Enhancing Translational Research and Clinical Development in Alzheimer’s Disease and Other Dementias: The Way Forward
ABOUT THE WORKSHOP

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.

#ADLausanne

www.oecd.org/sti/biotech/alzheimers-dementia-research-workshop.htm
DAY 1
11TH NOVEMBER 2014

Welcome and Opening Remarks
09:00 – 09:20

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
09:20-09:40

Dr Dennis Gillings CBE, World Dementia Envoy

Accelerating innovation for Alzheimer’s disease and other dementias is a key challenge. In response to this challenge, the World Dementia Council (WDC) was established at the invitation of the UK government following the G8 Dementia Summit in December 2013. It aims to stimulate innovation, development and commercialisation of disease-modifying therapies, and care for people with dementia. The WDC follows a collaborative approach with all stakeholders along the value chain of biomedical research, health innovation, and care. Examples of issues it seeks to address are: How to achieve transparent and predictable governance in a fast moving multi-stakeholder environment? What are the key components of “integrated drug development” and what are the measures for simultaneous support? In a resource-limited environment, what are the most critical and achievable global actions needed in research, drug development and regulatory science as the focus shifts to developing disease-modifying treatments? The Council has established a framework to enable and incentivise the eco-system around dementia and a plan to achieve its goals.

Session 1 – Driving a Global Paradigm Shift to Stop Alzheimer’s by 2025
09:40 – 12:30 (170 min)

20 min each Presentation, 30 min Coffee Break
60 min Panel Discussion and exchange with Workshop Participants

Moderator: Raj Long, Bill & Melinda Gates Foundation, Senior Regulatory Officer - Integrated Development, Global Health, United Kingdom

The purpose of this session will be to discuss the translation of progress in the scientific basis of Alzheimer’s disease and other dementias into recent and future clinical and regulatory approaches. 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. This session will bring together insights from
the research basis, US and European regulatory landscape and the cost-benefits of the use of innovative research tools and technology in Alzheimer’s disease.

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

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, and intervention too late in disease progression. Researchers now focus on the development and early administration of disease-modifying treatments, the elucidation of pre-symptomatic disease processes, and the translation of innovative research approaches into new clinical trial designs. 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. These measures create additional challenges for the delivery of a robust evidence base on the early pathological mechanisms of Alzheimer’s and on potential pharmacological targets and biomarkers that are predictive of symptomatic presentation. 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.

1.B: The regulatory context – US and European perspectives (20 min each)
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

Medicines 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. In close collaboration with stakeholders, regulatory agencies identify and address the barriers in the translation of research discoveries into innovative therapies. 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. This session will explore what has been achieved in recent years, what are the challenges in adapting existing regulatory frameworks to the needs of innovative research strategies aimed at early stage and pre-symptomatic populations, and what can be expected from regulatory agencies in supporting the development of disease-modifying therapies as a new standard of care in Alzheimer’s disease.
1.C: Benefits and opportunities to accelerate Alzheimer’s disease research and development
Troy Scott, Senior Economist, RTI International, United States

The development of disease-modifying treatments for Alzheimer’s disease faces a number of barriers. Among these are the lack of surrogate biomarkers, the exceptional size and duration of clinical trials, difficulties in identifying appropriate populations for clinical trials, and the limitations of monotherapies in addressing such a complex multifactorial disease. This presentation provides a first estimate of the quantified cost-benefits resulting from coordinated, joint efforts addressing the barriers to developing disease-modifying treatments for Alzheimer’s disease, and from the use of innovative research tools and infrastructure.

LUNCH BREAK – 12:30-13:30
ALBERTVILLE FOYER | CONGRÈS BEAULIEU

Session 2: Biomedical Research, Diagnostics and Regulatory Science
13:30 – 15:30 (120 min)

20 min each Presentation
60 min Panel Discussion and exchange with Workshop Participants

Moderator: Zoltan Bozoky, Chief Strategy Officer, Dementia Innovation Unit, Cabinet Office/ Department of Health, United Kingdom

This session will explore recent progress and challenges in biomedical research, therapeutics and diagnostics development, and regulatory science related to Alzheimer’s disease. The presentations and dialogue with a range of stakeholders will elaborate on how new insights into the biochemical and molecular underpinnings of Alzheimer’s disease has led to a paradigm shift in research from symptomatic to disease-modifying therapeutics.

Andrea Pfeifer, Professor, CEO AC Immune SA, Switzerland

Although the underlying cause of Alzheimer’s disease remains unknown, amyloid-beta aggregates and tau tangles are the targets of many drugs in development. Other approaches address the oxidative damage and inflammation that are also seen. Failures in translational and clinical research for Alzheimer’s disease have triggered a rethinking of current disease models. The formulation of new conceptual models of the disease will increase the prospects of developing effective treatments and possible combination therapy approaches.

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

Emerging biomedical technologies can provide the resources to fill the persistent knowledge gaps in Alzheimer’s disease. Innovative research approaches, such as genomics, synthetic biology, artificial neuronal networks, and cell therapy can help to test hypotheses in pre-clinical research and to develop biomarkers for diagnosis and drug development. However, the impact
of an increased knowledge base and of the emergence of sophisticated molecular research tools on the health of patients remains limited. The pharmaceutical industry is still falling short in terms of implementing emerging biomedical technologies into its processes because of the limited experience with such approaches to date. There is a need for standardisation and validation to support the comparability of data and to enable evidence based decision making in clinical research and medicines regulation.

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

Diagnostic tools and biomarkers in particular, are at the centre of current research strategies to permit early disease detection and to facilitate prevention strategies. Until recently, research on biomarkers mainly focused on abnormal protein and peptide accumulations in the brain (i.e., amyloid-beta and tau). The development of disease specific, sensitive and accessible fast-readout biomarkers would be a significant step forward. Researchers and regulators are seeking quantitative and qualitative diagnostic information, to 1) deliver guidance for biomedical research in very early disease stages, 2) develop explicit biomarker-based regulatory frameworks, and 3) support evidence-based decision-making in safety and efficacy assessments.

Session 3: Speeding Innovative Medicines to Patients and Those at Risk
16:00 – 18:00 (120 min)

20 min each Presentation
60 min Panel Discussion and exchange with Workshop Participants
Moderator: Claus Bolte, Division Head - Clinical Review, Swissmedic, Switzerland

This session will explore measures to expedite and de-risk the drug development process for Alzheimer’s disease. A cross-sectoral, collaborative effort among governments, regulators, public research, the pharmaceutical industry, and patient organisations is needed to address medical, scientific and organisational barriers to the successful development of disease-modifying treatments for Alzheimer’s disease. Questions remain how to generate a robust evidence base at the entry of point of clinical research and allow for early failure without further extending the lag-time between discovery research and clinical use.

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 (20 min)
Ana Graf, Global Program Head Neuroscience, Novartis Pharma AG, Switzerland (20 min)
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 rate. In order to speed up the development process we need to learn faster and confirm more effectively. The set-up of 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 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.

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*

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 in the context of a robust global policy environment. Policy challenges 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.

**RECEPTION – 18:00-20:00**

*Sponsored by Canton de Vaud*

**ALBERTVILLE FOYER | CONGRÈS BEAULIEU**
DAY 2
12TH NOVEMBER 2014

Session 4: Perspectives from Stakeholders: Challenges & Options in Making a Paradigm Shift
09:00 – 11:00 (120 min)

15 min each Presentation
60 min Panel Discussion and exchange with Workshop Participants

Moderator: George Vradenburg, Convenor, The Global CEO Initiative on Alzheimer’s, United States

This session will provide an opportunity for different stakeholders to offer suggestions as regards the way forward, including the role they can play in making progress towards effective therapies.

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 Mr. Claude Bilat, Swiss Alzheimer Association

Patients’ rights and therapeutic needs are central in the setting-up of clinical research programmes, especially for the inclusion of patients at the very early stages of the disease or healthy volunteers at risk for Alzheimer’s disease. Creating the conditions for translating promising therapeutic options into “first-in-human” studies is one of the biggest challenges in health innovation for Alzheimer’s disease. Issues include: patient selection and stratification, the voluntary involvement of well-informed patients, and protection of privacy/confidentiality to prevent unauthorized or inappropriate use of personal information. Patient organisations play a significant role in global Alzheimer’s trials to address ethical, legal and regulatory issues, to support patient recruitment and retention in long-term clinical trials and to provide input to regulators assessing the risks and benefits of approving proposed new medicines.

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

Government, academia and start-up biotech companies focus resources on research and discovery projects upstream in the value chain. In the traditional research and health innovation model academia conducts much of the basic research that leads to the biochemical and molecular understanding of disease. There is a need for closer collaboration between academia, small and medium-sized biotech companies and the pharmaceutical industry in order to expand the precompetitive space further down the value chain of product development and to accelerate the transfer of research findings to clinical applications. Empowering academic research as a source of patient-oriented innovation can help to overcome the translational research gap.
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

The role of governments as a facilitator of research and innovation spans through the whole life cycle of medicinal products. As science moves forward, regulatory officials worldwide are increasingly having a dialogue about the possible approaches that might be taken to drive research and development in Alzheimer’s disease and other dementias. At the interface with public and private stakeholders, governments and agencies seek to foster the translation of biomedical innovation to the point of care. The increasing complexity of the research and drug development environment is triggering a rethinking of government’s function in the definition of norms, processes, policies and regulations through which information is shared and decision-making is exercised. Emerging technologies in biomedical research, health innovation and diagnostics development deliver valuable information that needs to be shared and analysed to enable evidence-based decision making. The unique characteristics of Alzheimer’s disease and other dementias, and use of innovative research tools create additional challenges in balancing early access to effective medicines with evidence based decision making.

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

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. 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.

COFFEE BREAK – 11:00-11:30
ALBERTVILLE FOYER | CONGRÈS BEAULIEU
Closing session: Conclusions from the Workshop
The view from here: how to move forward on Alzheimer’s disease?
11:30 – 13:30 (120 min)

*Moderator: Dirk Pilat, OECD*

**Session Summary: Key messages and lessons learnt from the sessions (30 minutes).**

The first part of the closing session will briefly summarise the main messages and lessons learnt from the various sessions. It will involve short oral presentations by the moderators, followed by a discussion with the audience.

**Final Panel Discussion: Shared challenges – shared solutions (90 minutes)**

The purpose of the final panel discussion will be for all stakeholders to explore potential future steps that could be taken to jointly drive a paradigm shift in biomedical research and health innovation for Alzheimer’s disease and other dementias. This includes options for global thinking and joint action, as well as recommendations for policy action. The session will involve representatives from across the stakeholder community, but will mainly be based on interactive discussion with the audience.

Following the Workshop, the OECD will prepare a summary report and a short note with suggestions and recommendations for policy action that will be provided to policy makers and feed into ongoing processes at the international level, including the work of the World Dementia Council.

**Concluding remarks**

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


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 ophthalmology 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
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

Honors and 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 Biochemistry & 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.
Mr. 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, in the Netherlands, where he also earned his PhD in Economics.

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
Philip Scheltens, MD, PhD

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

Positions and Honors
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 Parelsoen Instituut (PSI)
2013-present  Vice-chair Board of Directors Dutch “Deltaplan Dementie”
1998  Medaille d’Or Université de Lille.
2000  Membre d’honneur a titre étranger 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)

Research activities and funding
Past research support:
Between 2004 and 2014 I have got funding for 55 projects for a total of >18 million euro’s

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 USAgainst Alzheimer’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 USAgainst Alzheimer’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 Northwestern 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 WORTMAN
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.
The construct of treating cognitive disorders early in the spectrum of evolution is a popularly accepted approach. 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.

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. The original approach depicted the clinical evolution of events as shown in Figure 1, and a later version of this model expanded it to include alternate scenarios of the development of the pathophysiology. As Figure 1 shows, presumably, the deposition of $A\beta$ 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 $A\beta$. 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 $A\beta$, 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 pathophysiological events remains to be elucidated.

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 centers 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. While normal and abnormal levels of amyloid deposition can be agreed upon, the construct of normal and abnormal tau imaging measurements become more problematical. 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. 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 harbor 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 comorbidities, 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 computerized 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.

INDUSTRY PERSPECTIVE ON CHALLENGES IN DEVELOPING DISEASE-MODIFYING AD 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 reevaluation 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 coprimary 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 ENROLLMENT

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 enrollment, 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 enrollment 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.

**REFERENCES**


ADI POSITION PAPER ON: IMPROVING THE REGULATORY ENVIRONMENT FOR DEMENTIA RESEARCH

Marc Wortmann¹, Serge Gauthier², Helga Rohra³, Lynda Hogg⁴, Nicole Batsch⁵, Mike Splaine⁶

1. 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.

2. 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.

3. 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!

4. 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

5. 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.

6. 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.
7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

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1 Executive Director ADI
2 Chair Medical and Scientific Advisory Panel, ADI
3 Chair of the European Working Group of People with Dementia
4 Representing People with Dementia in the ADI-Board
5 PhD student and consultant ADI
6 Policy Advisor ADI
ABOUT OUR ORGANIZATIONS

The mission of the Organization for Economic Co-operation and Development (OECD) is to promote policies that will improve the economic and social well-being of people around the world.

The CEO Initiative represents an acceptance of the invitation from public authorities, domestically and internationally, to the private sector to forge robust public-private partnerships to stop Alzheimer’s disease and dementia. Our vision is that the CEO Initiative becomes the leading business voice on this seminal public health issue of our time, which will have profound impact in fiscal, social and political matters as we “change the game” on Alzheimer’s.

The State Secretariat for Education, Research and Innovation SERI is the federal government’s specialised agency for national and international matters concerning education, research and innovation policy.

Alzheimer’s Disease International (ADI) believes that the key to winning the fight against dementia lies in a unique combination of Global Solutions and local knowledge. As such, it works locally, by empowering Alzheimer associations to promote and offer care and support for people with dementia and their careers, while working globally to focus attention on dementia.