data) in pre-symptomatic and early disease. Dr. Philippe Nuss argued that much can be learnt from other neurodegenerative diseases and psychotic disorders. Even though psychosis develops in young individuals, it presents pathologic and clinical characteristics that show parallels with Alzheimer's disease. Like Alzheimer's disease, psychosis has a long premorbid phase with significant cognitive impairment and brain alterations (e.g. oxidative stress, chronic brain tissue inflammation, decreased neuroplasticity, genetic predisposition) become visible several years before the first clinically observable symptoms. Evidence and high quality data from clinical trials and management of psychotic patients can be used to optimise management of clinical trials in Alzheimer's.

Dr. Luc Truyen discussed the many costly late stage failures of putative disease-modifying drugs for the treatment of Alzheimer's disease. In fact not a single new drug has been approved in the last decade. This has compounded the growing urgency towards finding a cure for this devastating disease and has led

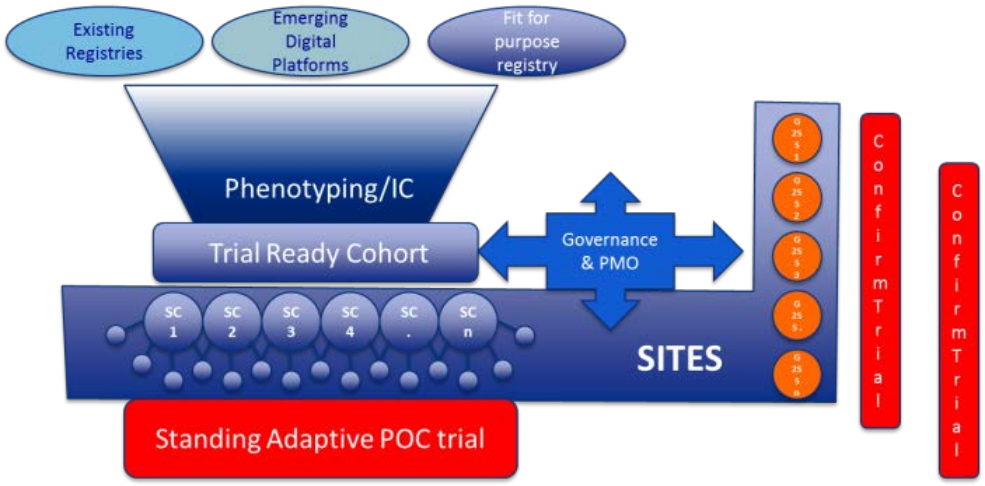
to further disconnect between funding needs and availability. Several factors are typically assumed to have contributed to this failure,

- Inadequate intervention (too late and insufficient dose) to meaningfully impact disease processes;
- Diagnostic uncertainty with up to 20% of participating subjects not having amyloid pathology;
- Insufficient learning both within and across intervention trials;
- Limited number of targets and therapeutic options in development.

A great part of the solution would lie in a better understanding of the disease, its risk factors, its evolution and the identification of tractable targets. Dr. Luc Truyen pointed out that significant contributions to our advancing knowledge in these areas have been furnished by collaborations through public-private partnerships. For example the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Innovative Medicines Initiative-European Medical Information Framework (IMI-EMIF) and AETIONOMY have been looking at evolution of disease and pathogenic hypotheses. In addition, the Accelerating Medicines Partnership (AMP) and Innovative Medicines Initiative 2 (IMI-2) aim to find new targets for treatment and identifying novel biomarkers to track disease progress as well as treatment impacts.

A logical complement to these efforts is to take clinical development lessons from the past and find ways to more effectively and efficiently determine if a new treatment will make a relevant difference. Here regulators are key partners for the pharmaceutical industry to accelerate the development of disease-modifying treatments for Alzheimer's disease. Core enablers would be: reliable means to identify and track participants in early stages of disease, well trained and equipped sites to conduct the studies and, lastly, more innovative trial designs that would allow for faster learning and adaptation based on emerging data as well as more efficient ways to conduct confirmatory studies. A key feature would be a standing trial ready platform combining direct access to well characterized subjects with sites certified and ready to engage trial participants. Figure 4 shows a template of what this could look like. The new IMI-EPAD (Early Prevention in Alzheimer's disease) project recapitulates most of these features. Through the Global Alzheimer Platform initiative similar efforts in the US, Canada and Australia are emerging where initiatives could link up so that, through alignment and standardization, truly global trials can be run efficiently on these connected platforms. Dr. Janet Woodcock concurred by highlighting that clinical trials are often too slow, too expensive, and may leave too many questions unanswered. Thus, a continuous and open dialogue between all stakeholders on many of the features of the Global Alzheimer's Platform is required.

Figure 4. A standing trial ready platform.



Dr. Janet Woodcock and Prof. Dr. Bateman noted that the use of adaptive, seamless-trial designs with master protocols through the engagement of multiple stakeholders can save valuable time and costs in the development of new treatments for Alzheimer's disease. Public and private researchers need to avoid the huge inefficiencies that exist in traditional clinical trial processes. Clinical research programmes in Alzheimer's disease should not be split into separate trials, which need to be set-up, approved, implemented, conducted, and analysed sequentially. Instead, the aim should be for a flexible, continuous trial conduct in close collaboration between stakeholders. Doing this will result in: significantly faster cycle times, more efficient resource use, higher quality data and higher probability of success. Speakers summarised opportunities in developing more efficient, flexible and global clinical trial systems for Alzheimer's disease, for example:

- Strengthening of early, small, parallel-design trials supported by biomarkers;
- Development of master-protocols for "adaptive, seamless-design" trials, which allow for a continuous trial conduct and adaption of intervention supported by multiple stakeholders;
- Global clinical research networks which allow for multiple stakeholder engagement and testing of biomarkers and combination treatments;
- Central Institutional Review Board(s) and harmonised country-clinical trial application procedures;
- Fast-response regulatory access and advice for clinical trial set-up and conduct;
- Globally convergent and synchronised regulatory environments on, for example, subject population definitions, definition of clinical meaningfulness and endpoint requirements, biomarker evidentiary standards, adaptive regulatory and clinical trial mechanisms, guidance on the development of combination therapies, etc.

Dr. Ana Graf presented the API APOE4 Trial, a collaboration between Banner Alzheimer's Institute and Novartis. She pointed out that Alzheimer's is a global disease affecting people with different co-morbidities, genomic characteristics, and of different social-economic status. Because of the unique disease

characteristics, and the heterogeneity of at-risk populations, clinical trials have become increasingly complex and long with high failure rates. In order to speed up the development process we need to learn faster and confirm more effectively. A standing Global CT Platform comprised of trial ready cohorts of well characterized subjects and highly qualified sites and use of adaptive- and randomised-start trial designs will significantly shorten timelines and increase efficiency, flexibility and quality. However, the lack of sensitive and specific biomarkers in Alzheimer's disease remains a critical need for more efficient translational and clinical research. As an alternative model for a public-private partnership, Novartis has entered into a collaboration with Banner Alzheimer's Institute (BAI), also supported by National Institutes of Health, on a study in Alzheimer's disease prevention. The multi-national study will determine whether two investigational anti-amyloid treatments can prevent or delay the emergence of symptoms of Alzheimer's disease. Using an innovative trial design, the two treatments will be given in cognitively healthy people at genetic risk of developing the build-up of amyloid protein in the brain that may eventually lead to Alzheimer's disease.

The need to harness big data, and to promote global collaboration and data sharing, in order to accelerate research and development of new therapies and care models for Alzheimer's disease and other dementias is undisputed. A substantial number of multi-site federated data networks and regional collaborative consortia have emerged. However, these efforts will only lead to earlier and effective treatments if they are implemented at scale and in an integrated fashion in the context of a robust global policy environment. Policy challenges, including endpoints, measurement tools and biomarkers cross national borders and need to be tackled at the international level. Questions remain to be answered about the benefits of and obstacles to the linking and sharing of patient data for research and care. The principles of open-science encompass the reusability of scientific data (open-data), the accessibility of scientific communication (open-access), and the sharing of scientific tools (open-research)[5].

In his presentation, Dr. Troy Scott explored the cost implications of the development of disease-modifying therapies for Alzheimer's disease. Dr. Scott highlighted that research and drug development in Alzheimer's disease is more costly in comparison to disease areas with a better understanding of the pathology, for which disease models, biomarkers (for patient selection and stratification in clinical trials, and for predicting clinical efficacy of drug candidates), and other tools are better developed. A recent study estimated the expected cost of a disease-modifying drug to be between USD 3.7-9.5 billion, in comparison to the range of USD 1-2 billion commonly cited as being representative of the pharmaceutical industry on the whole (Scott et al., 2014). As documented in this study, the higher expected cost of development reflects the lower probabilities of successful development perceived by the pharmaceutical industry.

Key to improving the chances of successful development (which would bring development costs in line with the pharmaceutical industry average and, most importantly, speed the delivery of effective therapies to patients) will be to expand the base of knowledge supporting research and development – improving models for translating basic science into promising drug targets and drug candidates, investigating the clinical validity of drug targets (i.e., determining whether engaging the biological target will have the intended effect on cognition and function), improving our understanding of the performance characteristics of biomarkers for enrichment and predicting treatment effect, and answering fundamental questions such as whether a monotherapy can be effective or whether combination therapies will be needed for disease modification.

Clinical trials of disease-modifying drug candidates can contribute much to the creation of this knowledge. But because this knowledge is a public good, with value that cannot be appropriated exclusively by companies investing in the clinical trials that could generate it, too little of this kind of knowledge is generated. Too often, clinical trials are designed to maximize the expected value of a given company's proprietary drug candidate rather than to generate knowledge that could move the entire field forward – while also giving the drug candidate its best chance for success. As long as pharmaceutical

companies fund clinical trials and their return on that investment requires marketing drugs under patent, their incentive to maximize the private value of their intellectual property will impose a formidable barrier to the optimal amount of knowledge creation and diffusion. Because the knowledge that could be generated by clinical trials is such a critical input into research and development efforts, overcoming this barrier should be a top priority for public policy aimed at bringing forth effective Alzheimer's therapies.

One initiative that has been successful in bringing together companies willing to collaborate in a clinical trial and share the data produced is the Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU). The incentive for companies to collaborate and share data in this case comes from the opportunity to test drug candidates in an ideal patient population: individuals with an Autosomal Dominant Alzheimer's disease gene mutation that puts them at high risk of developing Alzheimer's before the age of 60 years. The Innovative Medicines Initiative (IMI) Alzheimer's study aims to achieve similar collaboration and information sharing by providing sponsors with a global clinical trials platform – a standing, adaptive, proof-of-concept trial with a large trial-ready patient cohort. These initiatives are laudable to the extent they can succeed in aligning the private interests of sponsor companies with the public's interest in knowledge creation and diffusion—and the advancement of the most promising drug candidates without regard to their ownership or remaining patent life. However, sponsors' commercial interest in their own proprietary drug candidates still presents challenges to be overcome within these initiatives, and it is useful to consider how public policy might mitigate these challenges and to what end. Specifically, it is useful to consider a more direct way of overcoming the intellectual property barrier to collaboration and information sharing in clinical trials: by combining public funding and public oversight of clinical trials with early patent buyouts of candidate drugs[6]. The idea is similar to that of IMI's global clinical trials platform, but with sponsor companies' commercial interest in their own drug candidates removed by buying out the patents when candidates enter the trials. In place of the revenues anticipated from drugs approved for marketing, companies would receive royalties at predetermined milestones based on the progress of their candidates—and, to further encourage collaboration, the progress of other sponsors' candidates. The royalties would be structured so that a company's expected internal rate of return of participating (agreeing to place relevant patents in the public domain and share data on its candidate drugs) is at least equal to the rate of return the company would expect by developing its own candidates and marketing the resulting drugs under patent.

Because of the difference between federal governments' cost of borrowing and pharmaceutical companies' cost of capital, compounded over the long duration of clinical development, royalties could match pharmaceutical companies' expected internal rate of return on research and development while affording the public substantial savings over what it would expect to pay for a new therapy marketed under patent. A numerical example based on an 11% cost of capital for the pharmaceutical industry and 4% cost of borrowing for government yields USD 4 billion (40%) cost savings for one new drug. Further savings could be attributed to buying out the patents so that drugs, once approved, would be manufactured and distributed as generics, avoiding the costs of detailing and otherwise marketing the new drugs to physicians and patients and addressing the important consideration of patients' access to effective treatments.

These savings are side benefits of a policy that would make it possible to maximize the social net present value of clinical trials to:

- Realise the full potential of clinical trials to expand the base of knowledge on which research and development efforts draw;
- Allow objective science rather than commercial interest to determine which candidates to advance, and how, and when; and,
- Bring forth sooner more effective treatments for Alzheimer's disease.

Open science and smart data for Alzheimer's disease research and health innovation

Box 5. Key Messages

- *"More global data is clearly an advantage, but data quality and comparability is critical. For the future development and qualification of biomarkers we need to increase confidence from more data especially in the early stages of the disease. We have to share responsibilities, because the challenges are still too high and going alone would be too hard." (Dr. Diane Stephenson)*
- *"Despite general agreement among the research community that greater sharing will lead to greater scientific innovation, the research community alone lacks the resources to drive this change and break from these traditional models of discovery. Support from governments, charities, funders and other public bodies at an international level are required in order to bring about meaningful change." (Prof. Dr. Martin Rossor)*
- *"One option to bridge the 'valley of death' between biomedical research and clinical application would be to share positive and negative clinical trial results. However, a more open research environment might require new structures for compensation of IP." (Dr. Troy Scott); "'My idea is my idea' but the data may produce a larger public good." (Dr. Diane Stephenson)*
- *"I think that two of the most important parameters for data usage are variety and uniformity. Clinical trials are the most reliable and useful source of data which can be used for regulatory purposes. Stakeholders should share this data, because any success in research is another step forward in treating Alzheimer's disease." (Prof. Dr. Randall Bateman)*
- *"Is there something specific in Alzheimer's data? Do we need Bermuda Principles for data generated around research and health innovation for Alzheimer's disease or are these more generic and similar to other disease areas?" (Prof. Dr. Martin Rossor)*
- *"In most cases it is the academic technology transfer unit or small and medium-sized company who have concerns about data sharing. This might be due to the fact that data and information are monopolisable assets for these institutions. Large pharmaceutical industries are more open to share data." (Dr. Rick Johnson)*
- *"Sharing and disclosure of patient information from clinical trials, such as a positive diagnosis for Alzheimer's disease, can lead to insurance coverage issues as for example in cancer. Ultimately, this can have an impact on the recruitment in large multi-national trials." (Dr. Kimby Barton, Director of Bureau of Cardiology, Allergy and Neurological Sciences (BCANS), Health Canada)*

Prof. Dr. Martin Rossor highlighted that clinical trial data and publically funded research data currently offer the biggest short-term gains to stimulate an open-science approach to healthcare research. Data acquired during clinical trials is an incredibly valuable resource, which is still largely underutilised. However, despite obvious challenges to share data (for example, misuse or misinterpretation of complex data sets), the pharmaceutical industry is aware and supportive of the demand for transparency in drug development. The European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) have published joint 'Principles for Responsible Clinical Trial Data Sharing' in which they outlined their commitment to release of anonymised patient-level and study-level data and study protocols from trials in medicines approved in the US and/or EU[7]. Remarkably rapid progress has been made to meet these commitments through the development of secure online portals set up to facilitate data requests and release[8]. In addition to these industry driven platforms for change, revision of EU wide governance of clinical trials is transitioning from the current directive to a new regulatory format in order to help streamline the trial process from inception to completion, and dissemination of results[9]. Inherent in the new regulations are mechanisms to facilitate transparency and data sharing among the research community and with the general public, with

prompting to extend this transparency to products that fail to gain market approval. However, as Dr. Diane Stephenson pointed out, there are substantial resource needs in processing, comparing, and analysing individual/patient derived data sets. Research incentives and funding schemes should not only support the generation and pooling of data, but should also allow for a thorough data analysis.

Traditionally, in non-commercial clinical research, access to unique data is the primary commodity available to researchers to generate funding and subsequently publications, and the ability to sustain this circular economy ultimately determines the success of most labs. The OECD has produced Guidelines for Access to Research Data from Public Funding in 2007[10], and now, with the establishment of the World Dementia Council, there is an opportunity to operationalise these guidelines at an international level. Work in this area is currently underway in the form of the EMIF Platform in Europe and the 'Global Alzheimer's Association Interactive Network' (GAAIN) platform in North America. Both will provide a framework for consistent reuse of patient-level data and plans are already in place to link both platforms and standardise data access and analysis on both continents[11] (Visser, Streffer, and Lovestone, 2014).

In addition to developing sustainable models for open-access and the reusability of valuable retrospective data, it is important to consider the influence timely release could have on the pace of scientific discovery in dementia research. Building on the Bermuda Principles established at the outset of the Human Genome Project[12], the "Omics" community continue to demonstrate the discovery stimulus that is provided by the rapid release of pre-publication data. If we are to discover disease-modifying therapies before dementia overwhelms the resources for care available in our ageing society, we must act quickly and could agree on a bold set of principles to overcome current disincentives to share. Through a strengthening of sharing we could produce both the dataset and tools required to help unravel the complexities of neurodegeneration. In order to be effective, sustainable and universally appealing, any proposed principles must consider what is appropriate to share, when is an appropriate time to share, and the practicalities of how sharing might take place. Every donation of patient data should be treated with the utmost respect, and through sharing we can maximise the value that can be derived from it. Requirements to recruit a suitably large cohort before the data is deemed worth sharing should be avoided, and instead multi-centre collaboration and harmonisation of data collection tools encouraged, such that all data contributes to a larger pool. In addition, the potential value of negative study results and data should also be recognised and publication of these data encouraged. Data sharing should extend to analysis tools and software, which may also help to promote pooling of valuable computational resources. In the case of wet biomarker data, such as CSF, where lab based analysis can have a major impact on the reported measure (Toombs et al., 2013), it may be useful to set up centres of excellence conforming to agreed lab standards, where locally acquired samples can be sent for analysis and the results subsequently made available to the wider community. Moreover, as dementia research moves towards preclinical trials it is essential to build on work already started in population based studies and encourage greater collaboration and integration with epidemiological research groups.

Prof. Dr. Martin Rossor argued that to make real progress in dementia research and achieve the ultimate goal of disease-modifying therapies, incentives must be in place to encourage the pre-publication release of data to the wider community. It may be efficient to release data in batches based on acquisition of an agreed number of participants. Furthermore, providing researchers with a central database of both completed and live studies could help to identify suitable sites for collaboration to speed up the data collection process. Importantly, incentives for pre-publication data release must safeguard the interests of data collection sites, such as allowing them to register their intentions to publish on a central database, and encouraging publishers to introduce unique publication opportunities based on detailed description of the data generation process. These incentives could also extend to the development of best practice guidelines for data collection and harmonisation of the collection tools currently available. Successful data sharing in dementia research must be undertaken responsibly, to protect the rights of research participants, implemented efficiently, to advance science and improve healthcare, and applied effectively, to ensure

agreement between the international research community and support from funding bodies and publishers at an international level. To start the whole process we must convince governments, charities and other public bodies of the merits of such endeavours and ask for their help in pushing for change.

PERSPECTIVES FROM STAKEHOLDERS: CHALLENGES AND OPTIONS IN MAKING A PARADIGM SHIFT

Box 6. Key Messages

- *"In view of the growing epidemic and the urgent need for effective therapies, we need to balance between traditional/ cautious approaches and new strategies with calculated risks." (Mr. Marc Wortmann)*
- *"We need to increase the rate of diagnosis in populations in order to enrich clinical trials and to move the development of effective therapies for Alzheimer's disease. This could be achieved through a stronger engagement of the wider public in our work." (Mr. Marc Wortmann)*
- *"Alzheimer's patients are very much willing to deeper engage into clinical research processes in order to drive the development of therapies with a disease-modifying or sustained symptomatic effect." (Mr. Claude Bilat)*
- *"Regulators are well aware that the individual patient is willing to accept risks in clinical trials to accelerate the development of new treatments for Alzheimer's disease. However, whether or not the society can take this risk remains to be answered." (Dr. Karl Broich)*
- *"In order to ensure a seamless conduct of adaptive clinical trials, we need patient advocacy groups to reach out to the community. Patients are out there, but they are simply not accessible right now to researchers in the way they would need to be." (Dr. Janet Woodcock)*
- *"Even though Korean researchers are strongly supported by their government and by the Korean Food & Drug Administration, they still need cooperation and collaboration with other countries in order to expedite the final goal of finding the cure for dementia. I hope that together we will soon find a cure for dementia. " (Prof. Dr. Inhee Mook-Jung)*
- *"There is still too little active involvement of the private sector for new drug development in Korea. New strategies are needed for both the government and the private sector to share investments and risks." (Prof. Dr. Inhee Mook-Jung)*
- *"Key questions to be addressed in order to drive the paradigm shift are: How can we de-risk the processes public research and the pharmaceutical industry is dealing with in Alzheimer's? How do we make the economic case for public and private investment in Alzheimer's drug development?" (Dr. Dirk Pilat)*
- *"The pharmaceutical industry is strongly committed to delivering the right therapies to Alzheimer's patients. However we still need to do more to engage with patients in order to discuss and understand their needs and how to translate these into actual endpoints. Respecting and understanding payers' perspectives will also be critical for the success of a future product for Alzheimer's disease on the market." (Mr. Mark Hope)*
- *"Efficient collaboration can only be built on high quality and standardised data. Therefore we need stronger investment into knowledge and data-sharing infrastructure." (Dr. Elisabetta Vaudano)*
- *"Collaboration in Alzheimer's research is vital – and this is what the EMA strives for throughout disease areas in order to increase regulatory efficiency. An early dialogue with stakeholders is of particular importance in Alzheimer's disease." (Dr. Manuel Haas)*

There is consensus that the engagement of all stakeholders, including people living with dementia and their carers in translational research and drug development processes would be of significant importance. There is a need to speed-up the translation of pre-clinical research into drug development processes, to

shorten trials, and to achieve a deeper involvement of dementia patients and care givers. People living with Alzheimer's disease and other dementias as well as their families, including those who feel at risk are very keen to take part in studies to find a cure or prevent the disease or develop effective care and social interventions. To continue to foster research in this area and accelerate the discovery of medicines that can slow or stop the disease, collaboration and openness to novel approaches must be embraced by industry, academia, regulatory agencies, payers and patient organizations.

Global patient advocacy: the impact on patients, families and communities

Mr. Marc Wortmann discussed that bringing new treatments to the market takes too much time given the urgent need to tackle the global problem of dementia. There is a great bolus of potential drugs in early phase development. However, the actual challenge is to bring these into large, costly, and high risk late stage clinical trials. Barriers can be found in every stage of the drug development process: first of all with patient recruitment, as not many are diagnosed and referred to studies. There is also a lack of standardised procedures; for instance ethical committees all have their own approach, not only from country to country but within countries. Putting together the contracts between a pharmaceutical company and academic research site is complex and requires time and resources. Finally, the regulatory process is time consuming. There are good reasons to look at all of this carefully, but we need to balance this careful approach with the need to tackle a growing epidemic.

Alzheimer's Disease International (ADI) believes that firstly there is an urgent need to diagnose more people. Currently this rate is between 25-50% in the most developed countries and less than 10% in lower and middle-income countries. For many reasons this is a missed opportunity for sufferers, one of them being the chance to take part in research. Benefits of (early) diagnosis for the individual and family include a better understanding of the disease and a greater possibility to plan for the future. For society there is a cost benefit of intervention versus doing nothing. In addition there is also a need for more public education and engagement in Alzheimer's and dementia research. Currently there are a number of initiatives of Alzheimer's associations in the USA (including Alzheimer's Prevention Registry, Brain Health Registry, TrialMatch), Canada, the United Kingdom and the Netherlands. These can help by informing and encouraging people to leave their contact details at registries that are now being created in several parts of the world. ADI was asked at the G7 meeting in Ottawa to take the lead in driving this work stream and make it global. However, ADI needs support with resources to set up a campaign. Following the example of Alzheimer Society of Canada ADI wants to train frontline staff and volunteers of the associations who are in day to day contact with patients and families. In many countries there are now public meetings, called Alzheimer's Café, Memory Café or for instance TSUDOI in Japan. This is a way to mobilise larger numbers of 'consumers' and engage them with the drug development process. Further, people with dementia who are currently taking part in trials can be ambassadors and even help to improve the trial process to maximise adherence. Dr. Dennis Gillings concurred: "Many patients are willing to take risks to prevent an unwanted destiny patients see in front of them. Patients should determine a lot of their own destiny."

Government support of biomedical research and health innovation for Alzheimer's disease: lessons learned from Korea

Prof. Dr. Inhee Mook-Jung presented a report of the support from the Korean government for basic and translational research as well as clinical trials in the field of Alzheimer's disease; notably, the Korean Food & Drug Administration (KFDA) have a strong impact on the Alzheimer's disease translational research and drug development. Currently, there is very good support from the Korean government for research and development of innovative medicines. Every year, the Korean government allocates about 10% of its total budget to R&D. Unfortunately, the total number of people with dementia is increasing rapidly in Korea. In particular, there are about 10% of people aged 65 or older who are afflicted(1% of the

total population). This number is expected to grow to 15% in 2050. This is a noticeable increase in the number of patients with dementia in comparison to other countries. Consequently, the social cost spent on taking care of these patients is also proportionally increasing, rendering Alzheimer's disease a major social problem. The budget which the Korean government allocates for basic research has consistently increased since 2011. Government policy has played a significant role in creating a research-friendly environment for Korean scientists intended to advance the field of Alzheimer's disease. More recently, the Korean government has placed more emphasis on diagnosis and prediction. and scientists have responded accordingly by redirecting their focus to Alzheimer's disease research and health innovation.

If the onset of dementia can be delayed for 2 years, then there will be a 20% decrease in the number of dementia patients by 2030. Not only will there be a decrease in the number of patients with the delay in the onset of the disease, but with such prevention, the cost of treatment will also be significantly reduced. Assessing both medical and socioeconomic perspectives, the importance of prevention of dementia cannot be overstated. With the support of the Korean paradigm shift in Alzheimer's disease, Korean scientists have generated an extensive knowledge base in fundamental research and scientific tools for the treatment of Alzheimer's disease.

Several factors make Korea an attractive place for research and clinical trials in dementia. First, in addition to the unequivocal support from the Korean government, there are many outstanding and experienced doctors and scientists who are highly trained to conduct clinical trials in the field of Alzheimer's disease. Second, there is a large pool of dementia patients available for Alzheimer's disease research and the elderly population of Korea is projected to continue to grow. Third, given the dramatic increase of the epidemic there is a strong support for dementia research– people show a high compliance in clinical trials, and, thus, increase the success of long-term studies. Finally, Korea is very open to share knowledge and research tools in the field of Alzheimer's disease and to play an active role in global networks. In order to further develop an innovative ecosystem for Alzheimer's disease in Korea, the four key research areas prevention, diagnosis, drug development, and new technologies need to be supported by systemic innovation approaches and global collaboration.

Stopping Alzheimer's disease by 2025 together – stakeholders' perspectives

Mr. Mark Hope stated that 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 validated 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. One important aspect is to balance flexibility in our research approaches with regulatory guidance along with the growing understanding of the disease. Adaptive trial designs and accelerated approval schemes will require a high involvement of all stakeholders, in particular patients and the wider public. There are various opportunities where regulators, researchers, and patient organisations discuss issues and opportunities in research and health innovation for Alzheimer's disease; we can learn from other disease areas how global networks collaboratively drive the development of innovative therapies. As stated by Dr. Janet Woodcock, this would also be welcome by the FDA, where disease communities actively participate in the development of regulatory guidance.

Dr. Elisabetta Vaudano presented the Innovative Medicines Initiative (IMI) as an example of a European public-private partnership for health. It funds collaborative research initiatives aimed to foster health science innovations to become concrete deliverables for patients and society. IMI was funded in 2008 and will run until 2024 with a total budget of more than 5 billion EUR, half coming from the budget of the European Commission (first FP7 and now Horizon 2020 framework programme), and half from the pharmaceutical members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and other associated partners. The idea behind the creation of IMI is that innovation is generated in many different contexts and organizations and that joining the private and the public spirit and culture is the most effective way to advance innovation. IMI works following a set of key principles: focus on unmet needs of patients and society, use of competitive calls for the transparent and fair use of public funding, in kind contribution from the private sector, and non-competitive open collaborative research based on data sharing and dissemination of results. To achieve its objectives IMI has developed an Intellectual Property policy that, while protecting its principles, is also flexible enough to adapt to the needs of the many different stakeholders and types of initiatives.

IMI has just concluded its first phase of activities fully committing a budget of around EURO 2 billion in a variety of projects (each a public private partnership) covering the full value chain of the pharmaceutical R&D. Its partners are more than 6.000 actors from Academia, the large EFPIA companies, research intensive small and medium size enterprises, patients and patient organizations and regulatory bodies. In particular IMI has a strong focus on the involvement of patients in all its activities.

While IMI is succeeding at producing high quality scientific results, the extent of its success will go beyond publication and is measured by the results of its activities being implemented as standards, as usual and best practice in the industry, and by their impact on regulatory science. In short what is considered as success in IMI is how much the best possible science is translated to the best possible decisions for health innovation. The IMI environment has made possible the sharing of data (e.g. toxicological legacy data, but also clinical trials data), of compound libraries between public and private partners and between private partners that in another standard context would be competitors. This has already lead to significant outputs such as new insights on how to run clinical trials for antipsychotic agents[13] in a faster and more efficient way, and the kick start of an integrated strategy for research and development in Autism Spectrum Disorder[14]. In the field of Alzheimer's disease IMI has four projects, of which three are already running. PharmaCog[15] is developing tools to improve the efficacy predictability and pharmacokinetic-pharmacodynamic profiling of drugs from the pre-clinical to the clinical stage. EMIF is pioneering the re-use of medical data for research (by creating the bases for knowing-accessing-using these data) and its pillar EMIF-AD is applying this to the understanding of risk and protective factors in Alzheimer's Disease. AETIONOMY is developing an innovative bioinformatics approach to a molecularly based grouping/taxonomy of Alzheimer's and Parkinson's disease starting from an unbiased analysis and modelling of all available data in the public domain plus data available from consortium members. Finally a new project, EPAD, is due to start activities beginning of 2015 with the aim to create the scientific bases and infrastructure for proof of concept clinical trials for secondary prevention in Alzheimer's disease using novel adaptive clinical trial designs. This will be made possible by the agreement of all the partners participating in the initiative that they will share all data generated in the project between all private and public consortium partners to allow learning from compounds to become learning on the disease and vice versa, creating a virtuous circle to boost and facilitate progress and success.

IMI has just started its second phase where the partnership will be enlarged. The scientific scope focusses on research and innovation not only for the development of new drugs and vaccines, but on how to transform innovation in treatments options for patients. The second phase puts an emphasis on improving patient access to innovative medicines (in addition to medicines development) in alignment with the priority areas identified by WHO in its recent report. Neurodegeneration has been identified as one of

the strategic areas of activities for IMI. While there are lessons learnt from the first phase of IMI that will help its future activities there are still several challenges, for example:

- Fostering the culture of collaboration not only between public-private, but also between private partners and among different types of industries in the health ecosystem;
- Successfully engaging all stakeholders to create relevant partnerships;
- Strengthening data and knowledge management;
- Fostering the culture of learning together to avoid bias;
- Providing creative and sustainable incentives for research and drug development.

NOTES

1 . www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338287.pdf

2. Cerebrospinal fluid (CSF) is a clear, colourless liquid surrounding the brain and spinal cord.

3 . The purpose of this trial is to assess the safety, tolerability and biomarker efficacy of Gantenerumab and Solanezumab in individuals who have an autosomal dominant Alzheimer's disease (ADAD) mutation.

4. Dominantly Inherited Alzheimer Network (DIAN) trial. The purpose of this trial is to identify potential biomarkers that may predict the development of Alzheimer's disease in people who carry an Alzheimer's mutation.

5 . www.science.okfn.org/, www.oaspa.org/, www.onsnetwork.org/

6 On public funding and oversight of clinical trials, see Tracy Lewis, Jerome Reichman, and Anthony So (2007) and Arjun Jayadev and Joseph Stiglitz (2009). On patent buyouts, see Rachel Glennerster and Michael Kremer (2000).

7 . European Federation of Pharmaceutical Industries and Associations and the Pharmaceutical Research and Manufacturers of America, Principles for Responsible Clinical Trial Data Sharing Our Commitment to Patients and Researchers, July 2013

8 . www.clinicalstudydatarequest.com/, www.medicine.yale.edu/core/projects/yodap/

9 . The European Parliament and the Council of the European Union, Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Official Journal of the European Communities,L121/34 April01. The European Parliament and the Council of the European Union, Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, Official Journal of the European Communities, L 158/1 April 2014

10 . OECD Principles and Guidelines for Access to Research Data from Public Funding, April 2007

11 . Global Alzheimer Association Network Platform: www.gaain.org/platform/, World-Wide ADNI Update Meeting, Copenhagen July 2014

12 . Bermuda principles, Policies on Release of Human Genomic Sequence Data 2003: web.ornl.gov/sci/techresources/Human_Genome/research/bermuda.shtml

13. www.newmeds-europe.com/en/news.php

14. www.eu-aims.eu/

15. www.alzheimer-europe.org/Research/PharmaCog

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ANNEX 1 – WORKSHOP PROGRAMME

ENHANCING TRANSLATIONAL RESEARCH AND CLINICAL DEVELOPMENT FOR ALZHEIMER'S DISEASE AND OTHER DEMENTIAS: THE WAY FORWARD

(11-12 November, Lausanne, Switzerland)

This workshop will provide an international forum for stakeholders to articulate achievements and opportunities in biomedical research and health innovation for Alzheimer's disease and other dementias. It aims to discuss the challenges and barriers to the development of disease-modifying treatments and diagnostics for Alzheimer's disease and other dementias. This includes the need to invigorate biomarker R&D, adopt more innovative clinical trials, and encourage an adaptive regulatory process. Stakeholders will engage in discussions to consider options towards more innovative research and governance models.

- Through an exchange on good practices, representatives from governments, regulatory agencies, academia, industry, and patient organizations will hear about progress in:

- Implementing innovative biomedical research tools in product development and regulatory models, including the scope for adaptive regulatory processes, enhanced clinical trial designs and a strengthened diagnostic environment;

- Addressing the individual needs, challenges and options of all stakeholders in biomedical research and health innovation through open, collaborative research approaches;

- Enabling a global paradigm shift from treating symptoms to changing the underlying progression of the disease – identifying challenges and gaps in the development of disease-modifying treatments in Alzheimer's disease and other dementias;

- This is a follow-up event to the OECD workshop on "Better Health through Biomedicine: Innovative Governance" in Berlin, Germany in 2010. It is intended to provide input to ongoing international policy discussions on Alzheimer's and other dementias, including the work of the World Dementia Council.

Workshop web site: www.oecd.org/sti/biotech/alzheimers-dementia-research-workshop.htm

Day 1 (11 November 2014)

- **Welcome and Opening Remarks**

  - Isabella Beretta, Chair of OECD Working Party on Biotechnology, Swiss State

  - Secretariat for Education, Research and Innovation, SERI, Switzerland

  - Dirk Pilat, Deputy Director, Directorate for Science, Technology and Innovation, Organisation for Economic Cooperation and Development, OECD

  - Tania Dussey-Cavassini, Vice-Director General of Swiss Federal Office of Public Health, Ambassador for Global Health, Switzerland

- **Keynote: Accelerating a Global Paradigm Shift in Biomedical Research and Health Innovation for Alzheimer's Disease and Other Dementias, The Challenge –** Dr Dennis Gillings CBE, World Dementia Envoy

- **Session 1 – Driving a Global Paradigm Shift to Stop Alzheimer's by 2025 –** Moderator: Raj Long, Bill & Melinda Gates Foundation, Senior Regulatory, Officer - Integrated Development, Global Health, United Kingdom

  - **Session 1.A: The scientific basis for a paradigm shift**; Philip Scheltens, Director of the Alzheimer Center at VU University Medical Center, Professor of Cognitive Neurology at VU, Netherlands

  - **Session 1.B: The regulatory context – US and European perspectives**; Europe: Manuel Haas, Head of Central Nervous System and Ophthalmology Scientific and Regulatory Management Department - Evaluation Division, EMA; Karl Broich, President, BfArM and Chair of CNS Working Party, EMA; United States: Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, United States

  - **Session 1.C: Benefits and opportunities to accelerate Alzheimer's disease research and development**; Troy Scott, Senior Economist, RTI International, United States

- **Session 2: Biomedical Research, Diagnostics and Regulatory Science –** Moderator: Zoltan Bozoky, Chief Strategy Officer, Dementia Innovation Unit, Cabinet Office/ Department of Health, United Kingdom

  - **Session 2.A: New insights into Alzheimer's disease and future therapeutic options**; Andrea Pfeifer, Professor, CEO AC Immune SA, Switzerland

  - **Session 2.B: The potential of emerging technologies in translational research, diagnosis and therapy**; Diane Stephenson, Executive Director, Coalition Against Major Diseases (CAMD), Critical Path Institute, United States

  - **Session 2.C: Progress in Alzheimer's disease diagnostics – validation and use of cognitive endpoints and surrogate markers**; Randall Bateman, Director, Dominantly Inherited Alzheimer's Network Trials Unit, Washington University School of Medicine

- **Session 3: Speeding Innovative Medicines to Patients and Those at Risk –** Moderator: Claus Bolte, Division Head - Clinical Review, Swissmedic, Switzerland

- **Session 3.A: Opportunities in developing more efficient, flexible, and global clinical trial systems for Alzheimer's disease**; Luc Truyen, Vice President Neuroscience External Affairs, Janssen R&D LLC, United States; Ana Graf, Global Program Head Neuroscience, Novartis Pharma AG, Switzerland

- **Session 3.B: Using open science to shorten the time lag between discovery research & clinical use**; Martin Rossor, NIHR National Director for Dementia Research, University College London, United Kingdom

Day 2 (12 November 2014)

- **Session 4: Perspectives from Stakeholders: Challenges & Options in Making a Paradigm Shift –** Moderator: George Vradenburg, Convenor, The Global CEO Initiative on Alzheimer's, United States

  - **Session 4.A: Global Patient Advocacy: the impact on patients, families and communities**; Marc Wortmann, Executive Director Alzheimer's Disease International, United Kingdom; co-presented with Claude Bilat, Swiss Alzheimer Association

  - **Session 4.B: Bridging the "Valley of Death": the potential of public-private partnerships**; Elisabetta Vaudano, Coordinator Scientific Pillar, Principal Scientific Manager, Innovative Medicines Initiative (IMI), Belgium

  - **Session 4.C: Strengthening biomedical research and health innovation for Alzheimer's disease: Lessons Learned from Korea**; Inhee Mook-Jung, Professor and Chairman, Seoul National University College of Medicine, Department of Biomedical Sciences, Korea

  - **Session 4.D: Industry: commitment to stopping Alzheimer's disease by 2025**; Mark Hope, Global Head of Neuroscience, Ad Interim Head EU/ International Regulatory Affairs, F. Hoffmann-La Roche, Switzerland

- **Closing session: Conclusions from the Workshop – The View from here: how to move forward on Alzheimer's disease –** Moderator: Dirk Pilat, Deputy Director of the Directorate for Science, Technology and Innovation, OECD)

  - **Session Summary: Key messages and lessons learnt from the sessions**

  - **Final Panel Discussion: Shared challenges, shared solutions**

  - **Concluding remarks –** Isabella Beretta, Chair of OECD Working Party on Biotechnology, Swiss State Secretariat for Education, Research and Innovation, SERI, Switzerland

ANNEX 2 – WORKSHOP SPEAKERS AND MODERATORS

Randall Bateman

Dr. Randall Bateman, the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University School of Medicine, received BS degrees in Biology and Electrical Engineering from Washington University, and his MD from Case Western Reserve University School of Medicine. Dr. Bateman is the Director of the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) which coordinates with pharmaceutical, regulatory, and patient advocacy groups for clinical trials in the DIAN. Dr. Bateman serves as Associate Director of the DIAN, DIAN Clinical Core leader, and Washington University's DIAN Performance Site PI. Dr. Bateman's laboratory investigates causes and future diagnostic tests and treatments of Alzheimer's disease utilizing many assays and techniques from quantitative measurement of stable-isotope labelled proteins to clinical translational studies for Alzheimer's disease. Recent awards include the Glenn Award for Research (2011), the Metlife Promising Investigator Award (2012), and the Chancellor's Entrepreneurship and Innovation Award (2013).

Isabella Beretta

Isabella Beretta, Dr. sc. nat. ETH; Chair of the OECD Working Party on Biotechnology; Scientific Advisor International Cooperation in Research and Innovation; Swiss State Secretariat for Education, Research and Innovation SERI.

Claus Bolte

Claus Bolte MD, MBA trained as a General and Transplant Surgeon in Europe and North America, held clinical and academic positions for 10 years, subsequently worked for the research-based pharmaceutical, biotech and medical device industry. Since 2012 he is Division Head of Clinical Review (Marketing Authorization) at Swissmedic in Bern, Switzerland. Claus also teaches at ETH Zürich, previously at the University of Erlangen-Nuremberg, and currently is an ICH expert working group member.

Zoltan Bozoky

Chief Strategy Officer, UK Government Dementia Innovation Unit at the UK Department of Health; Zoltan has over 10 years' experience in health policy and public health and in the past 5 years has held senior research and development roles in the UK government. Zoltan brings a wide range of experience having worked in immunisation policy (UK government), R&D (UK government), health technology assessment programmes (NICE) and health reform technical assistant projects (Latvia, Kazakhstan governments). During his career Zoltan has led various teams and provided strategy and advice across a range of levels including being an Advisory Board Member to the Centre for Blast Injury (Imperial College London) and technical supportive leadership for the UK G8 Dementia Summit.

Karl Broich

1985-2000 clinical and research work at hospitals of the universities of Bonn, Halle/Saale and Philadelphia (PennU) (Board certifications in Neurology, Psychiatry, Behavioural Psychotherapy). 2000 to 2005 Head of the Section Neurology/Psychiatry, 2005 to 2009 department head, 2009-2014 deputy head (Vice-President) since 08/2014 head (President) at the Federal Institute for Drugs and Medical Devices (BfArM) in Bonn (Germany). 2005 to 2009 German alternate member at the Committee for Medicinal Products for Human Use (CHMP), since May 2013 chair of CNS-Workgroup at the European Medicines Agency (EMA). Current research activities: clinical trials methodology CNS, biomarkers in drug development, Alzheimer's disease and other neurodegenerative disorders. Author und Coauthor of more than 120 Publications (peer reviewed articles, reviews, book sections). Membership in several learned societies of the CNS field.

Tania Dussey-Cavassini

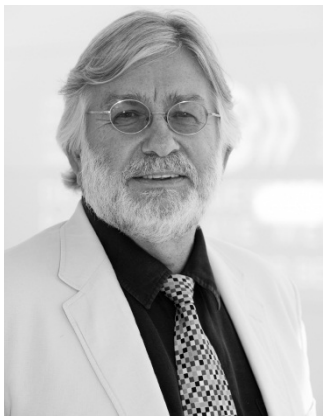
Tania Dussey-Cavassini combines experience in global health, management consulting, executive education, diplomacy and law enforcement. Since August 2013, she serves as Swiss Ambassador for Global Health and Vice- Director General of the Swiss Federal Office of Public Health, in charge of International Affairs. In 2012, she was selected as a Fellow at the Weatherhead Center for International Affairs at Harvard University. From 2006 to 2012, she worked at IMD, a world leader in executive education. As Director of Partnership Programs, she was responsible for developing IMD's custom programs for multinational companies, designing transformational learning and development initiatives that blend capability building with business impact. 2010-2012, she consulted for the United Nations Institute for Training and Research (UNITAR), training diplomats across the African continent and in Asia in multilateral diplomacy, negotiations and complex decision- making. Prior to these activities, she served as a Swiss career diplomat for more than ten years and was posted in Paris, Berne, Moscow, and Geneva. Tania started her career as a lawyer in 1991 working with the Swiss Federal Department of Justice and Police in the realm of international criminal matters and extraditions proceedings. She was educated in management at IMD, in law at the University of Lausanne, and music at the University of Music Lausanne, Switzerland.

Dennis Gillings

Dr Dennis Gillings was appointed as the World Dementia Envoy in February 2014. As the founder and executive chairman of Quintiles, the world's largest provider of biopharmaceutical development and commercial outsourcing services, Dr Gillings has more than 30 years' experience. He has worked with numerous biopharmaceutical companies and with many health organisations. Prior to this Dr Gillings spent some time in academia as Professor of Biostatistics at the University of North Carolina. Dr Gillings also has personal experience of dementia, as his mother lived with the condition for 18 years until her death in 2013. Having seen first-hand the devastating effects of the condition and lack of effective treatment, he is passionate about harnessing innovation in care; bringing together ideas from around the world to try to prevent the condition and improve the lives of those living with dementia the condition. Other key priorities of the World Dementia Council are to reduce barriers to investment in research and speeding up drug development, with the ultimate goal of finding a cure or disease modifying therapy by 2025. Dr Gillings, who was born and educated in the UK, was awarded a CBE in 2004 for services to the pharmaceutical industry.

Ana Graf

Dr. Ana Graf has been with Novartis for 20+ years. During this time, she had roles of increasing importance, primarily in clinical development. Her main research focus has been on Neurodegeneration, in particular Alzheimer disease. She was involved in global Phase III and IV development of a cholinesterase inhibitor in AD, Mild Cognitive Impairment and vascular dementia, and ran Proof of concept studies and Phase II studies in Chronic pain, Parkinson disease-Levodopa Induced Dyskinesia and Fragile X Syndrome. Since 2004, she has been heading the development of an amyloid-based active immunotherapy for AD. Most recently, she also took on the leadership role for another potential disease-modifying treatment. Dr. Graf holds M.D. degree from Universities of Zagreb, Croatia and Zurich, Switzerland.



Ken Guy

Mr. Guy, is the Head of the Science and Technology Policy Division of the Directorate for Science, Technology and Innovation. He leads the OECD's work on science and technology policy and provides support for the Committee for Scientific and Technological Policy (CSTP) and its subsidiary bodies. Mr. Guy has over 30 years' experience in the field of science, technology and innovation policies, as well as extensive expertise in providing high-level advice to policy makers and assessing STI policies. He has held a wide range of positions, including Senior Research Fellow at the Science Policy Research Unit (SPRU) at Sussex University. Mr. Guy was chairman and author of the Expert Group responsible for the report that underpinned the European Commission's Action Plan for Investing in Research, a member of the UK's academic panel advising the government on its Innovation Review, a visiting scientist at the European Commission's Institute for Perspective Technological Studies (IPTS) and a member of the European Commission's Task Force responsible for the recent Innovation Union Communication. He has also founded two innovation policy consultancies, notably Technolopolis Ltd., which is recognised as a leader in its field. Mr. Guy, a British national, holds Masters' Degrees in Science and Technology Policy from the University of Manchester, and in Natural Sciences from Selwyn College, University of Cambridge.

Manuel Haas

Manuel Haas is Head of the office CNS and Ophthalmology in the European Medicines Agency's Evaluation Division. The office is responsible for safety, efficacy and risk management aspects related to medicinal products in the CNS and ophtalmology therapeutic areas. He is a clinical pharmacist by training. He started his career by working in hospitals in France and the UK before joining the pharmaceutical industry in 2003. He soon after joined the European Medicines Agency in 2004, and has been in his current role for the past 5 years.

Mark Hope

Mark Hope is currently the Global Head of Neuroscience, Pharma Development Regulatory Affairs at F. Hoffmann-La Roche Ltd., located in Basel, Switzerland. Mark is also Ad-Interim Head EU and International Regulatory Affairs. Mark has been in Roche for 21 years, working in various different roles and different locations in the Regulatory group. Prior to his current role, Mark was EU/ROW Head of Oncology and EU/ROW Head of Program Management, Pharma Development Regulatory Affairs, based in Basel Switzerland. Mark has also been Group Director of Oncology, Regulatory Affairs and Global Regulatory Leader on various programs while based in Nutley, NJ USA, where he spent 7 years. Prior to being located in Nutley, NJ, Mark was based in the UK at the Roche Welwyn Garden City site, where Mark started his career with Roche in the OTC Regulatory Group before moving to the Pharma Division where he was in various roles within the regulatory group.

Raj Long

Senior Regulatory Officer – Bill & Melinda Gates Foundation, London, UK. Raj is a senior executive with over 20 years of experience in the pharmaceutical industry. Raj brings a wide range of expertise in regulatory strategy having worked with the EMA, US FDA, CFDA and other BRIC regulatory authorities. She is currently a Senior Regulatory Officer at the Bill &Melinda Gates Foundation (BMGF). Previously, she was the Global Head of Regulatory GEHC-MDx in the UK responsible for the regulatory organization and regulatory access globally in Americas, EMEA and Asia. Prior to joining GEHC, she was VP of Regulatory International AGL) both in Novartis, Switzerland and at Bristol-Myers Squibb, Princeton, USA. She was responsible for implementing strategic organizational model in Asia, Latin America, Middle East and Africa with a strategic focus on early access. She is currently a Senior Regulatory Officer with the Bill & Melinda Gates Foundation and works in malaria and neglected infectious diseases. In 2014 Raj was invited by the UK Secretary of State to be a member to the World Dementia Council (WDC)as a global regulatory expert In addition she is also appointed by the UK Government as Director – Integrated Development to lead innovative approaches in the regulatory development of clinically relevant therapies for dementia. Raj has a double Masters in Psychology and in Nursing Education from the University of Glasgow and Edinburgh, Scotland respectively.

Inhee Mook-Jung

Education/Major Activities: 1986 B.S., Seoul National University, 1995 Ph.D., University of Arizona, U.S.A.; Major Activities: 1987-1991 Researcher, UC Irvine; 1995-1996 Post-doc, UC San Diego; 1996-2003 Assistant/Associate Professor, Ajou University School of Medicine; 2004-Present Professor, Dept. Biochemistry & Biomedical Sciences, Seoul National University College of Medicine; 2011-present Editor, Journal of Alzheimer's disease; 2012-present Editorial Board member, Experimental Molecular Medicine; 2013-present Director, Graduate School of Biomedical Sciences, Seoul National University. Honours/Awards: 2004 Korea Loreal-UNESCO Woman Scientist Award; 2008 Excellent Researcher Award (MyungJoo Wan Award), Seoul National University Hospital; 2011 Macrogen Woman Scientist Award, Society for Biochemisty & Molecular Biology; 2011 Award from the minister of Education, Science and Technology; 2013 Award from the minister of Health & Welfare Department; 2013 Excellent Researcher Award (Shim Hosup Award), Seoul National University Hospital, 2013 Global Creative Researcher Award, Seoul National University Research Interests; Functional analysis of protein-protein interaction using molecular imaging, Pathogenesis of Neurodegenerative diseases, Identification of blood biomarker for Alzheimer's disease.

Andrea Pfeifer

Founder, Chief Executive Officer of AC Immune. In 2003 Prof. Dr. Andrea Pfeifer co-founded AC Immune where she holds since foundation the position of CEO. She is the former head of Nestlé Global Research where she managed more than 600 people. She has more than 25 years of senior management experience that included broad, worldwide R&D and business responsibilities. Dr. Pfeifer is a co-founder of the Nestlé Venture Fund, Chairwoman of Biotechmedinvest AG Investment Fund, a member of the Supervisory Board of Symrise, AG and a member of the CEO Initiative on Alzheimer 's disease. As a recognized leader in the field of the development of Alzheimer's disease therapeutics Dr. Pfeifer was asked to testify before the US Congress, in 2013. She was named Swiss Entrepreneur of the year by Ernst & Young in 2009 and in 2013 won the BioAlps Prize and was named to FierceBiotech's list of the Top Ten Women in Biotech. Dr. Pfeifer completed her studies and doctoral work in Pharmacy and Pharmacology at the University of Würzburg, Germany and did post-doctoral work in Molecular Carcinogenesis at the National Institutes of Health in Bethesda, Maryland. She has published more than 200 papers and abstracts in leading scientific journals.

Dirk Pilat

Dr. Dirk Pilat, a Dutch national, is Deputy Director of the OECD Directorate for Science, Technology and Innovation. As Deputy Director, he supports the Director of STI in pursuing the Directorate's programme of work and contributing to the achievement of the strategic goals of the Organisation as defined by the OECD Secretary-General. He joined the OECD in February 1994 and has worked on many policy issues since then, including the OECD Innovation Strategy and OECD Green Growth Strategy, as well as work on information technology and economic growth, climate change, labour markets, product market regulation, global value chains, productivity and entrepreneurship. He currently coordinates the work of STI on dementia, such as work on big data, biomedical research and research funding, and represents STI at the World Dementia Council. He was Head of the Science and Technology Policy Division from 2006 to January 2009, with responsibility for the OECD's Committee for Scientific and Technological Policy, and Head of the Structural Policy Division, with responsibility for the OECD's Committee on Industry, Innovation and Entrepreneurship, from February 2009 to December 2012. Before joining the OECD, Mr. Pilat was a researcher at the University of Groningen, where he also earned his PhD in Economics.

Martin Rossor

Martin Rossor trained in Neurology at the National Hospital, Queen Square and undertook research into the neurochemistry of degenerative disease at the MRC neurochemical pharmacology unit in Cambridge. He is Professor of Clinical Neurology at the National Hospital for Neurology and Neurosurgery, and established a specialist cognitive disorders clinic which acts as a tertiary referral service for young onset and rare dementias. Clinical research interests are in neurodegenerative disease and particularly in familial disease. He has been editor of the Journal of Neurology, Neurosurgery & Psychiatry, and President of the Association of British Neurologists. Martin is the Director of the NIHR Queen Square Dementia Biomedical Research Unit, a NIHR Senior Investigator, and was appointed as the NIHR National Director for Dementia Research in April 2014. The National Director's office facilitates the Department of Health's research response to commitments under the Prime Minister's Dementia Challenge and the G8 Dementia Summit.

Philip Scheltens

Education/Training: Vrije Universiteit (VU) Amsterdam, Medicine, 1976-1984, with the following examination dates: Bachelor degree: June 1980; Masters degree: November 1982; MD.: August 1984; PhD.: 3 March 1993; Vrije Universiteit Amsterdam after a public; defense of the thesis: 'MR Imaging in Alzheimer's disease'. Positions/Honours: 1991-present Staff neurologist; 2000-present Full Professor of (Cognitive) Neurology; 2000-present Director of the Alzheimer Centre, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; 2008-present Member management team Neuroscience Campus Amsterdam; 2011-present Scientific director Dutch Parelsnoer Instituut (PSI); 2013-present Vice-chair Board of Directors Dutch "Deltaplan Dementie"; 1998 Medaille d'Or Université de Lille; 2000 Membre d'honeur a titre etranger de Societe Francaise de Neurologie; 1997-1998 visiting Professor, Karolinska Institute, Stockholm, Zweden; 1998-1999 visiting Professor, Institute for the Health of the Elderly, Newcastle upon Tyne, UK; 2004 visiting Professor, University of British Columbia, Canada; 2008-present Honorary Professor of Neurology, University College of London; 2011-present Member Royal Academy of the Arts and Sciences (KNAW).

Troy Scott

Troy J. Scott, Ph.D., is a Senior Economist at RTI International, where his work focuses on the determinants of the rate and direction of technological change, and its effects on economic growth and social wellbeing. Dr. Scott was Principal Investigator on a study of opportunities to accelerate the development of disease-modifying therapies for Alzheimer's, conducted in 2013 for the New York Academy of Sciences' Alzheimer's Disease and Dementia Initiative. The study estimated substantial reductions in the cost of drug development that could be expected if industry, academic, and government stakeholders were to co-invest in pre-competitive infrastructure supporting preclinical and clinical development. These cost reductions were largely attributable to potential reductions in the risk of failure in Phase II and III clinical trials and therefore relate directly to the acceleration of successful drug development. Subsequent work has focused on how best to facilitate this sort of productive cross-sector collaboration.

Diane Stephenson

Dr. Diane Stephenson is a neuroscientist by training with 30 years combined experience in academic neuroscience and drug discovery. She is passionate about translational science and is dedicated to the discovery and advancement of therapies to treat diseases of the nervous system. Dr. Stephenson received her undergraduate degree in Biochemistry at University of California, Santa Barbara, and her Ph.D. in Medical Neurobiology from Indiana University. During her academic career, she focused her research on Amyotrophic Lateral Sclerosis and Alzheimer's disease. In industry (Eli Lilly, Pharmacia and Pfizer), she contributed to identification and validation of novel targets and biomarker discoveries for the treatment of Alzheimer's disease, stroke and Parkinson's disease. As an ambassador for public-private partnerships, she has initiated many external collaborations, including IMI's European Autism Interventions (EU-AIMs) initiative. Dr. Stephenson joined Critical Path Institute August 1, 2011 as Director of the Coalition Against Major Diseases (CAMD), a consortium dedicated to accelerating drug development for Alzheimer's disease and Parkinson's disease.

Luc Truyen

Luc was trained as a neurologist in Belgium and the Netherlands with in addition a PhD in Medical Sciences from the University of Antwerp. After a career in academia with special interest in multiple sclerosis, stroke and neuro-degenerative disease he joined Janssen Research Foundation (JNJ) in 1998. He was part of the team that developed Reminyl/ Razadyne™ for the symptomatic treatment of AD in early 2000's. After that he has had roles of increasing responsibilities and scope within JNJ from leading compound development teams to large functional groups like Global Clinical Operations of the Pharm division of JNJ for several years. In 2011 he joined Janssen Alzheimer Immunotherapy LLC. After serving as its CMO and Head of R&D he joined the Office of the Chief Medical Officer of JNJ as Head Clinical Innovation early 2013. In recognition of the increasing sense of urgency and required focus Luc was named VP Neuroscience External Affairs and Chair, Johnson&Johnson, Global Fight against Alzheimer's disease in April 2014. This to coordinate all efforts for JNJ in the external environment related to AD (GAP, IMI, G7, etc).

Elisabetta Vaudano

Italian born Elisabetta Vaudano is responsible of the portfolio of Brain Disorders projects (currently 6 projects, for >180 M EUR investments in EC public funds and in kind EFPIA contributions) at the Innovative Medicines Initiative (IMI), the largest European Public Private partnership in Health Sciences with a total budget of more than 5 billion EUR. Elisabetta is a doctor in veterinary medicine, holds a PhD in neuroscience and an MSc in Laboratory Animal Science. Elisabetta started her carrier as scientist in Academia working in the field of neuronal degeneration, regeneration and plasticity in Italy, UK, Sweden and Denmark. Elisabetta moved to industry in 2000, when she joined Lundbeck as group leader of their Parkinson's disease in vivo Neuroprotection Group. In 2004 she became Head of Pharmacology and CNS Biology at ENKAM Pharmaceuticals. Elisabetta joined IMI in 2010.

George Vradenburg

George Vradenburg is Chairman of USAgainstAlzheimer's, which he co-founded in October 2010. George was named by U.S. Health and Human Services Secretary Kathleen Sebelius to serve on the Advisory Council on Research, Care, and Services established by the National Alzheimer's Project Act and has testified before Congress about the global Alzheimer's pandemic. He is a member of the World Dementia Council. George and USAgainstAlzheimer's co-convene both the Leaders Engaged on Alzheimer's Disease (LEAD) Coalition and the Global CEO Initiative on Alzheimer's Disease. He and his wife, Trish, have long been dedicated members of Washington's civic and philanthropic community. George is Chairman of the Board of The Phillips Collection, Trustee of the University of the District of Columbia and a member of the Council on Foreign Relations and The Economic Club of Washington. He has served in senior executive and legal positions at CBS, FOX and AOL/Time Warner. George and Trish published Tikkun Magazine for 10 years (Editor-in-Chief Rabbi Michael Lerner is Trish's brother).

Janet Woodcock

Janet Woodcock is Director of the Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration (FDA). Dr. Woodcock first joined CDER in 1994. For three years, from 2005 until 2008, she served FDA's Commissioner, holding several positions, including as Deputy Commissioner and Chief Medical Officer, Deputy Commissioner for Operations, and Chief Operating Officer. Her responsibilities involved oversight of various aspects of scientific and medical regulatory operations. Before joining CDER, Dr. Woodcock served as Director, Office of Therapeutics Research and Review, and Acting Deputy Director in FDA's Center for Biologics Evaluation and Research. Dr. Woodcock received her M.D. from North-western Medical School and completed further training and held teaching appointments at the Pennsylvania State University and the University of California in San Francisco. She joined FDA in 1986.

Marc Wortmann

Marc Wortmann is Executive Director of Alzheimer's Disease International (ADI). Marc studied Law and Art in the city of Utrecht in the Netherlands and was an entrepreneur in retail for 15 years. During this time Marc was a member of the Parliament of the Province of Utrecht and worked closely with various charities and voluntary organisations. He became Executive Director of Alzheimer Nederland in 2000. From 2002 to 2005 he chaired the Dutch Fundraising Association and was Vice-President of the European Fundraising Association from 2004 to 2007. Marc joined ADI in 2006 and is responsible for external contacts, public policy and fundraising. He is a speaker at multiple events and conferences on these topics and has published a number of articles and papers on dementia awareness and public policy.

ANNEX 3 – BACKGROUND PAPERS

Clinical Trials Considerations

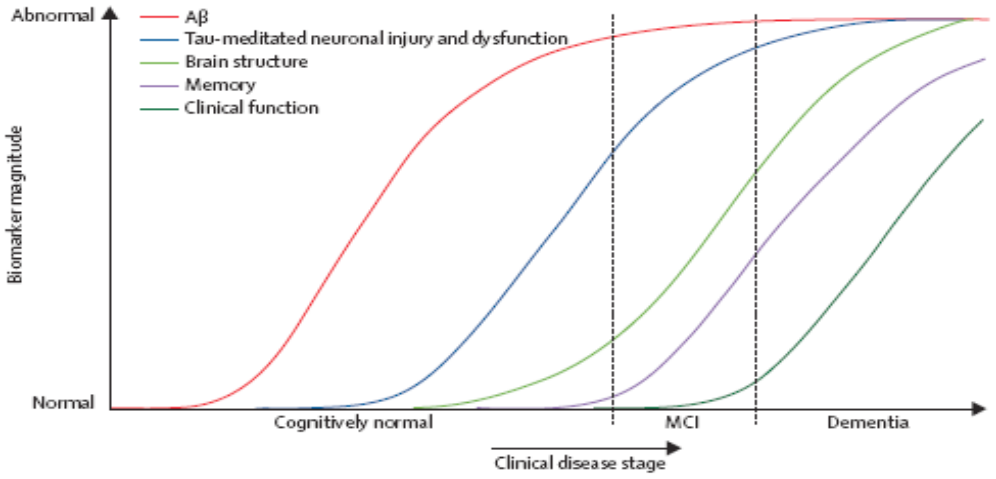
Ronald C. Petersen and Clifford R. Jack, Jr., Mayo Clinic Rochester, MN

The construct of treating cognitive disorders early in the spectrum of evolution is a popularly accepted approach (Sperling, Jack, and Aisen, 2011). From a public health perspective, it would be necessary to identify the earliest biological and clinical manifestations of these disease(s) to enable clinicians to intervene as early as possible. It is only through this strategy that we will be able to delay the onset and/or slow the progression of these disorders since both of these tactics will have huge effects on the impact of the diseases. While this strategy is reasonable and plausible, there are many issues that need to be addressed to make this a reality. While this strategy is reasonable and plausible, there are many issues that need to be addressed to make this a reality.

Theoretical

Prior to addressing these challenges, insight into the theoretical underpinning of the disease processes is relevant. Jack and colleagues have portrayed a hypothetical sequence of events that likely unfold along the Alzheimer's disease (AD) pathophysiological continuum (Jack, and Holtzman, 2013a; Jack et al., 2013b; Jack et al., 2010). The original approach depicted the clinical evolution of events as shown in Figure 1 (Jack et al., 2010), and a later version of this model expanded it to include alternate scenarios of the development of the pathophysiology (Jack, and Holtzman, 2013a; Jack et al., 2013b). As Figure 1 shows, presumably, the deposition of Aβ triggers subsequent evolution of pathophysiology including tau, neurodegeneration, biomarker changes and, ultimately, cognition and then functional changes. As can be seen, in a primary prevention approach, interventions must be made prior to the onset of any detectable pathophysiology such as the deposition of Aβ. Next in the cascade comes secondary progression whereby amyloid is present and perhaps early deposition of tau and other markers of neurodegeneration may be unfolding. At this point, the intention would be to arrest the progression of and possibly reverse deposition Aβ, tau and other measures of neurodegeneration, but at this point, no clinical symptoms are apparent. Thus, finally, as the clinical symptoms of MCI and dementia appear, slowing of progression or reversal of underlying pathology would be necessary. While this proposed cascade of events is appealing, there are many underlying technical questions that need to be resolved, such as the threshold between normal and abnormal pathophysiology. In addition, the interaction of the various pathophysiologic events remains to be elucidated.

Figure 1. Clinical/biomarker profile.



Therefore, while this proposed set of events is appealing as a means of delaying onset or slowing progression of the disease, it is fraught with challenges. From a clinical perspective, the tools being used to assess subtle cognitive changes, particularly in the preclinical phase, need to be validated. Our current instruments most commonly used for randomized controlled trials include the Mini-Mental State Exam, Alzheimer's Disease Assessment Scale-cognitive subscale and the Clinical Dementia Rating, but all of these were developed decades ago to characterize the clinical distinction between age-related changes in cognition and dementia. As such, they are not reliably sensitive in the MCI or preclinical stage of the illness or in assessing the rate of long-term slowing of decline (as opposed to short-term improvements over baseline). As such, these tools would be inadequate to assess cognitive changes or the rate of change in cognitively normal subjects. The recent FDA directive suggested that new instruments that combine subtle cognitive features with functional measures be developed and used at that point in the cognitive continuum. For example, the Financial Capacity Inventory (FCI) is an example of a tool being developed to assess subtle changes in functional performance when people are cognitively intact. Another approach that is being explored involved the use of computerized instruments such as CogState, and while these have not been validated in this setting, they have considerable promise. A third approach is the development of composite instruments combining sensitive elements of existing cognitive and functional scales, subject to the demonstration of the clinical meaningfulness of any new instruments to regulatory agencies.

One observation from Figure 1 is that different types of deficits are expected to develop in a manner in which they are detectable, and possibly could respond to treatment, at different times along the continuum of the disease. This suggests that use of different types of outcome measures based on the stage of disease may be warranted. Thus, based on the figure, a cognitive outcome could be appropriate for regulatory approval in earlier AD stages (preclinical, MCI and mild AD), whereas cognition and function would be appropriate outcomes in later AD stages (moderate and severe AD).

Another major component of the model proposed in Figure 1 pertains to the role of biomarkers. Inherent in this model is our ability to identify appropriate biomarkers, measure them and determine their natural course. Our ability to detect and measure the presence of amyloid is advancing rapidly both with respect to amyloid imaging and cerebrospinal fluid measurement. Several PET tracers including C-11 and F-18 compounds are available, and new F-18 compounds have been approved by the FDA to assess amyloid presence. While technical problems continue for cerebrospinal fluid markers, the ability to measure the various analytes in the CSF is improving. However, our ability to use these markers for regulatory purposes remains challenging.

Challenges

Detection Thresholds

Models such as that shown in Figure 1 embody the notion of “normal” and “abnormal” biomarker measurements. This is not a trivial issue and requires a great deal of background research. Issues pertaining to differences in detection and repeatability of these measures across centres persist. What brain regions need to be assessed in imaging measures and multiple technical issues in CSF such as reagent variability continue to hamper progress (Mattsson et al., 2011a; Mattsson et al., 2011b; Shaw et al., 2009). While normal and abnormal levels of amyloid deposition can be agreed upon, the construct of normal and abnormal tau imaging measurements become more problematical (Maruyama et al., 2013; Chien, Bahri, and Szardenings, 2013; Villemagne et al., 2014). The latter may well incorporate anatomical spread as well as density of the tau deposition with respect to its impact, and the translation of these constructs to CSF tau measurements is complicated. These are tractable issues, however.

A major issue with all biomarkers pertains to their natural histories. While theoretical models of evolution of the various biomarkers are quite reasonable, a great deal needs to be understood more completely. For example, what is the course and distribution of the various markers? Are the accumulation curves linear, sigmoidal or variable at different ages? How do these markers interact? For example, models by several investigators contend that tau accumulates early in aging and advances slowly in most individuals, but when amyloid begins to accumulate, the tau deposition accelerates (Jack, and Holtzman, 2013a; Jack et al., 2013b; Duyckaerts, and Hauw, 1997; Delacourte et al., 2002; Price, and Morris, 1999; Musiek, and Holtzman, 2012; Jack et al., 2014). The interaction of these markers with other pathological elements, e.g., alpha-synuclein, TDP-43 and vascular changes, are largely unknown; so, these become salient issues for the field.

What is Needed?

Great progress is being achieved on several fronts, but basic scientific issues must be and are being addressed as will be outlined below.

Cognition

The field is in the process of developing new composite instruments including sensitive cognitive measures and subtle functional measures tapping into high-level instrumental activities of daily living. For example, data are emerging suggesting that people who ultimately develop cognitive impairment or harbour biomarkers while clinically normal may be slower at completing financial tasks than age-matched control individuals who are biomarker negative. Of course, the distinction between “cognitive” and “functional” measures may be artificial, as cognition underlies function. These subtleties may be important for detection of early meaningful clinical changes. In a similar vein, a great deal of interest is being generated around the role of subjective cognitive concerns on the part of aging persons. After controlling for many relevant variables such as age, sex, education, apolipoprotein E4 carrier status, depression, anxiety, cognition and medical co-morbidities, subjective cognitive concern may still predict subsequent cognitive decline in normal persons. In aggregate, work is progressing, developing more sensitive instruments that may show change even when subjects are cognitively normal. However, they are still in development with several important longitudinal observational studies underway for a decade or more. These studies will eventually provide essential validation of these measures. Similarly, the computerised cognitive instruments need to be evaluated more thoroughly.

Conclusion

While a great deal of work needs to be done, tremendous progress is being made across all these areas. Our knowledge of the time course of biomarkers and clinical progression has advanced significantly in recent years thereby allowing for the design and conduct of important prevention trials such as API, DIAN, A4 and AMP, as well as studies aimed at slowing disease progression in MCI/ prodromal and mild AD populations. Many of these trials incorporate novel clinical measures and relevant biomarkers that will shed light on these issues. It will be important to incorporate into regulatory science and agency qualification processes the learnings from these trials and studies as rapidly as possible in order to change the regulatory paradigm based on the best available science.

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Industry Perspective on Challenges in Developing Disease-Modifying Alzheimer's Disease Treatments

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which accumulation of amyloid-β (Aβ) in the brain and other pathological mechanisms (such as tau) occur years before symptoms are apparent. The first symptoms are subtle cognitive changes, most commonly memory loss. As the disease progresses, the cognitive symptoms become more pervasive and begin to interfere with daily function. Thus, for most patients with AD, the initial and primary concern early in the disease is the noticeable loss of memory and the threat of progressive worsening.

Although AD is one continuous, gradually progressive disorder, researchers and clinicians classify AD in multiple stages (Albert et al. 2011; McKhann et al. 2011; Sperling et al. 2011):

- Preclinical AD: biomarker evidence of AD pathology but clinically normal;
- Prodromal AD/mild cognitive impairment due to AD: biomarker evidence and cognitive symptoms with no or only subtle changes in function;
- Mild AD dementia: cognition continues to worsen, daily function begins to be impaired;
- Moderate AD dementia: cognition and function are more impaired and patient safety becomes a greater concern;
- Severe AD dementia: loss of most or all of ability to independently care for self.

These stages are artificial as there are no discrete time points at which an individual with AD transitions from one stage to the next, but they have been useful to estimate where patients may lie on the disease continuum for clinical trial research and to aid in treatment decisions and setting expectations for patients and caregivers.

The last new drug for AD received its first regulatory approval more than 10 years ago. Many potentially disease-modifying treatments are currently in development; there have been many failures, but some promising results have been reported in recent years, placing us at a pivotal point in the history of AD treatment innovation. With these new types of treatments, we may be on the cusp of a shift from a paradigm in which we are only capable of treating the symptoms of AD to one in which we can alter the underlying pathology, change the trajectory of disease, and reduce the individual and societal burden of AD. What are the implications of this shift? A paradigm shift of this magnitude may require re-evaluation of how we conduct some aspects of AD drug development and related activities, including clinical development programs, appropriate treatment outcomes and regulatory pathways.

Clinical trials across all disease states are complex and challenging. In addition, AD trials face challenges related to remaining gaps in understanding the disease, how to translate basic science into promising drug targets, how to discover drug candidates for identified targets and link actions on disease pathophysiology with clinical efficacy. In order to meet a 2025 goal for delivery of innovative products to AD patients, this paper will focus on issues specific to later stage development of disease-modifying treatments. This paper provides an industry perspective on the following potentially modifiable barriers to

delivery of effective disease-modifying AD treatments to patients as quickly as possible: clinical trial implementation, demonstrating clinical meaningfulness for disease-modifying treatments, and regulatory considerations.

Clinical Trial Implementation

To be successful in this changing model of drug development of disease-modifying treatments, corresponding changes in study implementation should be considered. In particular, what study implementation factors slow the initiation and completion of studies, drive up costs, increase business risk, and reduce incentives for sponsors to engage in this field?

Study Design

Key registration studies for approved symptomatic treatments were generally 3 to 6 months in duration. However, Phase 3 AD studies assessing putative disease-modifying agents must be at least 18 months in duration (CHMP 2008, Vellas et al. 2007), and potentially even longer for prodromal and preclinical AD, to detect a treatment effect because of the gradual nature of disease progression. Increasing study durations increase trial complexity and cost and add to participant/informant burden, resulting in greater discontinuation rates. Once surrogate biomarkers become available, trials could be shortened in duration. However, surrogate biomarkers that can predict clinical treatment outcomes will take a period of time to develop and validate.

Based on historic regulatory expectations for demonstration of clinical meaningfulness in a dementia population, studies of potentially disease-modifying treatments are required to use co-primary cognitive and functional endpoints (that is, for a study to be considered "positive," a statistically significant effect on both endpoints must be demonstrated, which is mathematically more difficult than meeting a single endpoint). As described above, AD begins with cognitive impairment, followed by functional impairment. Therefore at any given point on the continuum of AD, cognitive decline may be greater than functional decline. When using available scales, a functional treatment effect may be more difficult to demonstrate than a cognitive treatment effect, thus requiring greater sample sizes, which adds to the complexity, cost, and overall duration of the study.

Concerns about the feasibility of demonstrating an effect may not be confined to functional scales. Even existing cognitive endpoints often used in AD studies such as the ADAS-Cog may not be sufficiently sensitive to detect the difference between study drug and placebo for disease-modification studies in earlier stages of disease. Certainly, as populations earlier in the continuum of disease are being studied, more sensitive measures will be necessary. Multiple efforts are underway to develop appropriate scales; however this process takes time, and many disease modification trials are already underway and may report results before such scales have been qualified/accepted.

Lastly, although both FDA and EMA have developed guidance that addresses development of treatments for AD, given the lack of regulatory precedent supporting the registration of drugs to slow disease progression, agency dialogue on the designs for pivotal studies are especially important. This may be a lengthy process, particularly when several interactions may be needed to align study designs to meet expectations of different agencies, and may ultimately result in the delay of initiation of trials and/or implementation of important protocol amendments or a requirement for additional studies.

Site Activation

Another challenge with clinical trial implementation is the approval process for study protocols, informed consent documents, and other research tools, which while essential, is often lengthy. In Europe, while there is a centralized procedure for reviewing a marketing application, there is no such centralized

procedure for reviewing protocols. In addition to regulatory approvals from each region in which the study is being conducted, ethics review board (ERB) approval is also required, frequently on a site-by-site basis. This complex and sometimes fragmented process can lead to lengthy delays in the initiation of a study. Central ethics review boards are one way this fragmentation has been reduced. Additionally, some countries require separate approval processes, for example radiation safety committees, which are often not integrated with other review processes. Expansion of central ERBs, integrated review processes, aligned with similar and linked processes in other regions could be considered to further reduce time to study initiation.

Site activation also depends on the identification of large numbers of qualified sites and investigators (and in some cases, neuroimaging centers). As more research in the field is conducted, competition for the finite supply of sites and investigators will increase. An expansion of the infrastructure of expertly trained clinical trial sites, and an increase in clinical trial participation by patients (as described below), could have a substantial effect on the time required to provide one or more disease modifying treatments for AD.

The recently adopted Clinical Trial Regulation in the EU is expected to bring further alignment with the promise of a single EU-wide regulatory review of clinical trial applications. The objectives for this regulation were to enhance efficiency in the process and to provide more timely patient access to new innovative treatments. Efforts should be made to minimize the extension of regulatory review timelines allowed in the regulation and to foster increased collaboration between ERBs.

Patient Enrolment

Challenges in clinical trial recruitment are indicative of future challenges in clinical practice. Currently, patient flow and referral patterns are not established and many AD patients are waiting undiagnosed in general practitioners' offices without easy access to information about clinical trials. This dynamic not only impacts patient enrolment, but will ultimately impact patient care. An example of a more systematic model has recently been established in France, wherein patients flow from general practice to specialists to memory clinics/clinical trial sites in a defined process; other countries are in discussions regarding similar models. In addition, international work streams have been established to evaluate the development and implementation of large AD patient registries.

Identification of appropriate patients for a study is critical to its success. With AD, this has been a particular challenge as approximately 20 to 25% of clinically diagnosed mild to moderate AD patients do not have evidence of amyloid pathophysiology. Cerebrospinal fluid (CSF) testing for amyloid has been widely available for some time, but is invasive and burdensome for patients and sites. Amyloid imaging allows determination of amyloid status with less patient burden and is becoming more widely available, but this adds to study complexity and cost as it is not commonly available in clinical practice. Tau imaging technologies are in development, but none are currently widely used in clinical trials. In addition, development and broad implementation of diagnostic tools that allow recognition of more subtle symptoms may improve clinical diagnosis.

Unlike some obstacles to AD drug development that may be ameliorated as more experience is accumulated and scientific understanding deepens, clinical trial implementation challenges have the capacity to intensify over time if they are not addressed. While there is significant difficulty in enrolling AD dementia patients, it may be even more challenging in a secondary prevention population with subtle or no cognitive symptoms. As more clinical development programs are initiated and conducted, more studies will be competing for sites, investigators, and patients, potentially creating a bottleneck for ongoing research. There is an urgent need for a coordinated effort to screen potential patients for early AD (preclinical, prodromal and mild AD dementia).

Demonstrating Clinical Meaningfulness for Disease-Modifying AD Treatments

Functional scales measuring activities of daily living have been used for long-term studies of potentially disease-modifying agents to ensure the clinical relevance of an effect on cognitive symptoms in AD trials. However, in contrast to symptomatic treatments, which may provide shorter-term improvement in symptoms, disease-modifying agents should slow worsening of the disease itself. One interpretation could be that demonstrating disease modification alone is clinically meaningful, but Phase 3 data to inform expectations for disease modification as well as clinical meaningfulness are limited to date.

AD begins with cognitive decline which progresses to affect function. Several analyses have demonstrated that cognitive decline precedes and predicts functional decline (Zahodne et al. 2013; Liu-Seifert et al. 2014). Thus, a cognitive treatment effect would be expected to lead to a later functional treatment effect. Scales to measure activities of daily living were developed to assess later stages of AD and may be less sensitive to early functional loss. Even in patients with mild AD dementia (who have some functional decline), drug effects using existing functional scales with currently-approved symptomatic AD treatments have been difficult to demonstrate. Thus, while functional outcomes are important, based on the relationship between cognition and function, as well as challenges with existing methods of assessment of function across the AD continuum, it may not be appropriate to rely solely on measures of function to demonstrate clinical meaningfulness of a cognitive effect.

Other quantitative analyses, such as time to conversion to dementia or rate of progression, have been suggested as clinically meaningful measures. These analyses may be conceptually appealing, but are associated with practical difficulties, such as dichotomizing two disease stages that exist along a continuum (FDA 2013).

With the shift to disease modification, a broader approach to clinical meaningfulness should be considered, and we encourage dialog among all stakeholders to achieve that objective. Recently, there has been much focus on the challenges of studying treatments in the preclinical and prodromal stages of AD; however, as described above, these issues are also relevant to mild AD dementia. The following factors could be considered in assessment of clinical meaningfulness of new disease modifying therapies across the disease continuum:

- AD is primarily a disease of cognition and cognitive decline is important to patients and caregivers (Ropacki et al. 2014), even before it affects function. Therefore, an effect on cognition should be the principal consideration in an assessment of clinical meaningfulness.

- A treatment that targets the underlying pathophysiology of AD should slow cognitive decline and its effect should grow over time during long-term treatment, which could be demonstrated by an increasing magnitude of effect, point difference over time, or percent reduction in decline.

- A biomarker showing an effect on the underlying pathology of AD should be considered evidence of disease modification and may be potentially clinically meaningful.

- A delayed-start analysis (that is, the effect among patients started later does not "catch up" to the effect among patients started earlier) can show a lasting effect of early treatment on the disease course and support the clinical meaningfulness of a treatment.

- The effect of new treatments should be over and above the effect of standard symptomatic treatments in clinical trials that include patient populations already taking standard treatments.

Consideration of these factors can contribute to the evaluation of the overall weight of evidence of the clinical meaningfulness of the effect of potentially disease-modifying therapies.

Regulatory Pathways

An encouraging degree of regulatory flexibility has recently been demonstrated in the AD field; in particular, FDA has developed a draft guidance that outlines new regulatory pathways for early AD (FDA 2013), and EMA has recently published a discussion paper on that subject (EMA, 2014) and has invited industry and academia input. However, further refinements to regulatory pathways or expectations could allow treatments currently in development (that cannot benefit from changes to study design, new scales, etc.) to reach patients more quickly, while still maintaining high standards for demonstration of safety and efficacy, as well as reduce uncertainty for sponsors considering initiating new clinical development programs. Current regulatory expectations are largely based on the established requirements for symptomatic AD treatments. As described above, a broader approach to clinical meaningfulness could be considered by regulators when evaluating disease-modifying agents, especially earlier in the disease continuum.

In addition, expedited or flexible regulatory pathways may also be of importance for future development in AD. FDA has granted expedited pathway status (for example, Fast Track) for several AD treatments in development, and the advantages of these pathways should be fully utilized, including resourcing of timely review of rolling or standard submissions. The FDA draft guidance proposes that treatments for preclinical AD could use the accelerated approval mechanism, in which a cognitive measure could be used as a single primary outcome for approval, and then additional studies or continuation of initial studies could be required post-approval to demonstrate persistence of benefit. EMA is currently planning to revise its own guideline on AD, but it is feasible under their existing regulatory framework that a similar scenario could lead to a Conditional Marketing Authorization in the EU. However, questions remain about the ethics and operational feasibility of these mechanisms.

Another option that could be considered for studies across the disease continuum is the potential for a traditional standard approval pathway with a single primary outcome and a post marketing study to further evaluate persistence of benefit as well as potential effects on other outcomes. Additionally, an accelerated approval/conditional approval mechanism could be developed based on a surrogate biomarker if it were to be validated by demonstration of predictive value in one or more pivotal studies.

A more recent initiative of interest is EMA’s pilot project with adaptive licensing, which aims to maximize the positive impact of new medicines on public health by balancing timely access for patients with the need to provide evolving information on benefits and risks. Questions remain on implementation in the field of AD, for example, whether a suitably restricted population could be defined to enable the initial approval following positive clinical findings in a Phase 2 study. Pilot projects like these could be considered by other regulatory authorities as well.

Conclusions

The first wave of potentially disease-modifying agents that could reach the clinic are currently in late phase clinical development. It benefits all stakeholders to try to accelerate that availability despite some uncertainty about expectations. If we can reduce the impact of the obstacles described above to the development of disease-modifying treatments, we will be able to speed the delivery of such treatments to patients and reduce the burden of AD to individuals, societies, governments, and economies. While not all inclusive, we have described some of the most important barriers and some potential solutions. These barriers span scientific, operational, and regulatory issues over both short and long term. While solutions from all perspectives will be necessary, we recommend prioritizing solutions that will allow delivery of

new innovation to patients by 2025. Enabling the realization and regulatory approval of the first wave of disease-modifying treatments will benefit patients and attract investments that secure further advances toward the goal of preventing AD.

Potential next steps

- Use new data from recent clinical trials to evaluate existing and future regulatory guidance;
- Develop country-wide central ERBs for AD clinical protocol review;
- Obtain government and regulatory support for establishment and use of fast-start networks of clinical trial sites utilizing AD patient registries and cohorts for timely enrolment of clinical trials;
- Enhance coordinated processes and shorten the timeframe for obtaining joint FDA/EMA advice on AD development plans;
- Gain FDA commitment to begin review of a rolling submission for an AD treatment at the time of the initial portion of the submission;
- Establish conditional approval pathways for AD in additional countries;
- Increase alignment across regions regarding regulatory expectations and processes for potential disease-modifying treatments.

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ADI Position Paper on: Improving the Regulatory Environment for Dementia Research

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People with Alzheimer's disease and other dementias, and their care partners, want to be more involved in research and also in the design of clinical trials and selection of endpoints. Finding enough people for trials is currently difficult and might become harder in the future when more studies are going to be conducted, especially in the very early and prodromal stage of the disease.

Research can be done to find a symptomatic or disease modifiable treatment, but also into prevention or effective care interventions. Although not everyone who is diagnosed with any form of dementia will be interested, we believe a much larger part of the dementia community may want to be involved in studies, either to benefit them or help finding solutions for the next generation.

However the average time for a compound to be identified in basic lab research towards a drug that can come onto the market is estimated at 12-15 years. We appreciate the importance of proper testing but also think that this timeframe is unacceptable in nowadays rapidly ageing societies. With 7.7 million new cases estimated in 2010, every year we gain gives this number of people potentially access to disease-modifying treatments. Think about the impact on individuals, families and societies!

In various stages of drug development reasons for delay are due to slow negotiations between research institutions and industry, bureaucracy within pharmaceutical companies, delay within regulatory bodies due to lack of capacity and problems in recruiting enough participants

Governments, Alzheimer Societies, and civil society in general need to create a stronger ethos about the value of clinical research into dementia and a culture of participation in trials and other research as normative, not exceptional. While an examination of regulatory barriers is warranted, regulatory structures should be informed by and based on strong science. Scientifically-driven and sensible regulations have prevented unsafe and ineffective drugs from gaining approval, which has protected patients. Providing more resources to regulatory agencies will speed up the process without putting patient health at risk.

Nearly every government dementia plan has a finding that diagnostic rates are a mere fraction of prevalence. Many have a finding or data suggesting that even when a formal diagnosis is made, it is not always revealed to the patient. Pro-diagnosis policies and investment in needed infrastructure for the early detection of cognitive impairment and determining its source supplement other regulatory reforms by creating the largest possible pool of research subjects.

Patient centered outcomes, and participation by patients and patient organizations in the design of clinical trials is essential. People living with dementia lack choice in the types of studies in which they are recruited. Due to the research silos, individuals are only invited to studies offered by the recruiting institution and may not be aware of the myriad of studies available to them. Furthermore, there may be fear of invasiveness of the research which prevents their desire to participate. If given choices, they may choose a less invasive study over a more invasive study. They may also desire to participate in a study where there is likelihood of direct benefit during their disease course. Greater effort should be made to communicate to individuals the value of studies where relatively invasive techniques (such as lumbar puncture) may be very important, including how such studies could provide the basis for development of an effective treatment.

There is an opportunity to create a ground-breaking global collaborative between drug research and non-drug research to benefit people currently living with dementia as well as reducing the future prevalence. The potential for a global collaborative may also assist in increasing recruitment numbers.

ADI, as an international body connected to both pharmacologic and non-pharmacologic research is well placed to assist the G7 and World Dementia Council in potential efforts.

Materials could be developed through ADI working with Alzheimer Europe and member associations, to educate and provide information to lay audiences in a user-friendly manner. Furthermore, ADI can lead efforts globally to develop an innovative collaboration between people living with dementia and research sites to improve user experiences and expand potential benefits of research to people currently living with dementia. The global effort to emphasize both drug and non-drug research, which ADI is recommending in this paper, may increase individuals' willingness to participate and subsequently see recruitment numbers improve overall for both types of studies.

EMA and FDA and other regulatory bodies should work to avoid all unnecessary duplication of clinical investigations, using common applications, measures, and oversight criteria. Results in an EU based trial should be acceptable in US and vice versa. In addition, clinical trials outside US and EU should have joint oversight and regulation in order to make their results acceptable in the licensing process.

Regulators should automate posting approved clinical trials to national and if feasible global clinical trial databases such as http://apps.who.int/trialsearch/ to increase participation.