Finding a Path for the Cure for Dementia

An independent report into an integrated approach to dementia research

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Foreword from Raj Long

Dementia is a disease that robs millions of people around the globe of their right to grow old with dignity. It is currently estimated that 47.5 million people worldwide suffer from dementia (WHO, 2015). It devastates the lives of both patients and their care givers and families. The World Health Organization (WHO) estimated that the global cost of dementia care in 2010 was US$604 billion – 1.0per cent of global GDP. By 2030, it is estimated that the cost of caring for people living with dementia worldwide could rise to around UDS$1.2 trillion. Despite huge investments by innovators in the last decade, there is still no cure or treatment for slowing down disease progression. This, coupled with a steadily increasing aging population, means we are highly likely to face a public health 'tsunami' across geographies if we continue to do business as usual in the dementia world.

We all want to see discovery bench science turned into useable human treatments. Yet there is an ongoing and growing record of failure in dementia drugs. While there is growing pressure and appreciation that we need to do something different, the key questions are **Why** are we failing, **What** are the strategic drivers, **Who** do we go to, **Where** can we get greatest impact and **When** do we start this ?

Following the G8 Summit on Dementia held in London in December 2013, I was asked by the UK Government to lead work to better understand what and where are the 'hurdles' that fuel the development failures, and more importantly can anything be done to catalyse dementia drug development success.

Patients, research and regulatory science are the centre of my approach. A logical starting point was to drill down to learn from the moratorium of failures the have been seen in dementia drug trials, deploying a structured and analytical approach – referred hereafter as the Attrition Analysis. Another historical context to learn from is other disease areas that have undergone a similar morphology in the evolution of those disease states – Cancer, HIV and Rheumatoid Arthritis. It was necessary to then identify potential gaps in the context of all of the above. There is a need to determine whether there is consistency of these gaps from the regulators' perspective of the regulatory science when the programs come for their review further downstream at the

different stages of development. Integrating the state of the research science with the regulatory science, together with the patient needs, could potentially be the start of facilitating guidance to increase success rates in dementia drug development.

This report reflects my views. It is informed by 25 years' of industry experience in pharmaceutical development, as well as learnings from Attrition Analysis of approx. 2000 trials by the Office of Health Economics, input from researchers and developers, and an assessment carried out by a collective of 10 regulatory agencies from Canada, Japan the EU (EMA, Germany, Italy, Netherlands, Denmark and the UK) , Switzerland, and the United States of America.

I am very grateful to those who have given generously of their time in support of my role as the Director of Dementia Integrated Development. They include Dr Dan Hartman and the leadership team of the Bill and Melinda Gates Foundation, Dr Ian Hudson of the Medicines and Healthcare Products Regulatory Agency in the UK, and Jon Rouse and his team at the UK Department of Health. Finally, I am hugely indebted to the international medicine regulators from the 10 countries who joined together without hesitation to address the dementia challenge and continue to share their expertise so generously to find a way forward for dementia patients globally. This is particularly significant as it is the first time this community of regulators have come together in a single forum to tackle dementia.

I believe that the recommendations in this report can create a new framework when brought together in a strategic integrated platform, which can potentially be a catalyst to facilitate success and breakthrough the dementia impasse. Dementia is a global crisis, and we cannot continue as business as usual. We need to come together to tackle it head on.

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Executive summary

Problem Statement: Drug Development for dementia is at a crossroads

Dementia research and development is at a crossroads. The past decade has seen very little in the way of progress in drug development, and the disease has suffered from a lack of funding in innovation, research and development. Part of the problem is the high failure rate of candidate drugs, predominantly in the early stages of development, which is symptomatic of the gaps in the biology. However, in order to confront this problem we need to understand the wider culture of breakdown in the development of dementia drugs. Gaps in knowledge around the disease biology and how conducive is that to the regulatory science, scant openness with data-sharing, and the need for better understanding of regulatory challenges all lead to slow and inefficient translation of research into successful clinical results that can pave the way.

Call for Action: Taking action now to avert a crisis

The global burden of dementia, both now and in the future, is too great to ignore. Alzheimer's disease is the most common cause of dementia but not all dementia is due to Alzheimer's. We need to take action to alleviate the problem for individuals, their families and health care systems in the global community. Achieving

the G8 commitment of identifying a cure or disease-modifying therapy for dementia by 2025 is going to take sustained, concerted and global effort.

Recommendations for action

This report was born out of a call for an exploration of ways to achieve greater alignment within current regulatory pathways. Through learning from the research state of dementia, gaining insight from the past failures and working with key representatives from medicine regulatory authorities it became apparent that while there were opportunities for better alignment within current regulatory platforms, many of the opportunities for improvement identified actually go beyond regulatory procedures. This is essentially because regulatory science cannot go beyond the basic research science. Therefore this report looks at the bigger picture of an integrated approach to the process, from dementia research through to drug development. Building on the five work streams developed and led by national medicine regulatory agencies (see Chapter Three) it outlines a series of recommendations which will get us collaboratively closer to an integrated approach for facilitating the delivery of a cure or disease-modifying therapy for dementia.

These recommendations are not the end of the story, but instead are a call for global action. We need to establish a common understanding that will create new opportunities in drug development and address the challenges at all stages of the development process.

Introduction – The challenge of Dementia and the importance of drug regulations

Dementia is a devastating illness that is affecting millions of patients and their families across the whole world

> *"I can think of no other disease that has such a profound effect on loss of function, loss of independence, and the need for care. I can think of no other disease so deeply dreaded by anyone who wants to age gracefully and with dignity. I can think of no other disease that places such a heavy burden on families, communities, and societies. I can think of no other disease where innovation, including breakthrough discoveries to develop a cure, is so badly needed."*
>
> – Margaret Chan, Director-General of the World Health Organization, March 2015

In 2015 dementia is already affecting 47.5 million people worldwide. By 2030 it is estimated that there will be 75.6 million people with the disease. By 2050 the estimate is 135.5 million (WHO, 2015).

People live for many years after the onset of symptoms of dementia, and the personal, social and economic consequences are enormous. The World Health Organization (WHO) estimated that the global cost of dementia care in 2010 was US$604 billion – 1.0 per cent of global GDP. By 2030, it is estimated that the cost of

caring for people living with dementia worldwide could rise to around UDS$1.2 trillion. Dementia is also truly a global burden, with 63% of people living with dementia living in low-and-middle-income countries (WHO, 2015).
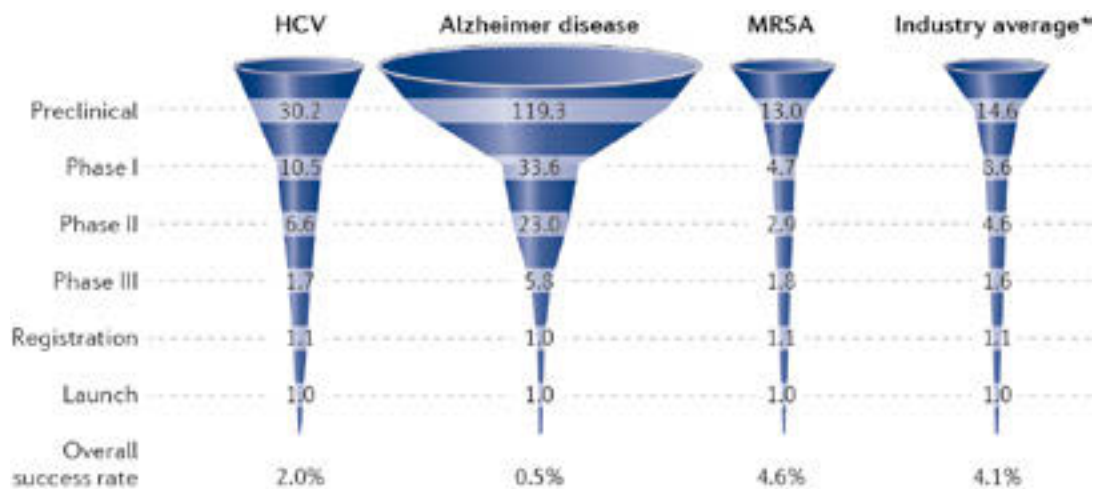
Why are there so few drugs for dementia?

As Schneider et al. noted, despite considerable advances in knowledge of the pathogenesis of Alzheimer's disease and in medicinal chemistry, no practical treatments have been introduced over the past quarter of a century (Schneider et al., 2014).

Only four cholinesterase inhibitors and memantine have been marketed for the treatment of Alzheimer's Disease and none since 2002 in Europe and 2003 in the USA (Schneider et al, 2014). This essentially means that no drugs have been approved for any aspect of dementia in over a decade, despite the high medical need and enormous 'block buster' potential. In contrast, in Type II Diabetes for example, 6 new products were approved during 2013 – 2014, a disease that already has multiple treatments available. The distinct lack of a medical cure for dementia is reflected in the fact that of the US$604 billion worldwide costs of dementia in 2010, just 15 per cent of the money was spent on direct medical costs (Wimo, A and Prince M, 2010).

However, these low figures don't mean that there has been no investment in finding drugs for dementia. Indeed from 1995 to 2014, developers produced 1,120 unique pipeline drugs (Calcoen at al, 2015). Despite this proportionately high input into the pipeline, there has been a huge failure rate of candidate drugs getting through the development cycle, as illustrated in Figure 1.

Figure 1: Attrition profiles across therapeutic areas (Calcoen et al, March 2015)

	HCV	Alzheimer disease	MRSA	Industry average*
Preclinical	30.2	119.3	13.0	14.6
Phase I	10.5	33.6	4.7	8.6
Phase II	6.6	23.0	2.9	4.6
Phase III	1.7	5.8	1.8	1.6
Registration	1.1	1.0	1.1	1.1
Launch	1.0	1.0	1.0	1.0
Overall success rate	2.0%	0.5%	4.6%	4.1%

Dementia drug research has experienced an unprecedented failure rate. The funnels illustrate the average number of compounds needed at each stage of drug development in order to get one drug approved. As a result of these unprecedented failure rates, dementia has become uncompetitive compared to other diseases. This becomes a direct driver for disinvestment, due to huge investment costs, with no or virtually no return on the investment – so dementia becomes a high risk disease area for investment.

Chapter 1: The G8's challenge to find a cure or disease modifying therapy for Dementia by 2025

The UK Government took the decision to bring the dementia challenge to a global forum by hosting the first ever G8 Summit on Dementia, in December 2013.

The Summit led to a number of commitments, including the commitment to find a cure or disease modifying therapy for dementia by 2025 (G8, 2013). This is a bold commitment, with a timescale that would be challenging for any disease area, let alone one with dementia's clinical development challenges. It has been estimated that a new drug that delays onset of dementia by five years could reduce the expected numbers of people with the disease by as much as 50 per cent. This would save around $450 billion a year by 2050 and an incalculable amount of human pain (Prince, M et al. 2015).

The UK Prime Minister, David Cameron, was clear that steps would need to be taken to mitigate the market failure that is undermining dementia research and drug development efforts. He stressed that no one country or organisation can tackle this issue alone, and that there is a need to have much greater collaboration between government, industry, regulators and the scientific community (Cameron, 2013).

With that in mind, the UK Government appointed me to lead a piece of work that has become known as 'Integrated Development'. The aim of the work has been to assess what collaborative efforts could be undertaken in the regulatory space to create a more conducive environment to facilitate successful dementia drug development, thereby breaking the dementia impasse.

Following the G8 Summit, we have also seen; the appointment of a World Dementia Envoy, establishment of a dementia 'Discovery Fund', and a series of events around the World, bringing experts and patients together. I have been engaging closely in all of these activities, learning from the full breath of key stakeholders to inform my position on the role that regulatory science and research science can play in facilitating a more conducive drug development environment.

In March 2015, the WHO hosted the first ministerial conference on Global Action Against Dementia, with 91 countries in attendance. At that meeting I first presented my key recommendations. This report provides the analysis and discussion behind those initial recommendations (Long, 2015).

Chapter 2: Context – State of the interface between regulation and science

I was delighted that the UK Prime Minister acknowledged the key role between regulators and science in unblocking the barriers in finding a cure or disease modifying therapy for dementia (Cameron, 2014). I have worked in this field for over two decades and am familiar with the problems which are commonly rehearsed and repeated. However, I needed a solid evidence base and a distillation of the challenge against that evidence base, in order to allow me to propose further recommendations.

In order to build this evidence base, I have initially focused on four areas of work;

1. **Attrition Analysis** – learning from the failures to gather further evidence on the reasons behind the failures in drug development in dementia.

2. **Research Status Quo** – learning from the experience of researchers and industry developers, and their insight and encounters.

3. **Patient Viewpoint** – learning about the patient's perspective.

4. **Regulator Perspectives** – learning from the collective insights from international regulators regarding risks and opportunities as experienced from their perspective.
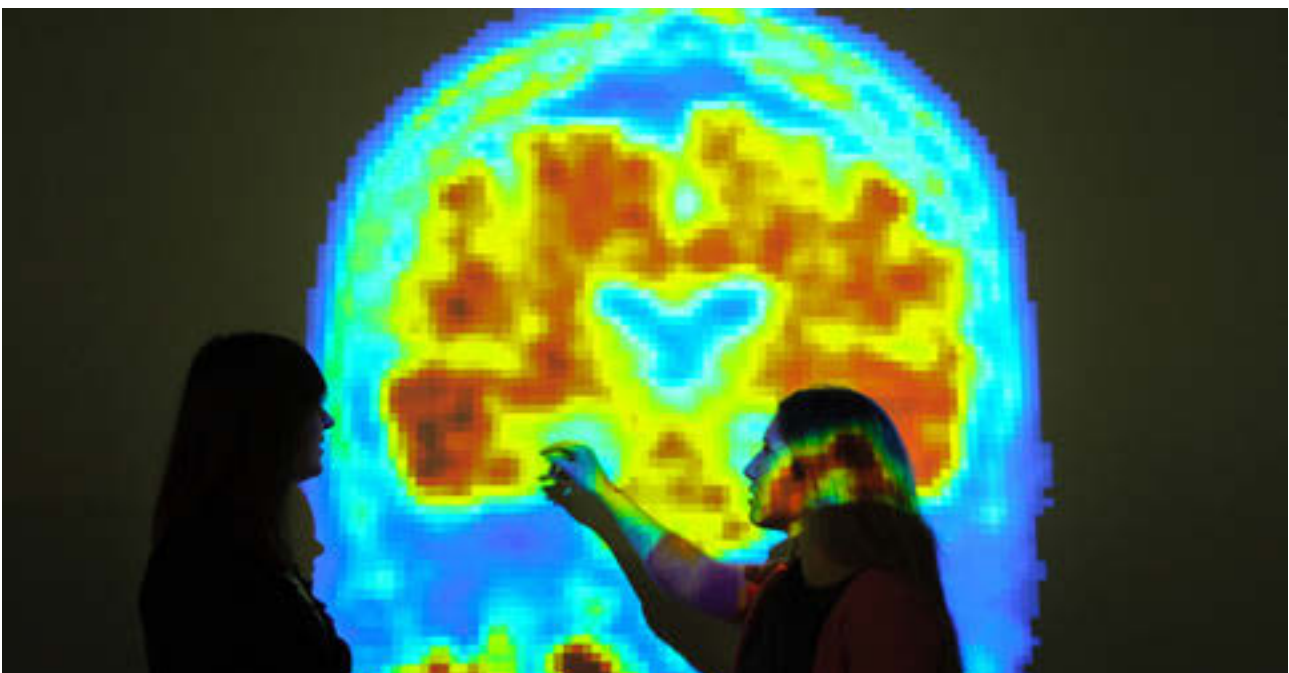
1.   Attrition Analysis

It was evident at an early stage in the process of this work, that there was a need to get a better understanding of why drugs have not been successfully progressing to market, as by far the majority do not. For this reason, I asked the UK government for an analysis of the dementia research and development (R&D) landscape.

The UK Government commissioned Imperial College London, led by Prof L. Middleton, to establish a Clinical and Technical Expert Group (CTEG) working with the Office of Health Economics (OHE), to produce an analysis of the R&D landscape of the past, to analyse the current pipeline for dementia treatments and to explore the possible reasons for successes and failures of dementia products. The findings from this work highlight some important messages that inform and shape the wider objectives of the Integrated Development initiative, and the issues that the regulators are seeking to address, as outlined in Chapter 3 of this report.

OHE carried out a literature review, a pipeline analysis and a comparison of dementia with other therapy areas. Through the literature review, it was found that research and development costs were higher for Alzheimer's Disease (as well as for respiratory and oncology) than for other diseases or research areas due to lower success rates and longer development times. OHE also discovered that problems in recruiting trial participants was found to be a key reason for the termination of trials (OHE, 2015).

Mestre-Ferrandiz et al. (2012) conclude that Neurology is currently one of the most 'expensive' therapeutic areas. This is due to both low success rates and high development times. Out-of-pocket costs, however, tend to be similar to other therapeutic areas.

OHE identified and analysed approximately 2,000 trials for dementia and found that 110 of the trials had been terminated early, with only 46% reporting a reason for this early termination. Of the 46% which did provide a reason the largest number was attributed to recruitment problems. However, as the reason for withdrawal/suspension/termination was not reported in 54% of the trials, it cannot be concluded that problematic recruitment is the most common reason for trial termination (OHE, 2015).

Figure 2: Reasons for termination of trials: results for the suspended, withdrawn, and terminated trials all together

- Not reported
- Data not required
- Trial results (including efficacy/safety concerns)
- Recruitment problems
- Other reasons

Key: Other reasons = staff attrition and organisational problemns, loss of funding and study objectives met
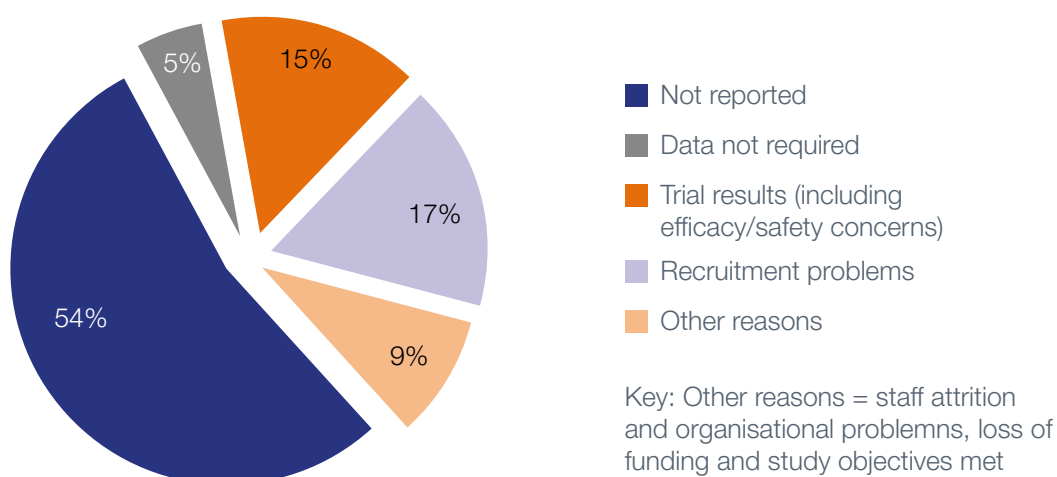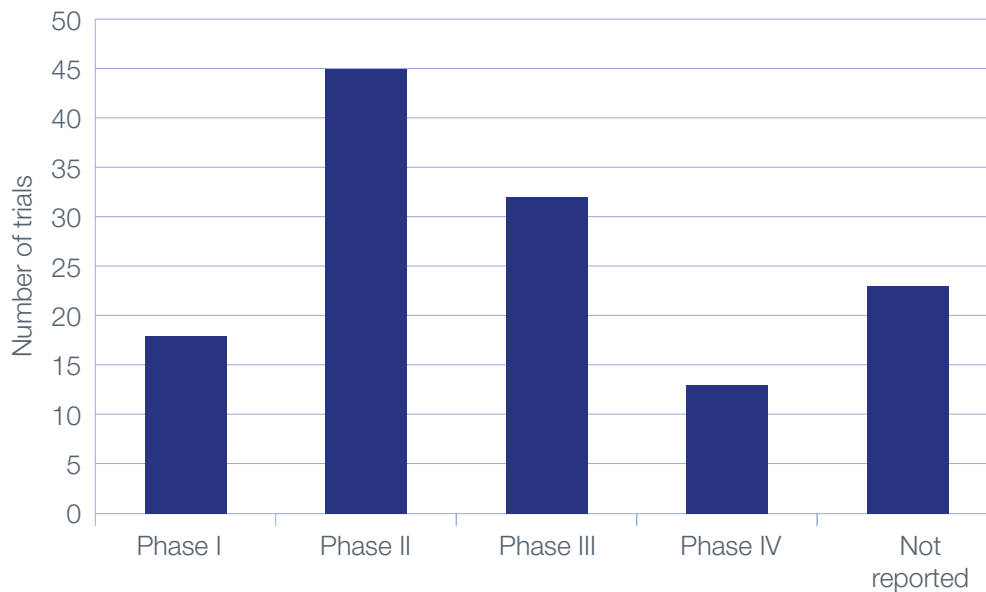
Figure 3: Number of suspended, withdrawn and terminated trials by development phase

The analysis revealed 900 different products for dementia, 197 of which were in active development. The majority (67%) in active development were classified as disease modifying rather than symptom modifying (30%). A further 216 products had been suspended/discontinued, mainly due to lack of efficacy or safety, although 74% did not report a reason. Phase success probabilities for dementia are consistently lower than those for all therapy areas. In terms of the phase success rate calculations, dementia indications have lower success rates than other therapy areas (likelihood of being marketed from phase 1 = 7.27% for dementia, and 15.3% for all therapy areas). This fits with OHE's other finding, that the proportion of dementia drugs declines as the phase of development advances (OHE, 2015).

Overall the key findings from the Analysis are that; success rates are significantly lower in dementia, phase failure is seen throughout the development cycle (Safety and Efficacy) but is pronounced in early development (Proof of Concept). The CTEG key findings here are consistent with the findings reported in Figure 1. The work does only look at a certain number of databases, and we are aware of other privately-owned databases that could complement this picture. However, this work does clearly illustrate the challenge faced for dementia.

2.   Research and Developers Status Quo – learning from the experience of researchers and industry developers and their insight and encounters.

The Global CEO Initiative against AD (an industry coalition of private-sector leaders, who are providing business leadership in the fight against Alzheimer's Disease) shared a draft white paper with me entitled 'Industry Perspective on Challenges in Developing Disease-Modifying AD Treatment' in November 2014 (CEOi, 2014). It raised an industry perspective on a number of key questions around the current development approach and *'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'*.

Overall, the paper raised the need for reevaluation of how we conduct some aspects of AD drug development and related activities, including clinical development programs, regulatory pathways, and appropriate treatment outcomes (meaningful end points) in clinical practice. The paper also highlighted the challenges of using the current regulatory requirements of functional and cognitive endpoints in early AD and the general need to have more sensitive measures. On the regulatory front the call was for *'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' (CEOi, 2014). Additionally, the proposal was for an accelerated approval/conditional approval mechanism that could be built on a surrogate biomarker if such a biomarker becomes available. To take it a step further it was indicated that in the absence of surrogate biomarker, a change in cognition alone should be the marker.

3.   **Patient Viewpoint** – learning from the patient's perspective

Over the last few years, patient groups have become increasingly vocal about their desire to stimulate patient participation in clinical trials. Equally patients who have been diagnosed are potentially willing to participate in trials that are deemed 'riskier'. Many wish to contribute to overall scientific learning, so that their experience of dementia may at least help others. As in a fight for a cure of any disease, keeping the needs and wishes of patients, carers and families central is critical. This is even more relevant in dementia given the nature of the disease and the impact it has on cognitive ability of the patient. Having had the privilege of talking to patients and their care givers, I know that it is imperative to have their needs and views at the centre of how we develop and deliver treatment and care. Perhaps the most resonating comment I heard was when a patient put a compelling and challenging argument to the regulators on the need to reassess the risk that patients are prepared to face in order to try innovative medicines. She said that *"as long as you have a reason for your decisions and you can explain those reasons, what more can anyone ask of you. You know, even if you have made a wrong decision, it is better to make a wrong decision rather than make no decision at all."* This raises multiple ethical and legal questions on whether the responsibility for risk/benefit lies with society (societal accountability) or is it as mandated by law with regulators; this is a debate that is out of scope for this report although one could say that regulators are acting on behalf of society as part of society.

4.   **Regulator Perspectives** – learning from the collective insights from international regulators regarding risks and opportunities as experienced from their perspective

Having gleaned insight from the Attrition Analysis, research and developers' experience, and marrying that with the patient perspective, the next step was to learn from the Regulators about what they see at the downstream level. Regulators are in an important position as they see applicants submit development plans across the board and are uniquely placed to bring research science and regulatory science together. Having worked in setting strategy for regulatory access in the international arena for industry for many years, I looked to the global leads in the regulatory space for dementia and identified 10 regulatory agencies and secured their support through individual dialogue and counsel to help us in this quest to learn more about the regulatory science in dementia.

The regulatory agencies who agreed to participate were as follows:

– Canada: Health Canada
– Denmark: Danish Health and Medicines Authority (DKMA)
– European Union: European Medicines Agency (EMA)
– Germany : Federal Institute of Drugs and Medical Devices (BfArM)
– Italy: Italian Medicines Agency (AIFA)
– Japan: Pharmaceuticals and Medical Devices (PDMA)
– Netherlands : Medicines Evaluation Board (MEB)
– Switzerland: Swiss Medic
– UK: Medicines and Healthcare Products Regulatory Agency (MHRA)
– United States: Food and Drug Administration (FDA)

Chapter 3: Methodology – How I have formed my position

In my role this past year, I have found myself in the privileged position of being able to frequently say "so what shall we do about it?", "what could be done differently?", and "let's not stay the same".

I have taken on board the views and evidence that have been gathered for me. I have heard and considered what matters to patients. Through my meetings with regulators, in particular, it has started to become clear where we need to focus our efforts and where we can have the biggest impact.

Regulator Workshop

I convened a meeting in November 2014 that brought together eleven of the drug regulators from 10 agencies in Europe, the United States, Canada and Japan, supported by a clinical working group, the WHO and the Organisation for Economic Cooperation and Development (OECD). This regulatory-research workshop sought to establish what we could do collectively to support innovation. This was the first time that this combination of 10 agencies and research have come together in a single forum to support the G8 call for the quest for disease modifying agent for dementia patents

All of the regulators involved agreed that there is a need to work collaboratively to address the challenges facing dementia drug development. We heard the perspectives of the clinical researchers, industry perspective and finally the patient perspective. Following on in a closed workshop, each regulatory agency presented their direct experiences on dementia, or learnings and observations from oncology, HIV and rheumatoid arthritis. These diseases posed similar challenges, over 20 years ago; so how did we tackle the unknowns then and how did it evolve to current state. Many of the regulators had seen the evolution of science and delivery of effective treatments for these challenging disease states within the time of their stewardship.

We then stacked all of the information (attrition analysis, research and industry perspective, patient perspective and the regulators' learning) layer by layer and distilled it to see where they came together as key areas of gaps/opportunities. These were captured and identified in five discreet work packages. The approach was in short a multi-dimensional analysis and collation of the past and present and what can be gleaned for

the future. These work areas span the whole spectrum of the dementia drug development pathway and when strategically integrated I believe can significantly impact on both in the translational design phase in early phase and clinical meaningfulness in late phase of the development pathway for dementia.

It is exemplary that each of the work packages is led by a regulator who volunteered to lead and work with others in the different jurisdictions to take it forward. I convened a second meeting in June 2015 hosted by AIFA in Rome, Italy as a follow up on the progress of the work packages.

The regulators are continuing this work as my report goes to print. Over the coming months we look forward to seeing more findings adding to the evidence base.

Workstream	Description
Clinical trial efficiencies Lead: SwissMedic (Dr Claus Bolte)	A number of clinical studies in Alzheimer Dementia were discontinued due to operational and methodological issues. This work will analyze (retrospectively) features and commonalities of failed studies relative to Scientific Advice obtained (design, endpoints etc.). Emerging learnings from this analysis will then be used to provide commercial sponsors of AD studies with just one joint Scientific Advice to run their global trials, thereby also avoiding duplication of efforts when dealing with different regulatory authorities.
Risk Benefit Balance Lead: Danish Health and Medicines Authority (Dr Jens Heisterberg)	This work considers the balance of benefits, risks and uncertainties for a future promising medicine for Alzheimer's disease and how to manage this balance from a licensing perspective. Issues considered include, for example, assessment of whether existing regulatory frameworks allow sufficient flexibility while still ensuring that inefficacious and/or dangerous medicines are not granted a license or taken off the market as soon as possible.

Workstream	Description
Multilateral Cooperation Lead: European Medicines Agency (Mr Manuel Haas)	This work focuses on promoting global regulatory efficiency and consistency, by building on existing international platforms and dialogue between regulatory agencies to foster opportunities for multilateral interactions in the specific situation of AD. So far the work has resulted in extending participation in the EMA 'data-sharing initiative' to US FDA, PMDA and Health Canada, helping to inform future scientific advice and guideline development. The workstream is also considering ways to optimise the use of the FDA-EMA parallel Scientific Advice and Qualification procedures for dementia. The workstream is also planning to conduct a comparative review of the FDA and EMA guidelines on dementia, focusing on main issues of relevance to, and from the perspective of global development. This exercise is anticipated to identify commonalities and possible differences between the guidelines, with the potential to promote a common understanding of their alignment and facilitate the design of global programmes.
Modelling and Extrapolation Lead: Italian Medicines Agency (Dr Valentina Mantua)	It is accepted that there is a need for quantifiable, reproducible outcome measures – including surrogate end-points – that are sensitive to change in order to assess treatment efficacy. There is currently no process for using modelling to fill in scientific uncertainty around the main areas of development; this workstream is therefore looking at how modelling and extrapolation could be developed to better support development in the uncertain scientific and regulatory environment of dementia drug development.
Composite end points Lead: Federal Institute of Drugs and Medical Devices (Prof Dr Karl Broich)	Whilst there many groups are working on assessment scales, there is no consensus making it difficult to compare drug development programmes. This workstream is seeking better standardisation and validation of cognitive endpoints, focusing on quantifying cognitive impairment in the earlier stages of dementia. A literature review is being carried out to compare preliminary data from drug interventional trials, with the aim of producing information to help companies to better qualify their methodologies on biomarkers.

Workstream	Description
Attrition Analysis Lead: Imperial College and Office of Health Economics (Prof Lefkos Middleton)	This work has analysed the current pipeline for dementia treatments and explored the possible reasons for successes and failures of dementia products. Following a study of three pipeline databases, approximately 2,000 trials for dementia were analysed, and over 900 different products for dementia were found. Of the trials that terminated early with a reported reason, the most common reason for termination was recruitment problems. However, 56% of the trials did not report a reason for termination, so it cannot be concluded that recruitment is the most common reason for termination. The analysis also found that research and development costs were found to be higher for Alzheimer's disease than for other diseases, and that success rates are significantly lower in dementia, and that trial failure is more pronounced in early development (proof of concept). This analysis provides further insight into why drugs have not successfully been progressing to market, and has provided information which has helped to underpin the other workstreams.

There are actions that we can take now, that the regulators could work to adopt straight away, and those that may take a little more development – but for which the impact could be significant. It is in bringing these recommendations together that we can be ground breaking and stop 'business as usual'.

Chapter 4: Next steps and recommendations

One of the most common assumptions I heard when this work began was that a new regulatory procedure would be needed to overcome perceived blocks in the process. However, my engagement with expert stakeholders such as the regulators, clinicians and academics has shown that the failure of drugs to reach patients is actually multi-factorial and that the solution cannot be found in regulatory processes alone. Tackling these issues strategically and at multiple levels will be imperative to break through and find more drugs for patients. The potential for overcoming barriers range extensively from; better understanding of targets, trial design issues, lack of effective bio markers, pre-clinical to clinical translational challenges, toxicity, and better endpoints/surrogates, not to mention the amyloid versus non amyloid debate.

A structured three-part work programme has been undertaken with clinical-scientific experts and regulators, to collectively evaluate approaches using existing laws and regulations in the most optimal way.

Part I identified research and development challenges in dementia drugs. Part II was to work with key regulatory agencies and researchers on the research gaps and development challenges. Part III is to establish a common understanding at the global level that will address the challenges and create new opportunities in drug development.

Conducting this work programme led me to make five recommendations to the first WHO Conference on Dementia, in March 2015. These recommendations were as follows:

- **Recommendation 1:** Learn from attrition analysis and reconsider molecules previously rejected by pharmaceutical developers, if the science could be viewed differently.

- **Recommendation 2:** Support the regulators who have identified and agreed a way forward on six areas of work throughout 2015

- **Recommendation 3:** Coordinate existing pathways that are conducive to current gaps in science within existing laws and procedures that can be achieved in the context of different regulatory pathways and help encourage innovators to seek early engagement with regulators eg joint scientific advice.

- **Recommendation 4:** Spearhead adaptive clinical development by focusing on accelerated regulatory pathways for dementia medicines. Employ a sensitive and patient centric approach to risk-benefit ratio, learning from other diseases like HIV, oncology and rheumatoid arthritis and assessing applicability to dementia.

- **Recommendation 5:** Build on existing Multilateral Cooperation between regulators, and create a multilateral advisory platform of research experts who can, working in conjunction with regulators, to advise companies on optimal development strategies, to facilitate increased outcomes for dementia drug development.

Actions for change

Building on the regulators' work, the recommendations that I made in Geneva, and based on the understanding that I have now formed of the way that regulators and research science can work together for the future, I have distilled the insight that I have gained into some key next steps. Taken individually they will help to make important improvements to the process for developing drugs for dementia. But if they are taken together, and we approach it as a single integrated platform that harnesses the cross cutting impact of each of these arenas, then the potential difference to drug development in dementia could be seismic. In short 'the whole is greater than the sum of the parts'. Indeed, the more regulators, governments etc that come together, the greater the potential achievement. 'Greater' is what is needed if we want to overcome the disease modifying impasse by 2025.

These actions are outlined on the basis of the best level of knowledge that we have at this point in time; many of these actions will evolve and need to be adapted as we work through and learn. Some deliverables can be achieved more quickly than others, and new areas for change may emerge. But for now these actions represent a concerted approach based on evidence gleaned from overwhelming attrition, current development research state, patient voice and the totality of experience and wisdom of 10 of the world's leading regulators, all brought together in a systematic approach for the first time. This is a unique opportunity at a unique time point in the evolution of drug development pathway for dementia that we must capitalise on.

The actions that I propose are as follows:

1. **Use the learnings from the regulators to agree principles for facilitating consistent global development pathways**

The action involves finalising the work that the regulators are already undertaking (as in Chapter 3) with the aim of taking their conclusions and translating them into globally agreed principles. This will then support developers through a more consistent development pathway. Making these happen will directly benefit innovators, as it will create more incentive in the system; each work package individually and taken together will provide greater

clarity, flexibility, minimise redundancy and facilitate 'global development. There would be an incentive in the context of time, which is cost. The Multilateral Regulator Cooperation platform (as described in Chapter 3) will allow focus on promoting global regulatory efficiency and consistency, by building on existing international platforms and dialogue between regulatory agencies to foster opportunities for multilateral interactions in the specific situation of AD.

This cohesive coalition of efforts by these 10 regulators have come together in a way that has never happened before in dementia. It is a very powerful concentration of strategic drivers that have the potential to truly shape regulatory science in the advancement of dementia. Their success needs to be enabled through collective support by the individual governments and researchers all coming together. Success in this collective will be a huge incentive for re investment in dementia drug development.

2.   Understand and agree on the gaps in the basic science (both amyloid and non-amyloid approaches) and take action to address these

There is a critical need to better understand the complex etiology of dementia. Different schools of thought exist on the controversies surrounding the amyloid hypothesis for Alzheimer's Disease including that pre clinical AD is not representative of human disease (Morris et al, 2014). The wide range of targets adds to the challenge. Past failures and the dichotomies of 'symptomatic' versus 'disease-modifying', 'early' versus 'late' and amyloid versus tau, suggest that there is still much to learn about late-phase development (Scheneider et al, 2014). In addition, the concept of a surrogate biomarker, as endorsed by the FDA Draft Guidance on Early AD Development, also needs to be collectively developed further to have more measures in the context of endpoints. The work on Modelling and Extrapolation by AIFA can play a critical role in potentially bridging key areas in the basic science that are currently evolving. The FDA and Critical Path have already done some work in this area (CPATH, 2013) but further development would be welcomed and needs to continue.

The lack of success, despite significant investment (CEOi, 2015), may be an indicator that the gaps in the research science still need to be further addressed and agreed. It is important to know what we know but it is more important to know what we don't know. I am calling for the global research community to be supported to come together in the same coalition of minds as the regulators have done, to evaluate and agree on a set of 'universal' guidelines on their collective insights and future opportunities. This could then act as a single blue print for innovators and regulators to use as a point of reference. This approach could be perceived as aspirational but the current rate of development science failures cannot be sustainable.

3.   Support the assessment of the necessary clinical evidence required in dementia development programmes for regulatory assessment

Clinical trial methodologies should be scrutinised to ensure that the design behind each phase is testing the intended hypothesis for that particular phase. For example, it is understood that no anti-amyloid therapy Phase 3 trial has been preceded by a positive Phase 2 proof of concept trial. Instead, an unfortunate characteristic of development programs for Alzheimer's disease has been that Phase 2 did not provide 'proof of concept' to predict Phase 3, but rather is used as a bridge to the next stage. Consequently the large Phase 3 trials, instead of being confirmatory, are often exploratory (Schenider et al, 2014). It is beyond the scope of this report to validate this but if it is the case then it may explain failures throughout the development cycle as noted in the Attrition Analysis as similar trial designs are being used for very different drugs, which is further compounded by the complexity of the disease.

Additionally innovators can share the data on the failed candidates in a controlled setting in order for others not repeat the same mistakes. Some of this thinking has started with the OECD initiative on Big Data (OECD, 2015) but more needs to be done at different levels. We should also review candidates in the 'moratorium' that

have been killed too early, using a systemic approach and perhaps can be resurrected as the science and the regulatory environment evolves.

Last but not least, time must be given to the consideration of combination therapies for dementia. Monotherapy has dominated the development pathway to date and given the almost universal attrition of this approach, the obvious question is whether there is room for combination therapy, targeting both disease modification and longer symptomatic control.

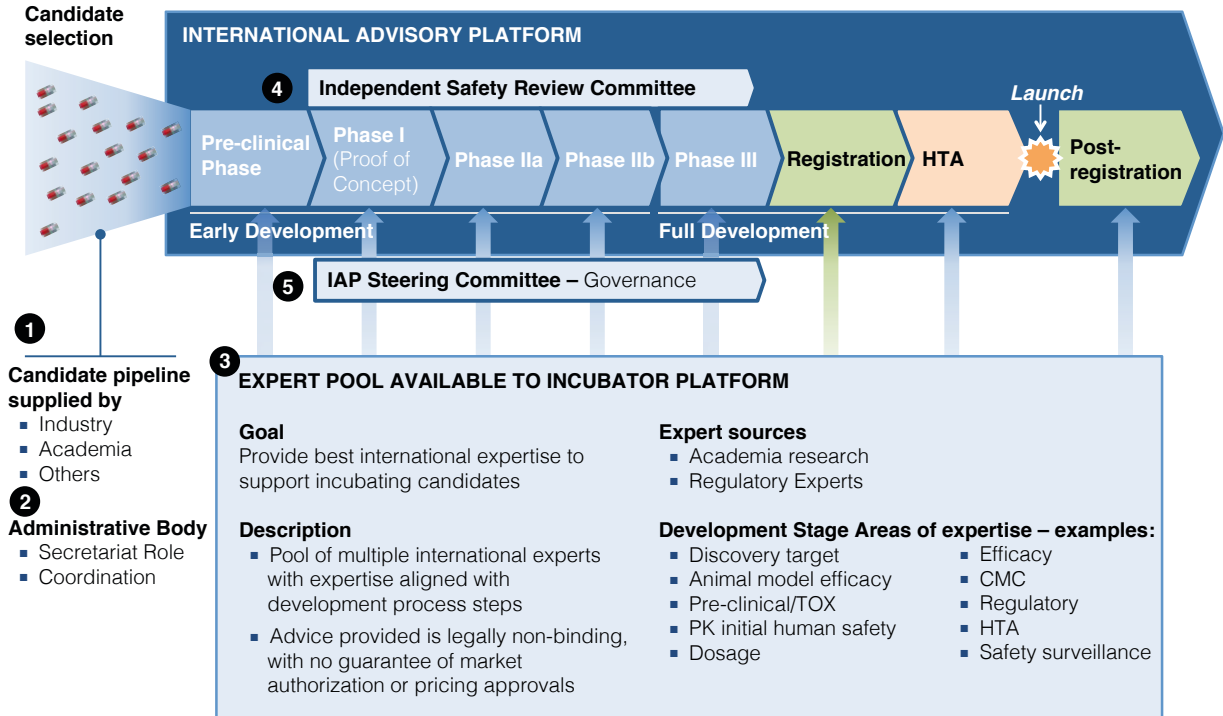## 4.   International Dementia Advisory Platform (IDAP)

I recommend that a multilateral advisory platform of international dementia experts is created, who would play an advisory role to future candidate development specific to each phase of development, covering end to end (ie from 'First in Humans' to end of Phase 3). The makeup of the panel would need to reflect all areas of expertise as illustrated in Figure 5. As different stages of development require different scientific and regulatory criteria to be met to fulfil the hypothesis for that phase. The experts can be drawn upon from a pre identified 'pool' of expertise globally, bringing together the best minds for a specific phase. In some ways this would be the equivalent to the concept of scientific advice dedicated to dementia, and would be complimentary to the MRC platform. However, regulators could not be directly involved in the IDAP to avoid potential conflict of interest, as they have the ultimate role of reviewing the development.

Companies today do go to external private advisory boards but however these can vary from region to region. Having the best expertise concentrated in a single source will not only potentially deliver the best informed advise, but will also enrich the panel itself through cross-learnings that could then be leveraged and fed back into the 'system'. To ensure safety is not compromised, I would recommend that an Independent Safety Review Committee is created that would monitor safety, independent of the advisory panel. Governance can be added to ensure a non-conflict operating model, and clearly the platform would require appropriate secretariat support.

I appreciate that this is a concept in its infancy and there are many aspects that still need to be thought through including operational sustainability. The principles are however very pertinent in that the IDAP can act as a glue that brings together all the initiatives in a single development for a given drug/drugs and potentially reduce risks for the innovator. If this is combined with seeking advice early in the development, using current joint scientific advice procedures, it can also optimise their search for a disease modifying agent.

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Figure 4: International Dementia Advisory Platform

INTERNATIONAL DEMENTIA ADVISORY PLATFORM – IDAP

Candidate selection

INTERNATIONAL ADVISORY PLATFORM

4 Independent Safety Review Committee

Launch

Pre-clinical Phase | **Phase I** (Proof of Concept) | **Phase IIa** | **Phase IIb** | **Phase III** | **Registration** | **HTA** | **Post-registration**

Early Development | Full Development

5 IAP Steering Committee – Governance

1
Candidate pipeline supplied by
- Industry
- Academia
- Others

2
Administrative Body
- Secretariat Role
- Coordination

3
EXPERT POOL AVAILABLE TO INCUBATOR PLATFORM

Goal
Provide best international expertise to support incubating candidates

Description
- Pool of multiple international experts with expertise aligned with development process steps
- Advice provided is legally non-binding, with no guarantee of market authorization or pricing approvals

Expert sources
- Academia research
- Regulatory Experts

Development Stage Areas of expertise – examples:
- Discovery target
- Animal model efficacy
- Pre-clinical/TOX
- PK initial human safety
- Dosage
- Efficacy
- CMC
- Regulatory
- HTA
- Safety surveillance

Conclusions

When I started this journey a year ago, my goal was to better understand what and where the 'hurdles' are that fuel the development failures in dementia, and more importantly to see whether anything could be done to catalyse dementia drug development success. I started with certain assumptions and have been humbled by what I have learned, and by the generosity of others who have been so willing to share and come to the call for help.

The work undertaken in the last year, supported by the UK Government, Regulators, Researchers, WDC Envoy, WHO, OECD and many others, has led to the identification of a number of key areas in which progress could be made.

They are as follows and are based on the actions for change detailed in Chapter 4:

I.   Learn from attrition analysis and reconsider molecules previously rejected by pharmaceutical developers, if the science could be viewed differently.

II.   Support the regulators who have identified and agreed a way forward on six areas of work throughout 2015 notably in relation to clinical trial efficiency, modelling and extrapolation and composite endpoints.

III. Coordinate existing pathways that are conducive to current gaps in science within existing laws and procedures that can be achieved in the context of different regulatory pathways.

IV.   Spearhead adaptive clinical development by focusing on accelerated regulatory pathways for dementia medicines.

V.   Create a multilateral advisory platform of regulators and research experts who can leverage and integrate the outcome of the above recommendations for dementia drug development.

These recommendations are by no means exhaustive but are a start to the wider challenge that was set by the G8 to find a cure or disease-modifying therapy for dementia by 2025. For the 47.5 million dementia patients worldwide, us 'doing nothing' is not an option. Neither is *'doing the same thing over and over again but expecting different results as that would be insanity'* (Albert Einstein). We must therefore be prepared to think creatively and act collaboratively so that we can overcome this challenge in an integrated way, together.

Annex 1: Abbreviations

AD   Alzheimer's disease

AIFA   Italian Medicines Agency

BfArM   Federal Institute of Drugs and Medical Devices

CEOi   The Global CEO Initiative on Alzheimer's Disease

CTEG   Clinical and Technical Expert Group

DKMA   Danish Health and Medicines Authority

EMA   European Medicines Agency

EU   European Union

FDA   Food and Drug Administration

FIH   First in Humans

IDAP   International Dementia Advisory Platform

IFPMA   International Federation of Pharmaceutical Manufacturers & Associations

MEB   Medicines Evaluations Board

MHRA   Medicines and Healthcare Products Regulatory Agency

OECD   Organisation for Economic Co-operation and Development

OHE   Office of Health Economics

PMDA   Pharmaceutical and Medicines Devices Agency, Japan

R&D   Research & Development

WHO   World Health Organization

Annex 2: References

Cameron, David, 11 December 2013, *G8 Dementia Summit: Prime Minister's speech,* [online], Available at: https://www.gov.uk/government/speeches/g8-dementia-summit-prime-ministers-speech [accessed 16th June 2015]

Cameron, David, 19 June 2014, *Global Dementia Legacy Event: David Cameron's speech,* [online], Available at: https://www.gov.uk/government/speeches/global-dementia-legacy-event-david-camerons-speech [accessed 16th June 2015]

Calcoen, D, Elias L and Yu, X, 2015, "What does it take to produce a breakthrough drug?", *Nature Review Drug Discovery,* 14 (3), pp.161-2

CPath, 2013, *U.S. Food and Drug Administration and European Medicines Agency Reach Landmark Decisions on Critical Path Institute's Clinical Trial Simulation Tool for Alzheimer's Disease* [available at: http://c-path.org/wp-content/uploads/2014/03/US-FDA-EMA-agency-reach-landmark-decisions-C-Path-clinical-trial-simulation-tool-for-alzheimers-disease.pdf] [accessed 20th July 2015]

CEOi, 2014, *A Shared Global Agenda to Fight Alzheimer's Disease: Addressing the Barriers to Innovation,* (November 12, 2014) [available at: http://www.ceoalzheimersinitiative.org/shared-global-agenda-fight-alzheimer%E2%80%99s-disease-addressing-barriers-innovation] [accessed 20th May 2015]

CEOi, 2015, *Applying Big Data to One of the World's Biggest Problems: Alzheimer's Disease,* (January 7, 2015) [available at: http://knowledgent.com/wp-content/uploads/2014/07/CEOi-KnowledgentBigDataandAlzheimersStrategyPaperSeries-FINAL.pdf] [accessed 20th June 2015]

Chan, M, 17 March 2015, *Opening remarks at the First WHO Ministerial Conference on Global Action against Dementia,* World Health Organization [online], Available at: http://www.who.int/dg/speeches/2015/dementia-conference/en/ [accessed 20th May 2015]

G8, 11 December 2013, *G8 Dementia Summit Declaration* [online], Available at: https://www.gov.uk/government/publications/g8-dementia-summit-agreements [accessed 12th June 2015]

Long, R, March 2015, *Independent expert reports on dementia drug development and regulation: Executive Summary,* [online] Available at: https://worlddementiacouncil.wordpress.com/2015/03/16/independent-expert-reports-on-dementia-drug-development-and-regulation/ [accessed 12th June 2015]

Mestre-Ferrandiz, J., Sussex, J. and Towse, A., 2012. *The R&D Cost of a New Medicine.* OHE, London: Office of Health Economics

Mestre-Ferrandiz, J., Marsden, G., forthcoming *"DRAFT: Dementia: the R&D Landscape"* OHE, London: Office of Health Economics

Morris, G, Clark, I and Vissel, B, 2014, "Inconsistencies and Controversies Surrounding the Amyloid Hypothesis of Alzheimer's Disease", *Acta Neuropathologica Communications,* 2

OECD, 2015, *Big Data for Advancing Dementia Research (12 March, 2015)* [available at http://www.oecd-ilibrary.org/science-and-technology/oecd-digital-economy-papers_20716826] [accessed 13 June 2015]

Prince, M, Guerchet, M and Prina, M, 2015, *The epidemiology, and impact of dementia. Current state and future trends,* World Health Organization, [online] Available at: http://www.who.int/mental_health/neurology/dementia/en/ [accessed 12th June 2015]

Schneider, L, Mangialasche, F, Andraesen, N, Feldman, H, Giacobini, E, Jones, R, Mantua, V, Mecocci, P, Pani, L, Winblad, B and Kivipelto, M, 2014, "Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014", *Journal of Internal Medicine,* 275(3), pp.251-283

Wimo, A and Prince, M, 21 September 2010, *World Alzheimer Report 2010: The Global Economic Impact of Dementia,* Alzheimer's Disease International

World Health Organization, 2015, *Fact sheet N°362: Dementia,* [online], Available at: http://www.who.int/mediacentre/factsheets/fs362/en/ [accessed 19th May 2015]