Office of Health Economics Research

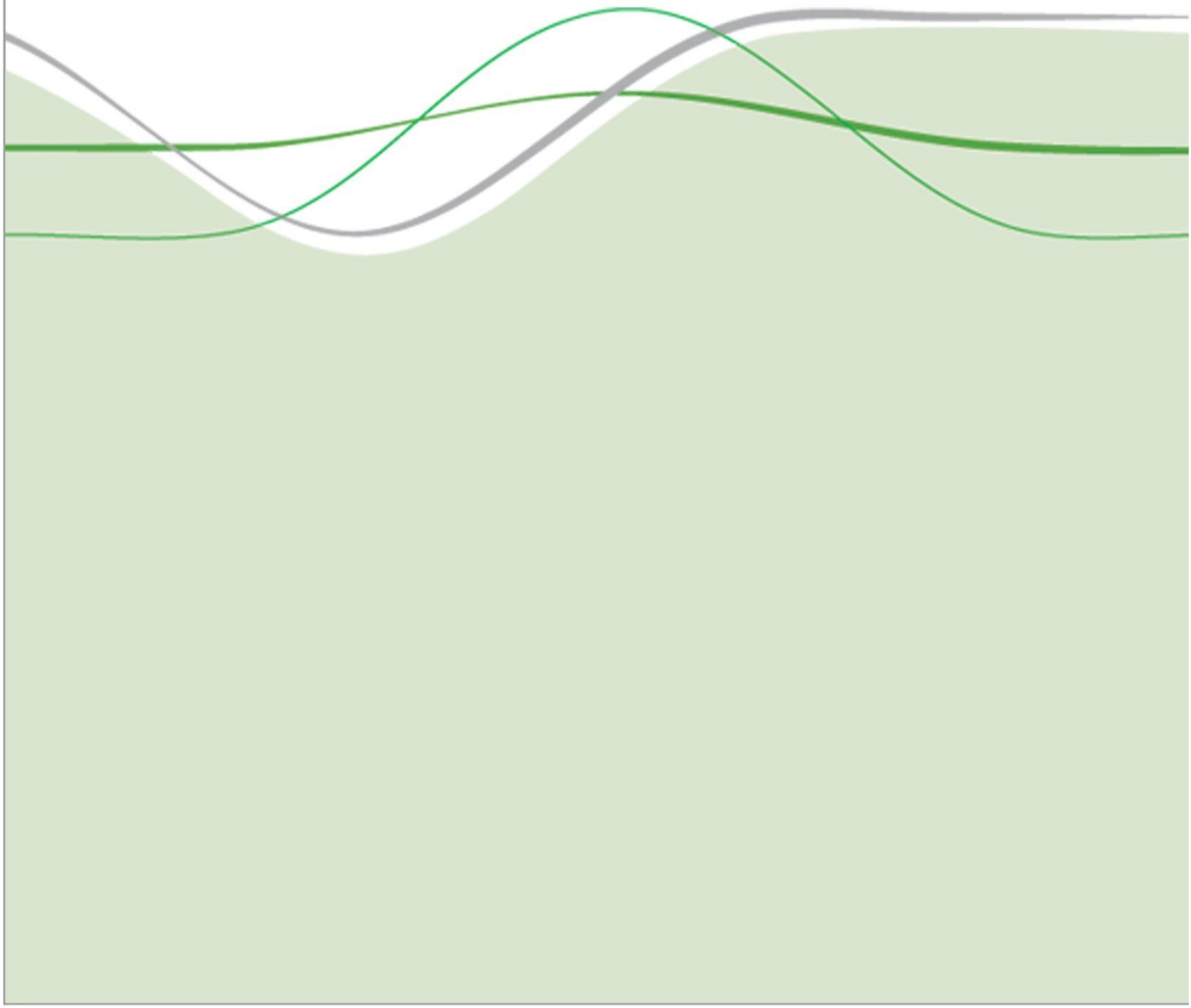
Research Report

Dementia: the R&D Landscape

28 July 2015

FINAL REPORT

Grace Marsden and Jorge Mestre-Ferrandiz



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EXECUTIVE SUMMARY

Dementia is an umbrella term for a group of conditions which typically affect memory and other cognitive functions. Dementia is progressive, costly, and can impose a substantial burden on quality of life. Much of dementia care is informal, meaning that the impact on quality of life is not restricted to the individual with dementia, but extends to carers, family, and friends. Yet, despite large numbers of people suffering with dementia at great cost to the individual and society, there are still few effective treatments.

The Dementia Integrated Development Initiative is a global programme led by the UK Government which aims to tackle the difficult topics of research gaps, development challenges, and regulation, in order to improve diagnosis and treatment of dementia worldwide. A Clinical and Technical Expert Group (CTEG) has been established by the UK Government as part of this initiative. The analysis presented in this report was commissioned by Imperial College London on behalf of CTEG to provide an overview of the R&D landscape of the past, an analysis of the current pipeline for dementia treatments, and to explore the possible reasons for successes and failures of dementia products. The report is to be used by CTEG to support the Dementia Integrated Development Initiative.

There were three stages to the analysis: 1) an initial literature review, 2) a pipeline analysis to provide an overview of the R&D landscape (including past years and current pipeline), and 3) a comparison of dementia with other therapy areas.

The literature review was a selective review, based mainly on key papers identified by members of CTEG. The pipeline analysis was extensive, and involved searching three major pipeline/clinical trials databases: The European Union Clinical Trials Register (a trial database), The U.S. National Institutes of Health database (a trial database), and IMS LifeCycle R&D Focus (a product database). The databases were searched using dementia relevant terms which were selected by CTEG, and then the databases were combined and cross-checked as far as possible. The data was analysed according to phase, stage of completion, intervention type (i.e. disease modifying and symptom modifying) and condition. Where products were listed as discontinued, we sought to identify the reasons for this termination of development. As well as detailed study of the databases, this involved approaching 13 companies to ask for additional information on the reasons for attrition of specific products. In the third and final stage, the number of treatments in the active development pipeline across all therapy areas was analysed in comparison to the number of treatments in active development for dementia, and phase success probabilities were calculated.

The literature review found that R&D costs are higher for neurology and Alzheimer's disease (AD) (as well as respiratory and oncology) than other therapy areas due to lower success rates and longer development times; this may go some way to explaining why there are fewer effective treatments in this area. In addition, the literature review highlighted recruitment of trial participants as a key challenge in the area of dementia.

Approximately 2,000 relevant trials for dementia indications were identified through the two trial databases. The majority of trials (57%) included AD as an indication, which most likely reflects the larger population size (and associated larger returns to R&D) of people with AD compared to other dementias. 110 of the trials had been terminated early, only 45% of which had a reported reason for this early termination. Of the 45% which did provide a reason, the most commonly quoted explanation was recruitment problems, echoing the findings of the literature review.

From the IMS Lifecycle (product) database, 900 different products for dementia indications were identified, 197 of which were in "active" development, and 17 of which were marketed. The majority of the products in active development were classified as disease modifying (66%) rather than symptom modifying (31%), but this split did not carry through to the marketed treatments (only 6% classed as disease modifying). A further 216 projects had been suspended or discontinued. The most common reason for suspension/discontinuation was a lack of efficacy or safety (11%). However, 74% did not report a reason. Three of the 13 companies that we approached were able to provide further information on the reason for discontinuation/suspension, but ten were not.

The discovery that 55% of prematurely ended trials, and 74% of suspended or discontinued products, did not have any information on the reason for termination, is significant. These substantial gaps drastically impede our analysis of the reasons for failures of drugs in this area, and uncover an alarming rate at which important information on the reasons for failure of drugs in this challenging disease area is lost. We are aware of at least four other privately-owned R&D databases, which OHE did not have access to. However, it is not clear whether these databases would provide more information on reasons for project discontinuation in dementia.

The comparison with other therapy areas showed that 4% of drugs in the discovery phase across all therapy areas have dementia listed as the lead indication. This proportion reduces to 1% at phase III, and 0.5% of those that are marketed. Phase success rate calculations echoed this finding, demonstrating that 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).

OHE was not able to compare the current R&D landscape for dementia with the landscape of five or ten years ago. This is because the consulted databases are "live" and hence historic versions of them are not available. We believe this comparison might provide an interesting analysis of how the R&D pipeline for dementia has changed over time. However, it will require a considerable amount of effort.

A discussion by CTEG of the implied knowledge gaps, and the reasons behind the difficulties that are highlighted in this report, is available elsewhere.

1. INTRODUCTION

1.1 Dementia

Dementia is an umbrella term for a group of progressive conditions which typically affect memory and other cognitive functions and have a substantial impact on quality of life, especially in severe cases when the individual becomes unable to look after themselves. In such cases much of dementia care is informal, as family members and friends take on a carer role, assisting the person with dementia. Indeed the vast majority of the cost of managing dementia has been attributed to informal care and social care, rather than direct medical costs (Wimo et al., 2013). The quality of life of these family members and carers can also be severely affected, as they give up their time and resources, and watch the deterioration of the people they care for.

In terms of prevalence, Alzheimer's Disease International estimated that 44.35 million people worldwide were living with dementia in 2013. This figure is predicted to increase to 75.62 million in 2030, and up to 135.46 million in 2050 (Alzheimer's Disease International, 2013). This steep projected incline in prevalence is largely due to an aging population, as the probability of developing dementia increases sharply with age. Alzheimer's disease (AD) is the most common form of dementia and is thought to be associated with abnormal accumulation of extracellular amyloid plaques and intracellular tau neurofliament (NFT) aggregates. Other forms of dementia have also been well documented, such as Lewy Body dementia, vascular dementia, and Fronto-Temporal dementia (FTD). However, the majority of late-onset cases seem to have mixed pathologies and/or may remain undetermined, in the absence of pathological evidence or other evidence ascribing to specific *known* types.

The total worldwide cost of dementia was estimated to be US$604 billion in 2010 (Wimo et al., 2013), and this figure is set to increase as prevalence figures soar over the next 20 years. Yet, despite large numbers of people suffering with dementia at great cost to the individual and society, there are still no effective treatments, other than for partial and transient symptomatic relief. Most research to date has focused on AD, but still only a handful of treatments are on the market, all of which are focused on mitigating symptoms, rather than modifying or reversing the disease. Dementia is, at present, irreversible.

1.2 Dementia Integrated Development Initiative

The Dementia Integrated Development Initiative is a global programme that has been initiated and led by the UK Government. The Initiative aims to tackle the difficult topics of research gaps, development challenges, and regulation, in order to improve diagnosis

and treatment of dementia worldwide. The initiative will call upon the expertise of regulators, clinicians, economists, patients, and the pharmaceutical industry.

The Clinical and Technical Expert Group (CTEG) has been established by the UK Government as part of the Integrated Development Initiative. CTEG's purpose is to advise on the "impact of current R&D efforts for early and late stage development within the existing regulatory pathways for dementia drug development in order to scrutinise why companies are failing, across the various models including β-amyloid peptide and tau dysregulation, ensuring one perspective does not over-dominate".

Specifically, CTEG aims to:

- Highlight successes and failures in R&D investments for symptomatic and disease modifying drugs for dementia and provide an in-depth evaluation of underlying factors, including economic and regulatory hurdles and gaps of knowledge.
- Focus in particular in gaps of knowledge in disease nosology (heterogeneity and underlying biological pathways) and in terms of R&D processes from early discovery to early development and later stages to market.
- Propose innovative approaches and methodologies to effectively address gaps and hurdles for R&D pipeline and support the Regulatory Lead in her active dialogue with regulators.

OHE were invited to conduct the analysis set out in this report to support CTEG in achieving these aims. Dr. Jorge Mestre-Ferrandiz is also a member of CTEG as a technical expert in Economics and Pharmacoeconomics; the full list of CTEG members is available in Appendix A.

1.3 Aims of this report

The aims of this report are to:

- Provide an overview of the R&D landscape of the past (over the last 10-15 years) and an analysis of the current pipeline for dementia treatments;
- Explore the possible reasons for successes and failures of dementia products.

This report will therefore provide an overall picture of the R&D landscape for dementia which will be used by CTEG to support the Dementia Integrated Development Initiative.

2. METHODS

The methods are separated into three stages; first, an initial literature review, second, a pipeline analysis to provide an overview of the R&D landscape in past years and analysis of the current pipeline, and third, a comparison of dementia with other therapy areas.

2.1 Existing literature

We sought to identify reasons for success and failures of dementia treatment, including the role of regulatory arrangements, as suggested in the literature. Key papers were identified by the CTEG and explored for discussions or analyses in this area. These papers were combined with OHE's experience and expertise in the economics of pharmaceutical R&D.

2.2 Pipeline analysis

Three pipeline databases were analysed in order to construct a detailed picture of the current pipeline for dementia treatments. The three databases consulted were:

1) The European Union Clinical Trials Register.
   This is a database of phase II-IV clinical trials that have been conducted in the European Union or European Economic Area since May 2004. The database can be accessed at https://www.clinicaltrialsregister.eu/ctr-search/search

2) The U.S. National Institutes of Health database.
   This is a database of medical studies, the majority of which are clinical trials, although there are also some observational entries. The database was set up following the US Food and Drug Administration Modernization Act (1997). The database was made available to the public in February 2000, and can be accessed at http://www.clinicaltrials.gov/

3) IMS LifeCycle R&D Focus[1].
   This is a product database which contains information on drugs undergoing development worldwide. The information in the database is gathered directly from sponsors, as well as from conferences, publications, regulatory data, and intellectual property sources. More information on this database can be found at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Technology/Syndicated%20Analytics/Lifecycle%20and%20Portfolio%20Management/IMS_Lifecycle_R&D_Focus_Factsheet.pdf. We do not know when this database started but it has information on projects since 1990.

Clinical members of the CTEG indicated that searches need to pick up the following terms:

- Late onset dementia

[1] OHE was granted free access to this database for the purpose of this project. We thank IMS Health for this.

- Familial Alzheimer's disease (fAD)
- Alzheimer's disease (AD)
- Lewy Body dementia or Dementia of Lewy Body (DLB) type
- Fronto-Temporal dementia (FTD) and Fronto-Temporal Lobe Degeneration.
- Vascular Dementia (VD)
- Mixed Dementia (i.e. late onset dementia with mixed pathologies)
- Mild Cognitive Impairment (MCI)
- Prodromal AD or pre-symptomatic AD
- Parkinson's disease with Dementia (PDD).

The exact search strategy varied according to the database, but all were designed to pick up the above terms (see Table 1).

Duplicates were removed, and clinical members of CTEG refined the datasets by excluding any studies which did not include either dementia treatments or dementia patients (for example studies of treatments for other neurological disorders). Trials of scoring mechanisms or severity tools were removed from the datasets.

Table 1: Search strategies

Database	Search strategy	Extracted
European Union Clinical Trials Register	Free text search using the following terms: • Dementia • Alzheimer's disease • Mild cognitive impairment • Fronto-Temporal Lobe Degeneration.	October 2014
U.S. National Institutes of Health database	We conducted a free text search for the term Dementia. The results were organised into disease categories. CTEG picked the following categories for extraction: • Alzheimer Disease • Alzheimer Disease Familial • Alzheimer Disease Type 2 • Cognition Disorders • Dementia • Dementia, Multi-Infarct • Dementia, Vascular • Frontotemporal Dementia • Fronto-Temporal Dementia, Ubiquitin-positive • Fronto-Temporal Lobar Degeneration • Lewy Body Dementia • Mild Cognitive Impairment • Parkinsonian Disorders.	December 2014/January 2015
IMS LifeCycle R&D Focus	We searched for the code "N7D" which is a code specific to Alzheimer's Disease. We also conducted a free text search using the following terms: • Dementia	October/November 2014

	• Mild cognitive impairment • Fronto-Temporal Lobe Degeneration	

Note that database 1 and database 2 are clinical trial registers for two different regions, and the third is a database of products. As a result, it was not anticipated that the results would be the same or similar for the three databases.

Some interventions in IMS LifeCycle have multiple indications, not all of which may be related to dementia. Therefore when extracting the data we recorded the information specific to the dementia indication as far as possible. In practice this meant that, for example, a molecule that is marketed for diabetes, but is in phase II development for a dementia indication, would be recorded as phase II.

Combining and cross-checking the databases

The databases were combined as far as possible, beginning with the two trial databases. The titles rarely matched across the two trial databases; therefore duplicates were found using the trial reference number. This was taken from the "Sponsor ID" field in the European database, and the "Other ID" field in clinicaltrials.gov. Where reference numbers from the two databases matched, the trials were checked to make sure they had the same intervention, comparator, phase and sponsor. If these criteria were met, the entry was marked as a duplicate. All duplicates were checked by a second Analyst. Where duplicates were identified the entry from the U.S. National Institutes of Health database was kept, and the entry from the European Union Clinical Trials Register was removed.

Sometimes the "other ID" field in clinicaltrials.gov also listed the European trials database reference code; this was used where possible to confirm matches.

Analysing the data

Systematic analyses were then undertaken of the combined trials database and the IMS LifeCycle database separately. Studies were analysed by phase, stage of completion, intervention type (i.e. disease modifying and symptom modifying) and condition. Hits which represented dietary supplements and imaging studies were identified by CTEG members and analysed separately from the main dataset. For the IMS database, clinical members of CTEG also categorised the hits according to whether they were symptom modifying, disease modifying, early genetic validation, or target identification and/or validation products. This classification was made based on the mechanism of action.

Following this the trial interventions listed in the combined trial database were matched with the products listed in IMS LifeCycle (using the "preferred name" as listed in the

database and common synonyms). A combined analysis (IMS lifecycle & trial databases) was then conducted.

2.2.1 Attempts to obtain further information on attrition

To explore the reasons for failure further, we approached the companies which had products listed in IMS Lifecycle that were recorded as terminated, suspended, or no longer active. We sought information on the specific reasons for failure for each product from each company. In order to ensure transparency and a systematic approach, we contacted companies through IFPMA (as a result only companies which were members of IFPMA in January 2015 were approached[2]), providing each company with a list of all hits for which we were requesting further information for. Responses were fed directly back to OHE, rather than through IFPMA, to ensure anonymity. The results were anonymised, aggregated, and analysed.

2.3 Dementia compared to other therapy areas

The pipeline for dementia treatments was compared to other therapy areas in two different ways: through looking at the absolute numbers of treatments in the pipeline, and by comparing development phase success rates.

2.3.1 Number of treatments in the pipeline

Details of pipeline drugs across all therapy areas were extracted from IMS Lifecycle in February 2015; this was to allow comparison of the number of drugs in the dementia pipeline relative to other therapy areas. We focused on projects in active development, and categorised drugs by their lead indication. It was necessary to concentrate on lead indications for this analysis so that each drug could be categorised into just one therapy area with no overlap (secondary indications may be for a different therapy area). We took the number of treatments with dementia as the lead indication directly from the dataset produced in the pipeline analysis; therefore this had been refined by CTEG, with all irrelevant hits removed. These hits irrelevant to dementia remained in the full database of all therapy areas. We analysed the numbers of drugs in each therapy area by phase, compared to dementia.

2.3.2 Success rates

IMS Lifecycle R&D focus indicates which products have been terminated, at which stage of development this decision was made, and in what year. We used this information, in combination with relevant information obtained from the companies (see section 2.2.1),

[2] With the exception of one non-IFPMA company, as a CTEG member knew the CEO of that company.

to calculate phase success rates for dementia treatments, and compared these to other therapy areas (as found in published literature). This was done with the aim of identifying whether there is a particular stage of development which is troublesome for development of dementia treatments, compared to other therapy areas.

Hay and colleagues (2014) calculate clinical development success rates across 835 drug developers using data on phase transitions for the period 2003 - 2011. They looked across the whole industry, rather than focus on one disease area, and also broke down their results into different disease categories (infectious, autoimmune, endocrine, respiratory, neurology, cardiovascular, oncology, and other) - dementia is represented as part of the Neurology category. Further evidence is provided by DiMasi et al. (2010) who examined the development histories of investigational compounds of the 50 largest pharmaceutical firms (by sales in the US) from the time point at which they first entered clinical testing during 1993 and 2004, and followed them through to June 2009, to calculate success rates. We use the same approach as these published studies to calculate phase success probabilities for dementia using the IMS data. We then compared our results for dementia to those for the whole industry (the latter provided by these two published studies).

To do this, let $drug_{NXT}$ represent the number of drugs which move to phase X+1, and $drug_{DIS}$ represent the number of drugs which were suspended, discontinued, or became non-active at phase X. Then, "Phase success" is calculated as follows:

$$n = drug_{NXT} + drug_{DIS}$$

and

$$\text{Phase success probability} = drug_{NXT}/n$$

We assume that all drugs in phases later than phase X must have completed phase X successfully. In practice this means:

$$drug_{NXT} = \text{sum of drugs in all phases post phase X}$$

Products still in active development in phase X were not included in the calculations for phase X as it was not known whether they will successfully complete their current phase. This is analogous to the approach taken by Hay et al. (2014) and DiMasi et al. (2010), who focus on data of phase transitions only. We do however, also calculate maximum and minimum phase success probabilities, in which all products in active development in phase X are assume to succeed (maximum), and fail (minimum).

Hay et al. (2014) also calculate likelihood of approval (LOA) which is the probability of reaching FDA approval. This is calculated as the product of the phase success probabilities leading to FDA approval. The n value is the sum of the n values for each

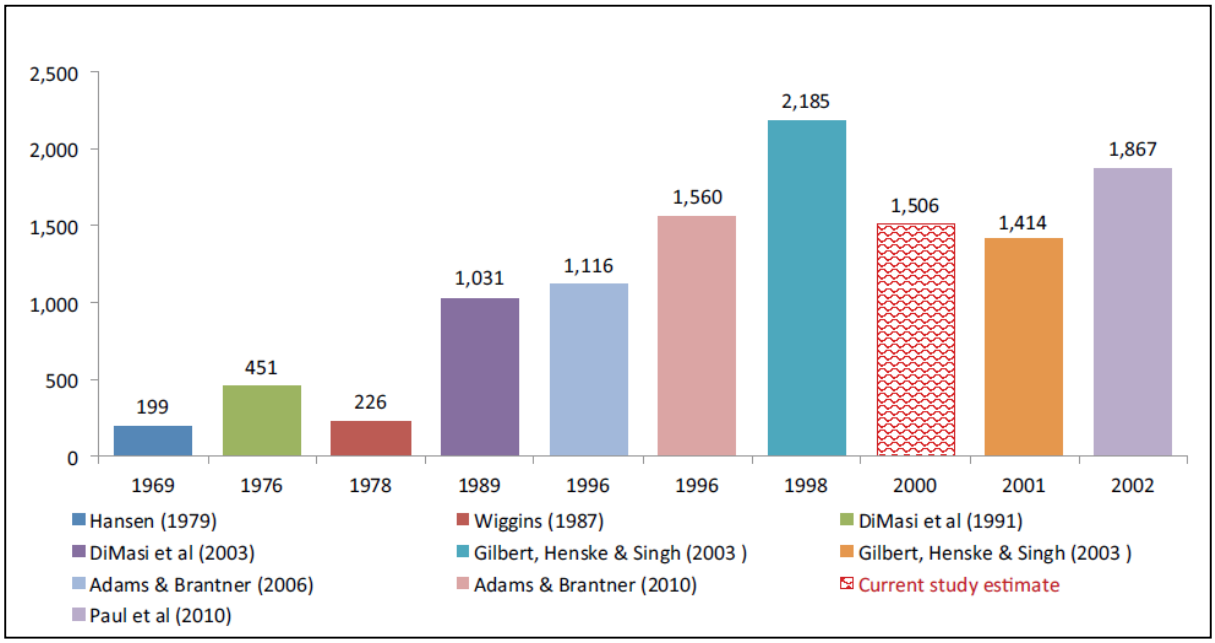
phase success probability leading to FDA approval. We calculate likelihood of reaching the stage “marketed”, as an approximation of LOA.

3. RESULTS – EXISTING LITERATURE

3.1 R&D costs in general

Mestre-Ferrandiz et al. (2012) present an overview of the studies estimating the R&D costs of a new medicine, as well as providing a new estimate. This work shows an increase in costs from £125 million ($199 million) per new medicine in the 1970s to £1.2 billion ($1.9 billion) in the 2000s (both in 2011 prices). The new estimate provided by Mestre-Ferrandiz et al. (2012), based on new data for 1998-2002, agrees with comparable analyses for the same time period. Figure 1 shows graphically how the estimates of mean R&D cost per successful new molecular entity (NME) differ across studies. Each bar represents one study, plotted at the middle of the time interval when projects in each study were first tested in humans. For example, projects included in Paul et al. (2010) were first tested in humans between 1997 and 2007; the middle year is thus 2002. The hatched bar represents OHE's new estimates based on CMRI[3] data.

Figure 1 Mean R&D costs per successful new molecular entity (NME) by middle year of study data (2011 US$m)



Source: Mestre-Ferrandiz et al. (2012)

Four major factors drive R&D costs: out-of-pocket expenses, success/failure rates, R&D times and the cost of capital. These four factors are increasing R&D costs, by: (1) higher out-of-pocket costs, up nearly 600% from the 1970s to the 2000s; (2) lower success rates for clinical development as tougher therapeutic areas are tackled, from 1 in 5 in

[3] CMRI, acquired by Thomson Reuters in 2006, began researching issues in R&D in the early 1980s as the Centre for Medicines Research (CMR). It maintains various databases of drugs/biologics and biopharmaceutical industry activities.

the 1980s to 1 in 10 in the 2000s; (3) increases in R&D times as both regulation and science have become more complex, from six years in the 1970s to 13.5 years in the 2000s; and (4) increases in the cost of capital — i.e. providing returns to funders that reflect the high risks of investing in medicines R&D, from 8% in the 1970s to 11% in the 2000s.

As argued by Mestre-Ferrandiz et al. (2012), mean estimates of R&D costs per new medicine, and in particular drawing conclusions based on comparisons between estimates, should be treated with caution because of important differences in the studies, particularly in the use of different databases of drugs. Moreover, important differences exist across subgroups of drugs—for instance, by therapeutic area. This is particularly important for dementia, as noted in the next section.

3.1.1 Reasons for project discontinuation

Several articles in the published literature explore reasons for project discontinuation. Overall, the analysis supports the view that commercial considerations have been increasingly important as a cause to discontinue projects. Two earlier articles (DiMasi (1995) and DiMasi (2001)) explore reasons for research termination, grouped in three major categories: Safety ('human toxicity' or 'animal toxicity'); Efficacy ('activity too weak' or 'lack of efficacy'); and Economics ('commercial market too limited' or 'insufficient return on investment'). This work shows that over time 'economic' reasons had become more prevalent and that compounds that failed for economic or efficacy reasons were terminated much more frequently in late clinical testing phase. Economic reasons (as defined above by DiMasi (1995; 2001) as 'commercial market too limited' or 'insufficient return on investment') were the most frequent reason for termination in late-stage clinical development.

Kola and Landis (2004) have confirmed that "commercial considerations"[4] have become more important, relative to more technical reasons, such as adverse pharmacokinetics (PK) and bioavailability. Other researchers (Gordian et al., 2006) have explored Phase III trial failures reported from 1990 to 2002 focusing on small molecules (i.e. excluding biologics) from large pharmaceutical companies and found that a significant predictor of failure was whether drugs used a novel mechanism of action, with drugs using novel mechanisms failing more than twice as often in Phase III. In addition, drugs that had

[4] Kola and Landis (2004) do not provide a definition of "commercial considerations" as a criterion for attrition; however, they argue elsewhere in their paper that "another area in which attrition can be reduced is the discontinuation of compounds for commercial reasons either by gaining alignment between the research, development and marketing functions much earlier in the drug discovery process, and/or by better due diligence with respect to competitor development programmes and the likelihood of true differentiation from such drugs that might be ahead in development" (page 714).

both a novel mechanism and less objective endpoints failed 70% of the time; drugs with a validated mechanism and objective endpoints failed just 25% of the time (Gordian et al, 2006). Wilsdon, Attridge and Chambers (2008) argue that pressure is greater to terminate products that will not be differentiated in the market.

3.2 R&D costs for dementia

When explaining the rise in R&D costs over the last decades, Mestre-Ferrandiz et al. (2012), highlight three particularly complex therapeutic areas to tackle: neurology (Alzheimer's), autoimmune diseases (arthritis), and oncology. In addition, the authors argue that most recent analyses suggest that the most expensive therapeutic areas in terms of drug R&D costs are neurology, respiratory and oncology. This is because drug discovery and development in these categories experience lower success rates and longer development times. By comparison, anti-parasitics and therapeutic agents for HIV/AIDS have the lowest R&D costs because of higher success rates and shorter development times. Table 2 shows how success rates compare across therapeutic areas – where the cumulative entry probability for Alzheimer's (and 'neurological' disorder) is amongst the lowest.

Table 2: Probability of market entry

Disorder		Entry probability (%)			Cumulative[1] (%)
	n	Phase II	Phase III	Approval	
Blood	163	60	57	25	9
Cardiovascular	280	69	4	22	6
Dermatological	122	8	44	29	11
Genitourinary	12	92	5	37	20
HIV/AIDS	108	75	50	36	14
Cancer	68	78	46	20	7
Musculoskeletal	134	73	41	22	7
Neurological	192	73	47	22	8
Anti-parasitic	20	100	67	53	36
Respiratory	165	68	31	16	3
Sensory	53	88	60	40	21
Primary Indication					
AD	46	65	46	25	7
Rheumatoid arthritis	51	91	33	23	7
Asthma	74	81	36	26	8
Breast Cancer	54	96	58	44	24
HIV/AIDS	89	83	56	44	20

[1]cumulative = the product of the three probabilities
Source: Adams and Branter (2006) as reported in Mestre-Ferrandiz et al. (2012)

When the four factors mentioned above are put together to estimate the R&D cost by therapeutic area, it is not surprising that costs for dementia treatments are amongst the highest – see Table 3.

Table 3. R&D Costs for new drugs by disorder and primary indication

Disorder	**Cost (2011 USDm)**
Blood	1,164
Cardiovascular	1,140
Dermatological	870
Genitourinary	816
HIV/AIDS	694
Cancer	1,339
Musculoskeletal	1,216
Neurological	1,306
Anti-parasitic	583
Respiratory	1,457
Sensory	833
Primary indication	
AD	1,161
Rheumatoid arthritis	1,203
Asthma	951
Breast Cancer	784
HIV/AIDS	616

Note: All values are adjusted to 2011 dollars using the US GDP implicit price deflator from the Word Bank
Source: Adams and Branter (2006) as reported in Mestre-Ferrandiz et al. (2012)

Mestre-Ferrandiz et al. (2012) conclude that "Neurology is currently one of the most 'expensive' therapeutic areas, i.e. total capitalised costs are higher for NMEs in this area. 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" (p.51).

Calcoen and colleagues (Calcoen et al., 2015) have reported success rates achieved in drug research and development for Hepatitis C, AD and drugs for antibiotic-resistant infections, in particular those due to methicillin-resistant Staphylococcus aureus (MRSA). For AD in particular, all four marketed drugs were approved a decade ago and are symptomatic treatments (donepezil, rivastigmine, galantamine, memantine). The Figure below is extracted from their paper, and shows the low overall success rate for AD (0.5%).

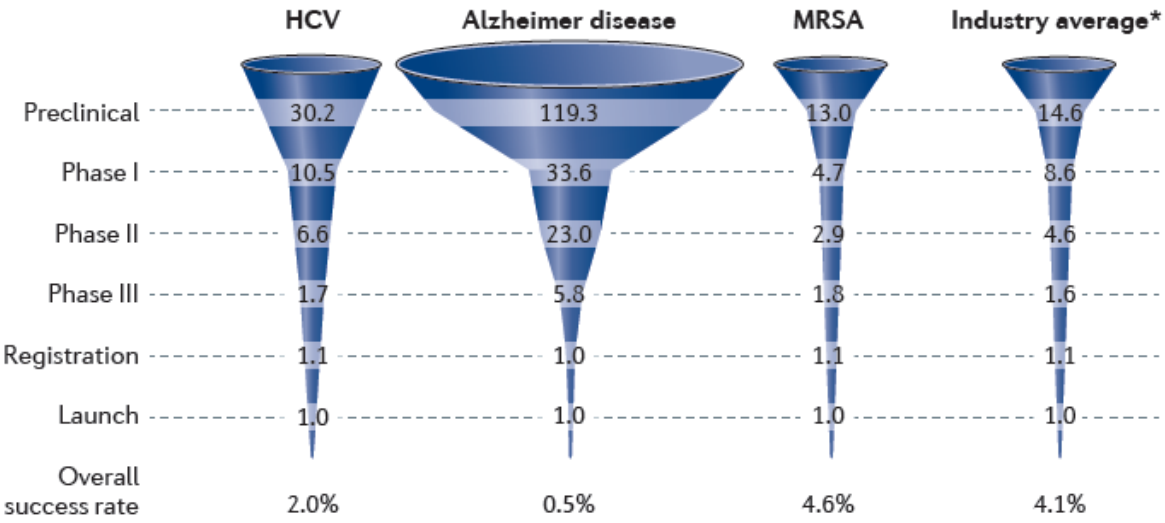


Figure 2 | **Attrition profiles across therapeutic areas.** The funnels illustrate the average number of compounds needed at each development stage to result in one launched drug for hepatitis C virus infection, Alzheimer disease and antibacterial indications that include infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). The preclinical stage includes lead optimization and preclinical phases, and the overall success rate from discovery to launch assumes 60% success rate in the discovery stage. Sources: *Paul *et al.* (*Nature Rev. Drug Discov.* **9**, 203–214; 2010); Pharmaprojects; EvaluatePharma; BCG analysis; see Supplementary information S1 (box) for details.

Source: Calcoen et al., 2015

The next section highlights some very preliminary findings based on a quick review of published papers which were shared between CTEG members, and further reviews carried out by OHE.

3.3 R&D for dementia – key challenges identified to date

A number of factors have been highlighted to reinforce the challenges around R&D for dementia, and AD in particular[5].

PhRMA (2013) has found that from 1998 to 2011, there were 101 unsuccessful attempts to develop drugs to treat AD. During this period, only three new medicines were approved to treat the symptoms of AD. This implies that for every one research project that yielded a new medicine, 34 fell short.

PhRMA (2013) have suggested that a key challenge for undertaking clinical trials for AD relates to recruiting patients – both for preventative studies (patients who have not yet shown symptoms for AD) and treatment studies (which require patient participants,

[5] Some of the references used here also offer some recommendations to address the challenges highlighted in this note. We have not reported on these for the purposes of this draft.

many of whom are already suffering from diminished decision making skills). Such challenges include (PhRMA, 2013):

- Recruiting and retaining clinical trial participants
- Gaining information consent from patients who are already suffering from the effects of the disease
- Involving caregivers in research trials, adding an extra burden to their daily routine.

Ousset et al. (2014) have conducted an analysis of the pipeline for treatments of AD, and have reached similar conclusions. They argue that during the decade from 2002 to 2012, 243 (99.6%) of the 244 agents tested failed to achieve their primary endpoint. Only one drug (the NMDA-receptor antagonist memantine, Namenda®), was approved for the symptomatic treatment of moderate to severe dementia. The following key challenges and reasons for failures in drug development for AD have been outlined by the authors:

- Tested compounds that were truly ineffective or unsafe
- Inappropriate trial designs, enrolment of subjects not likely to benefit from the treatment during the trial period
- Preclinical models that were not predictive of human outcomes
- Limited information from phase II studies that were unable to predict success in phase III
- The absence of an expected decline in the placebo arm of the trials, and/or
- High variability across multiple study sites interfering with signal detection.

Ousset et al. (2014) have also discussed the challenges and opportunities of the use of biomarkers in clinical trials for dementia, both as inclusion criteria and outcome measures. These authors found an increased use of biomarkers in clinical trials for AD between 2008 and 2013. The trade-offs in using biomarkers are:

- better identification and selection of affected individuals even when symptoms are subtle – enhancing the ability of the trial to correctly assess treatment efficacy
- reduction of volunteers who can be included in the trial because they do not meet inclusion criteria, and added patient burden (increasing difficulty of recruitment).

Overall, however, Ousset et al. (2014) conclude that "use of biomarkers as inclusion criteria…may complicate recruitment procedures, but is considered necessary to assess efficacy of targeted therapies" (p.42).

Schneider et al. (2014) set out to review the development of treatments for AD during the past 30 years and have addressed issues such as the evolution of inclusion criteria in

clinical trials, outcomes in clinical trials, introduction of biomarkers and regulatory considerations[6].

In an earlier paper, Mangialasche et al. (2010) have attempted to evaluate failures in the clinical development of disease-modifying therapies. They have outlined some key challenges and problems in randomised clinical trials (RCT) for AD, picking up some of the issues around drug choice and development programmes raised previously. These include target group selection, RCT protocols and multicentre, multi-country RCTs.

More recently, Vellas et al. (2013) have reviewed the lessons learned from the recent bapineuzumab and solanezumab trials. They listed the possible factors that "may have contributed to the disappointing results in phase III" (pp. 439), but concluded that "all of these possible explanations for the lack of an apparent treatment effect are speculative and require further investigation" (p.439). They argue, however, that biomarkers have the potential to be very useful at all stages of drug development. These authors provide three reasons for this: "first, to confirm that a test compound hits its target; second, to assess whether hitting the target alters the pathophysiology of the disease; and third, to determine whether altering the pathophysiology improves a person's clinical status, or reflects treatment response or side effects of new treatments. Used in clinical trials, therefore, biomarkers offer the potential for diagnosis, sample enrichment, characterising the mechanism of drug action, monitoring disease progression, and assessing response to treatment. In addition, because biomarker profiles reflect different stages of the pathogenic process, they can be used to select optimal subjects for trials of different drugs and different forms of dementia at different stages of disease" (page 441).

Solomon et al. (2012) explored the practical experiences of staff and participants in amyloid immunotherapy RCTs between 2005 and 2011 at the Clinical Trial Research Unit, Karolinska University Hospital (Sweden) and reached similar conclusions.

[6] Some of the regulatory considerations discussed by Schneider et al. (2014) include: provision of standards for later phase development and regulatory agencies encouraging companies to seek scientific advice meetings in early stages of development programmes.

4. RESULTS: PIPELINE ANALYSIS

4.1 European Union Clinical Trials Register

The search for "Alzheimer's" produced 241 hits; the search for "Dementia" produced 384 hits. The search for "Mild cognitive impairment" produced 52 hits, and the search for "Fronto-Temporal Lobe Degeneration" produced 0 hits. Having found no hits for Fronto-Temporal Lobe Degeneration we searched again for "temporal lobe". This search identified 12 hits.

Once duplicates were removed, 435 records remained. The screening of the records by clinical members of CTEG led to removal of 186 records (for example, trials concerned with schizophrenia [118 removed], fractures [four removed], and cancers [four 1removed]). One additional study was removed as the purpose was to validate a scale for measuring outcomes in AD. The final number of records included was 248.

4.2 U.S. National Institutes of Health database

The free text search for "Dementia" produced 2,506 hits, and 805 different categories. The number of hits per selected category were as follows:

- Alzheimer Disease: 1,240
- Alzheimer Disease Familial: 1,240
- Alzheimer Disease Type 2: 5
- Cognition Disorders: 2,247
- Dementia: 2,351
- Dementia, Multi-Infarct: 6
- Dementia, Vascular: 61
- Fronto-Temporal Dementia: 69
- Fronto-Temporal Dementia, Ubiquitin-positive: 69
- Fronto-Temporal Lobar Degeneration: 86
- Lewy Body Dementia: 36
- Mild Cognitive Impairment: 318
- Parkinsonian Disorders: 120.

Once duplicates had been removed 2,399 hits remained. The screening of the database of CTEG members led to removal of a further 223 hits. The final number included was 1,920.

4.3 Combined trial database: European Union Clinical Trials Register & U.S. National Institutes of Health database

The European Union Clinical Trials Register and the U.S. National Institutes of Health database were put together to produce the combined trial database. Removal of 158

duplicates left a total of 2,010 entries in the combined database.[7] Of these, 127 were imaging studies, and 64 were for dietary supplements; these are analysed separately from the main dataset.

Results are shown in Figure 2. We have differentiated between "commercial" and "non-commercial" trials. The European Clinical Trials register includes a category for whether the sponsor is commercial or not, therefore this information was taken directly from the database. For hits from the U.S. National Institutes of Health database, the commercial or non-commercial status was determined by OHE analysts. The sponsor was considered to be commercial if they were profit making organisations which produced and sold goods. By implication, the majority of the commercially sponsored trials included in this analysis are trials undertaken by the pharmaceutical industry. Note that non-commercial trials can be studies of commercial agents and also that in some cases the sponsor can be non-commercial but the study still funded by industry (for example a pharmaceutical company funding a non-commercial academic group, which in turn sponsors a trial).

Looking first at the imaging studies, nine of these were phase 0 trials, 35 were phase I, 22 were phase II, 21 were phase III, and six were phase IV. One trial reported it was phase I and phase II, two trials reported they were phase II and phase III, and one reported that it was phase II and phase IV (see Figure 2). Thirty did not report trial phase (some of these were observational studies). Forty-five different imaging agents were identified from these trials. Table A1 in Appendix B outlines each imaging agent and its latest phase in the trial database. Fifty-five of the 127 trials were completed; 15 had been terminated; 56 were ongoing or active. The status of the final trial was unknown.

Of the 56 dietary supplement trials, one was phase 0[8], two were phase I, 16 were phase II, 10 were phase III, and nine were phase IV. Three trials reported that they were phase I and phase II, two trials reported they were phase II and phase III, and one reported that it was phase III and phase IV (see Figure 2). Twenty did not report study phase. The trials included 58 different dietary supplements - Table A2 in Appendix B

[7] Three pairs of duplicates did not have the same "phase" information but all other information was the same, and thus these were considered duplicates. On all three occasions the phase of study was recorded as phase I in the U.S. National Institutes of Health database, and phase II in the European trial database. The European database only includes trials of phases II-IV, therefore it was assumed that these three trials had been recorded as phase II to allow inclusion in the database, but were actually phase I trials. They have been included in the analysis as phase I.

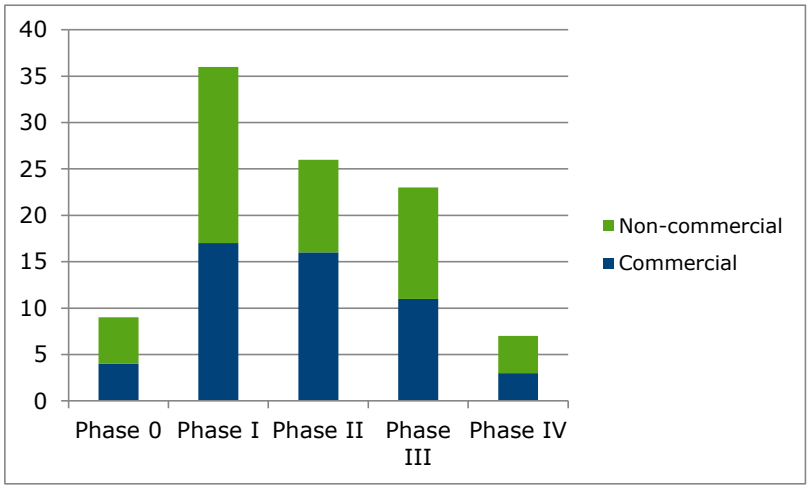
[8] Phase 0 trials are "experimental medicine" clinical studies in which participants are given micro/ sub-therapeutic doses of the drug in question, much lower than the therapeutic dose. They are used to establish at a very early stage whether or not the drug behaves in human subjects as was expected from preclinical studies. By definition, Phase 0 studies cannot provide safety or efficacy data.

outlines each dietary supplement and its latest phase in the trial database. Twenty-six of the 64 trials were completed; four had been suspended or terminated; 28 were ongoing or active. The statuses of six trials were unknown.

Of the 1,819 trials in the main dataset, 11 were phase 0, 230 were phase I, 383 were phase II, 231 were phase III, and 177 were phase IV. Forty trials stated they were phase I and phase II; 37 stated they were phase II and phase III; one study stated it was phase II, III and IV. Phase was not recorded for 709 trials, some of which were reported as being observational studies. This is shown in Figure 2.

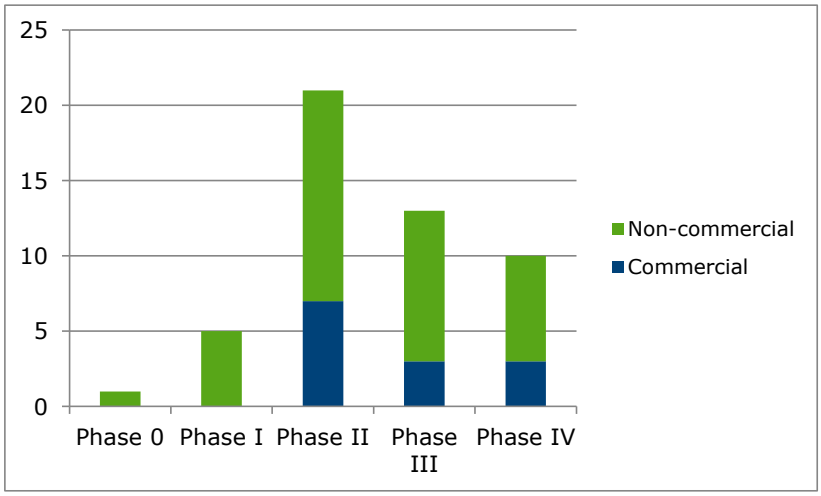
Figure 2. Number of trials by development phase (combined trials database)

2a. Imaging studies



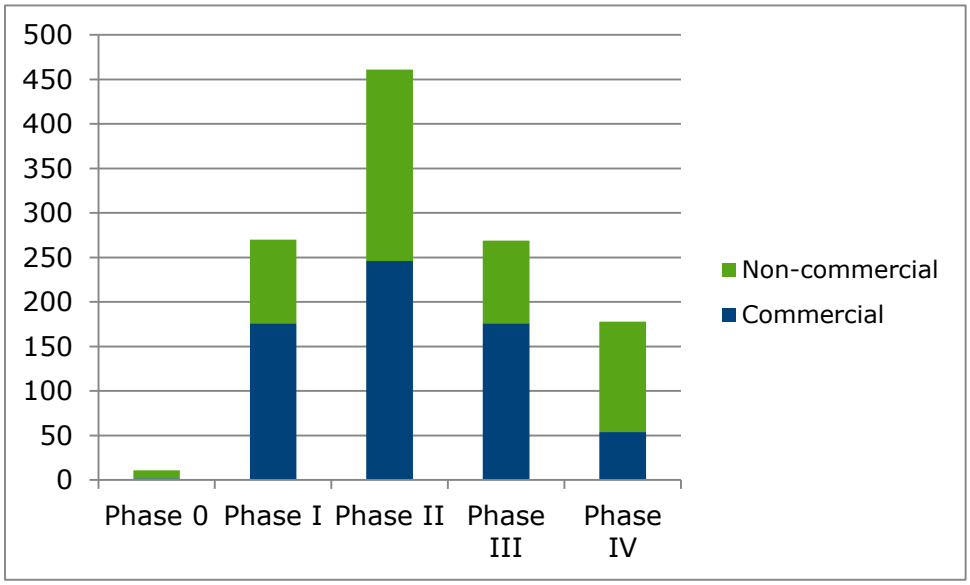
Source: OHE from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015)

2b. Dietary supplement studies



Source: OHE from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015)

2c. Main dataset



Source: OHE from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015)
Note: trials that report they are for more than one stage are shown in both columns

Considering trials of all phases (main dataset), 1,040 trials (57%) included AD as an indication. Other indications included MCI (165 studies; 9%), dementia (434 studies; 24%), Front-Temporal dementia (29 studies; 2%), vascular dementia (47 studies; 3%), Parkinson's disease or dementia associated with Parkinson's disease (56 studies; 3%), and cognitive decline or cognitive disorders (46 studies; 3%). Note that these figures are not necessarily additive, as some trials listed multiple indications. Still, it is clear that the vast majority of trials are undertaken for AD.

In terms of trial status, 862 of the 1,819 trials in the main dataset have been completed. A further 728 are ongoing (one of which had been restarted) in at least one of the trial countries, and a further 129 have been suspended (seven), withdrawn (12), or terminated (110). The status of 100 is unknown.

Of the seven suspended trials, one reported that this was due to recruitment/enrolment problems, and one due to staff attrition. No reason was given for the remaining suspended trials.

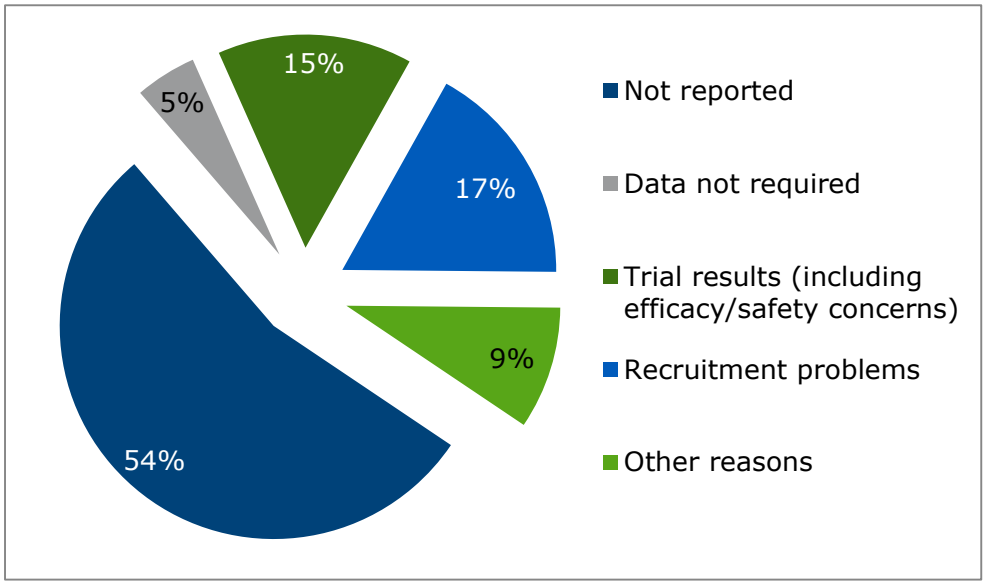
Of the 12 withdrawn trials, one reported that this was due to recruitment/enrolment problems; one reported that the trial had been redesigned, and one reported that the

study was withdrawn due to changes in the standard of care. No reasons were provided for why the remaining nine trials had been withdrawn.

Of the 110 terminated trials, 20 reported that this was due to recruitment/enrolment problems, 14 reported that the intervention did not demonstrate sufficient efficacy for the trial to continue (eight phase I, five phase II, one phase I and II), six reported that the data was no longer required for further development of the intervention, four reported that results of the trial or a parent trial suggested that the study should be terminated (two phase II, two phase III), four reported termination due to staff attrition or organisational changes, two reported a loss of funding, two indicated the study was being revised, one reported safety concerns (phase I and II), and one reported that the study objectives had been met. The remaining 56 terminated trials did not have a reason.

Figure 3 shows these results for the suspended, withdrawn, and terminated trials all together. It is clear from the figure that recruitment problems are the most common reason given for trial termination. This was discussed within CTEG. It was felt that recruitment should be raised as a problem for dementia development studies, to be further evaluated by the group. However, CTEG also noted that the reason for withdrawal/suspension/termination was not reported in 54% of the trials, therefore it cannot be concluded that problematic recruitment is the most common reason for trial termination.

Figure 3. Reasons for termination of trials (n = 129)

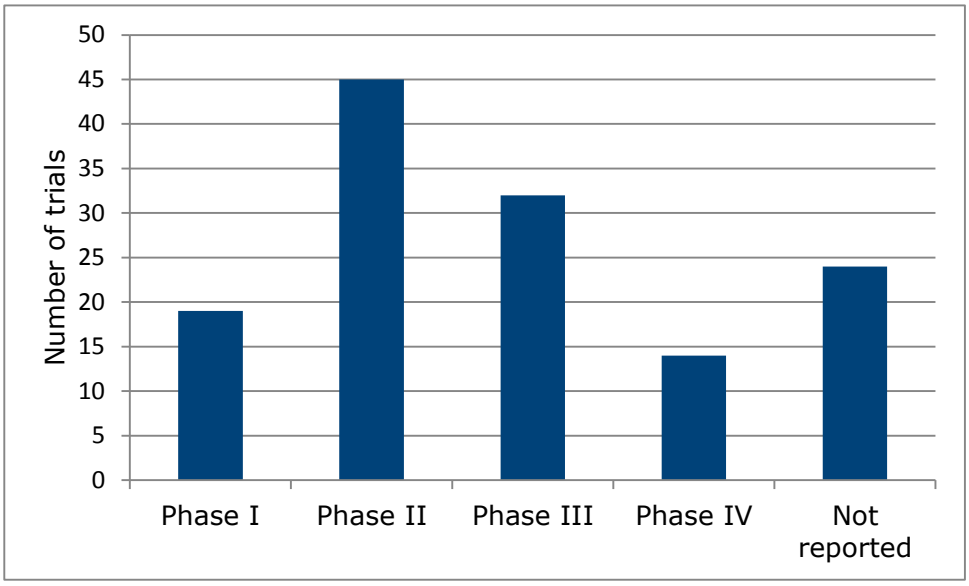


Key: Other reasons = staff attrition and organisational problems, loss of funding, study revision, and study objectives met

Source: OHE analysis from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015).

Figure 4 shows the suspended, withdrawn and terminated trials by phase; the majority of these were in phase II. However, the majority of the trials in the database were also in phase II (see Figure 2), therefore this does not necessarily indicate a particular problem with phase II trials. In fact, 45 out of a total 461 (9.8%) phase II trials had been discontinued, whereas 32 out of a total 269 (11.9%) phase III trials had been discontinued; therefore a larger proportion of phase III trials were discontinued than phase II. The equivalent percentages for phase I and phase IV are 7.0% and 7.9%.

Figure 4. Number of suspended, withdrawn and terminated trials by development phase



Source: OHE analysis from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015).
Note: trials that reported more than one phase are included in both columns.

We now repeat the analysis including only those trials which were sponsored by commercial organisations – those categorised as "commercial" trials in Figure 2. The dataset included 770 trials such trials (38% of the full dataset).

Fifty-four of these are imaging studies (four phase 0, 16 phase I, 14 phase II, 10 phase III, three phase IV; one phase I and II, one phase II and III, five not reported). These 54 trials were based around 20 different imaging agents (see Table A1 in Appendix B), compared to 45 when including non-industry sponsored trials. CTEG noted that some of these imaging agents have undergone additional trials in industry but within different populations, and therefore may not be picked up by our Dementia search of industry

trials. Thirty-three of the 54 trials were completed; five had been terminated or withdrawn; 16 were ongoing.

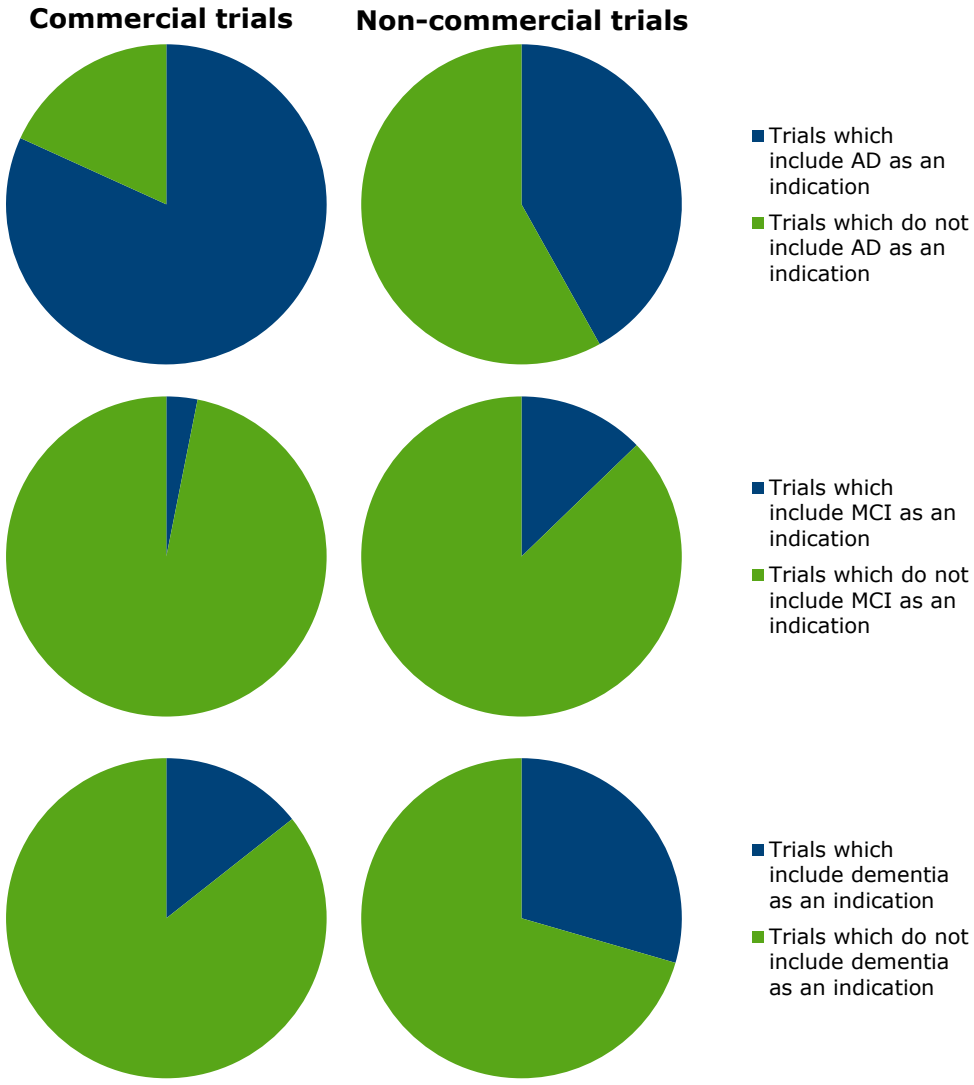
There were 16 trials of dietary supplements (six phase II; two phase III, three phase IV, one phase II and IV, and four with which trial phase not reported). These 16 trials included 14 different dietary supplements (see Table A2, Appendix B). Five trials were complete, eight were ongoing, one had been suspended, and the status of the final two was unknown.

There were 700 commercially sponsored trials in the main dataset (hits which were not dietary supplements or imaging studies), and 1,119 trials classified as "non-commercial". Two of the commercially sponsored trials were phase 0, 165 were phase I, 223 were phase II, 164 were phase III, and 53 were phase IV. Eleven trials were phase I and phase II, a further 11 were phase II and phase III, and one was phase II, III and IV. Seventy did not report trial phase (some of which were observational). This is shown in Figure 2.

Considering commercially sponsored trials of all phases, 575 (82%) trials included AD as an indication. Other indications included MCI (22 studies; 3%), dementia (101 studies; 14%), frontotemporal dementia (6 studies; 1%), vascular dementia (21 studies; 3%), Parkinson's disease or dementia associated with Parkinson's disease (11 studies; 2%), and cognitive decline or cognitive disorders (5 studies; 1%). As before note that these figures may not be additive, as some trials listed multiple indications.

Figure 5 shows the difference in the proportions of trials for AD, MCI, and Dementia. It is clear from the diagrams that there is a notable difference in the focus of commercial and non-commercial trials; a much higher proportion of commercially sponsored trials include AD as an indication, and a much lower proportion include dementia or MCI as an indication, compared to non-commercial trials. CTEG indicated that this may reflect a perception of a more lucrative market for industry in the area of AD than for other dementias, as AD is the most commonly diagnosed form of dementia.

Figure 5. Indications for trials (commercial and non-commercial)



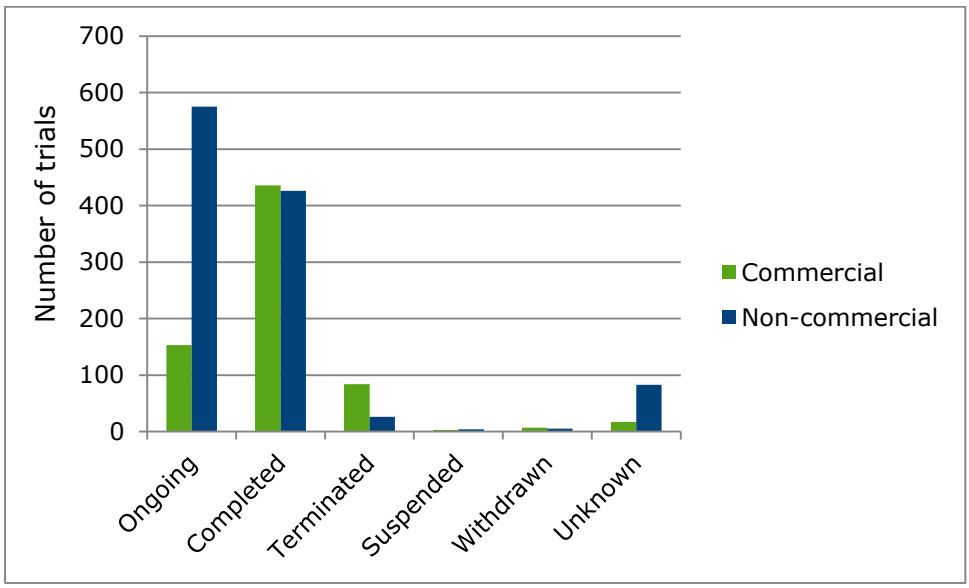
Source: OHE from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015)

Note: These different indications are not all shown in the same pie chart because the figures are not additive: one trial can report multiple indications. Each pie represents all commercial or all non-commercial trials, and the blue segment shows the proportion which includes AD, MCI or dementia as an indication respectively.

Figure 6 shows the status of the 700 commercial trials: 153 of the 700 (i.e. 22% of all commercial trials) are ongoing in at least one of the participating countries. A further 436 (62%) have been completed, and 94 (13%) have been terminated, suspended, or withdrawn. The status of 17 (2%) is unknown. Figure 6 also compares the status of the commercial and non-commercial trials as a percentage of the total number of trials in

each sponsor category; for example 153/700 = 22% of commercial trials are ongoing, compared to 575/1119 = 51% of non-commercial trials. The figure shows that a much greater proportion of the commercially sponsored trials (62%) have been completed compared to the non-commercial trials (38%). The majority of the non-commercial trials are ongoing (51%).

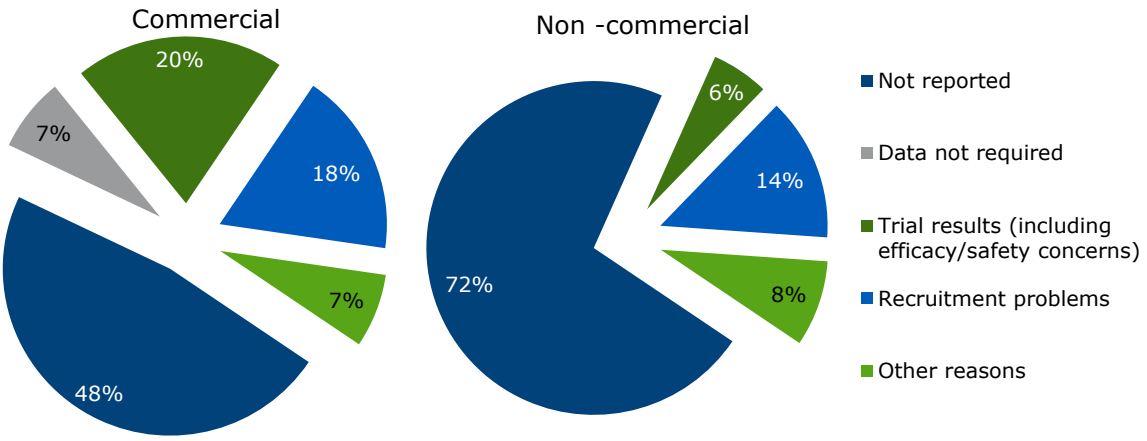
Figure 6. Status of trials (commercial and non-commercial)



Source: OHE analysis from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015).

Finally, Figure 7 shows the reasons for withdrawal, suspension or termination of commercial and non-commercial trials. The figure shows that a much larger proportion of non-commercial trials did not have a reason for withdrawal, suspension or termination than the commercial trials. The most commonly reported reason for withdrawal, suspension or termination of commercially sponsored trials was trial results (including efficacy/safety concerns), whereas the most commonly reported reason for non-commercially sponsored trials was problems with recruitment.

Figure 7. Reasons for discontinuation of trials (commercial and non-commercial)



Source: OHE analysis from the European Union Clinical Trials Register and the U.S. National Institutes of Health database (October 2014/January 2015).

4.4 IMS R&D Lifecycle

The search for "N7D" (the code for Alzheimer's using the Anatomical Therapeutic Chemical (ATC) Classification System) produced 863 hits; the search for "Dementia" produced 176 hits; the search for "mild cognitive impairment" produced 130 hits; the search for "Fronto-Temporal Lobe Degeneration" produced zero hits.

Combining these searches and removing duplicates provided a total of 1,029 hits. Screening for erroneous/irrelevant hits by CTEG members led to removal of a further 155 records, leaving 874 hits to be included in the analysis.

Sixty-five different ATC codes were identified within the dataset. Unsurprisingly, the three most common class codes were N7D9 ("all other Alzheimer's drugs": 736 hits), N6D ("Anti-dementia drugs": 135 hits), and N7X ("all other central nervous system drugs": 114 hits).

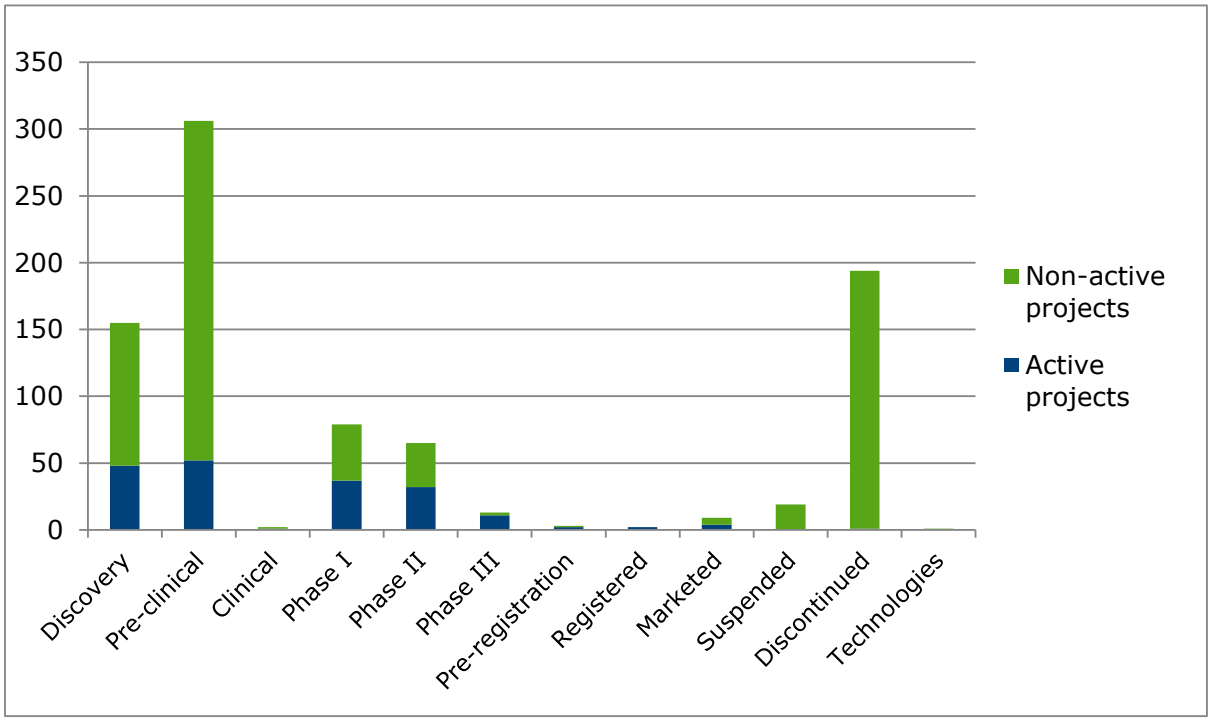
Eleven of the 874 hits were imaging agents, and eight of these 11 were active.[9] Of the eight, one was in phase II development, three were in phase III (NAV 5001, flutafuranol F 18, and florbenazine (18F)), two were registered (flutemetamol 18F and florbetaben (18F)) and two were marketed (florbetapir (18F) and 123I-ioflupane). Of the three non-active products, one was in preclinical development, one in phase I, and one suspended.

[9] Active projects are projects in current company pipelines. Projects that have been discontinued, suspended, withdrawn, or not updated within the last three years are classed, by the IMS database, as non-active.

A further 17 of the 874 records were dietary supplements, only two of which were in active development (idebenone and circadin, both marketed). Of the 15 non-active products, three had been discontinued, five were in preclinical development, one was in phase I, one was in phase III (tramiprosate), and five were marketed (acetyl-L-carnitine, ademetionine, bifemelane, choline alphoscerate, and huperzine A).

Of the remaining 846 hits in the main database (i.e. total hits excluding dietary and imaging studies), only 188 were marked as active. Of these 188, one was discontinued for dementia indications, leaving only 187 active projects. Of these, 48 were in the discovery phase, 52 were preclinical, 37 were in phase I, 32 in phase II, 11 in phase III, and two pre-registration for dementia indications. An additional 107 non-active projects were in the discovery phase, 254 preclinical, 42 in phase I, 33 phase II, and two phase III. Nine projects (of the 846 active plus non-active) were marketed (four marked as active; five marked as non-active). Full results are shown in Figure 8.

Figure 8. Projects by development phase (IMS R&D lifecycle)



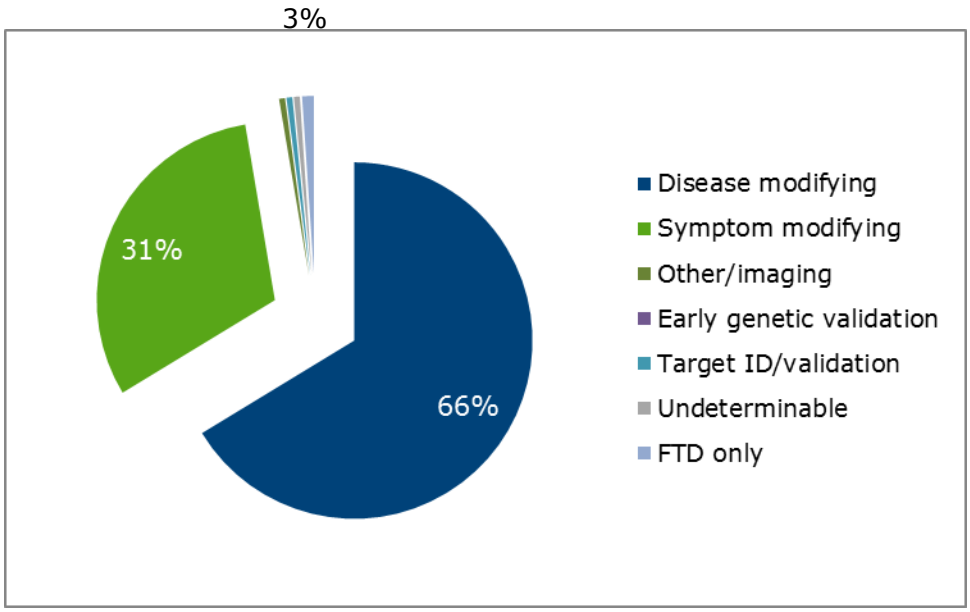
Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014)

Of the 187 active projects (not including dietary and imaging studies), 124 were classified as disease modifying agents, and 58 were symptom modifying. The remaining five studies were classed as either other/diagnostic (one study – phase II), undeterminable (one study - discovery phase), target ID/validation (one study –

discovery phase) or specifically for frontotemporal dementia (two studies – discovery phase).

Figure 9 shows clearly that the majority of the products in active development in the main dataset are disease modifying drugs.

Figure 9. Categories of active projects in IMS database (not including dietary or imaging agents) n=187



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014)
Key: FTD = front-temporal dementia

Of the two active pre-registration products, one was a disease modifying agent (safinamide), and the other was a symptom modifying agent (ADS 8704); of the 11 phase III products, eight were disease modifying (AC 1204, davunetide, gantenerumab, LMTX, MK 8931, nilvadipine, pioglitazone, solanezumab), and three were symptom modifying (encenicline, idalopirdine, neramexane). Further details are provided in

Table 4. Note that the table does not include information on marketed products as the separation between active and non-active treatments is not useful for marketed products – marketed products as a whole are discussed below.

Table 4. Number of drugs in active development by category and phase (IMS database – excluding dietary and imaging studies)

Category	Discovery	Pre-clinical	Phase I	Phase II	Phase III	Pre-registration
Disease modifying	32	37	27	18	8	1
Symptom modifying	12	15	10	13	3	1

Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014), and input from CTEG

Note: in addition to the numbers in the table, one other/diagnostic study was in phase II, one indeterminate and one target ID/validation studies were in the discovery phase, and a further two studies were in the discovery phase specifically for frontotemporal dementia.

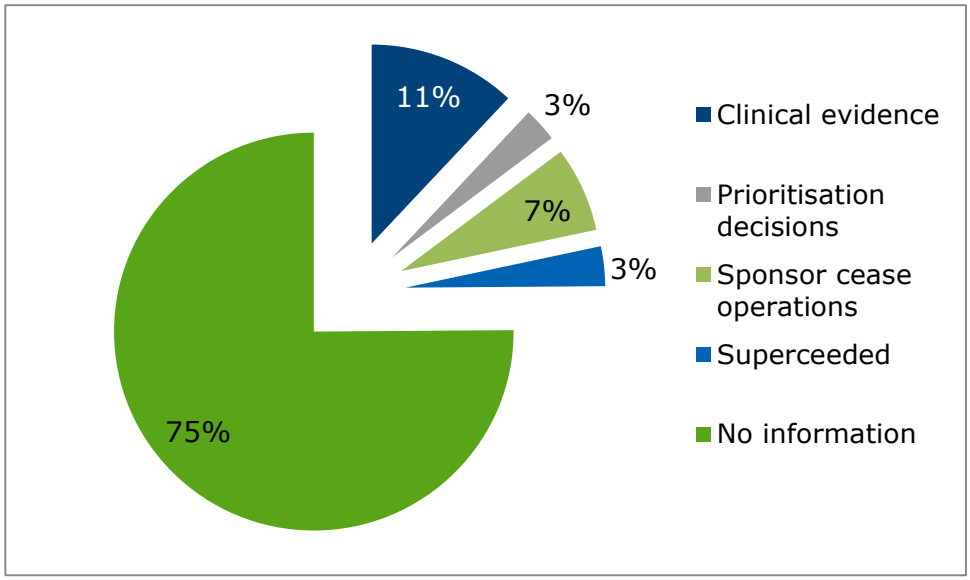
Of the full 874 projects (full dataset including dietary and imaging products, active and non-active products), 17 were marketed for dementia related indications; 24 were marketed for any indication. Of the 17 products marketed for dementia related indications, 12 were classified as symptom modifying, one as disease modifying, and four other/diagnostic (all four were imaging agents). Note that the one marketed disease modifying agent (idebenone) is marketed for cognitive defect in South Korea, Mexico, Japan, Italy, Argentina, Paraguay, Peru, Philippines, Portugal, Russia, and Uruguay. See Table 5 in section 4.5 for list of projects marketed for dementia, the specific indications, and the category (i.e. disease or symptom modifying).

OHE was not able to assess within the scope of this project what the R&D landscape for dementia looked like in earlier years; for example, in 2000 and 2005. This is because the IMS database is "live" and we did not have access to historic versions of the database.

4.4.1 Discontinued & suspended projects (including attempts to obtain further information on attrition)

Of the full 874 hits in the database, 197 projects had been discontinued and 20 suspended for dementia related indications. Of these 217 projects, 26 (11%) were reported as having been discontinued or suspended because of negative trial results, insufficient efficacy gains or adverse effects; six (3%) were reported to be strategic or prioritisation decisions by the sponsor, 15 (7%) were due to the sponsor ceasing operations, seven were superseded by other products (3%), and 163 (75%) did not have a reason for discontinuation or suspension (see Figure 10).

Figure 10. Reasons for discontinuation or suspension of development; n = 217 (IMS R&D lifecycle)



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014)

As noted in section 2.2.1, we approached companies that had products listed in IMS Lifecycle as terminated, suspended, or no longer active, but did not report a reason for this. This was an attempt to gather information on the reason for termination for the 163 (75%) terminated projects for which this information was missing from IMS Lifecycle.

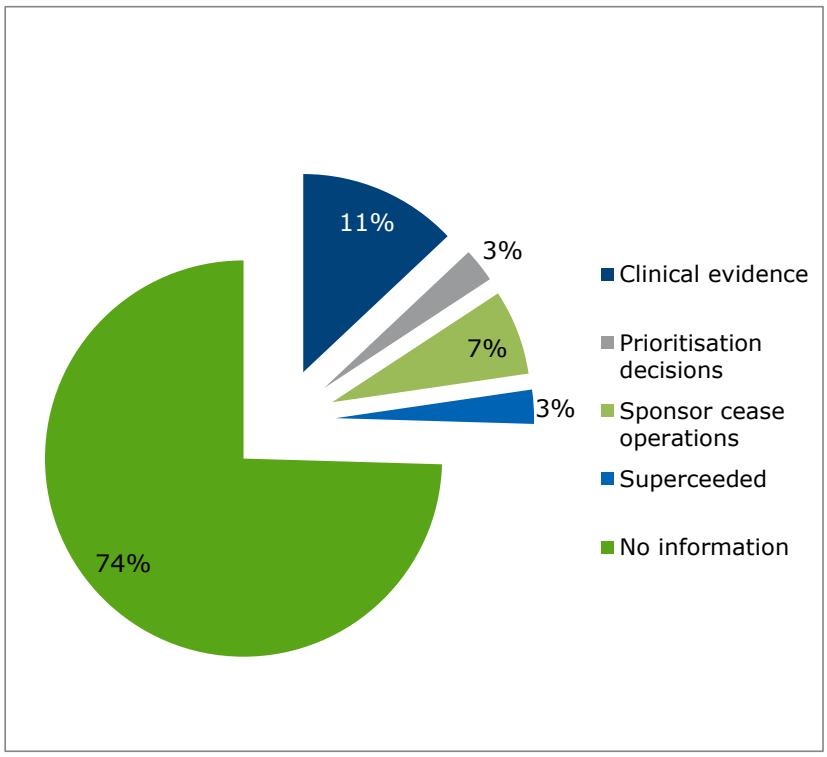
We approached 13 companies in total. Three companies responded, providing additional information on eight of the discontinued or suspended treatments[10]. This means we were only able to reduce the projects with no reason for termination by one percentage point (to 74%). Of the eight, one project (which had been marked as discontinued in the IMS database) had returned to phase II development, three had been discontinued due to side effects or safety concerns, and four had been discontinued due to a lack of efficacy, or because the treatment was deemed unsuccessful (two of these were at the discovery stage, one pre-clinical, and one phase II). The analysis of discontinued products in the remainder of this section is based on the combination of the information taken from the IMS Lifecycle database and the additional information obtained from companies.

Once the dataset had been updated with the information from the companies, 196 projects were marked as discontinued, and 20 suspended, for dementia related

[10] Information was also provided on one project which had been marked as non-active in the database which indicated that this project was in fact still active in phase II development. This is kept separate to the discussion in the main text above as it does not refer to a discontinued or suspended project, and is therefore not the main focus of this section. This information will be used in Section 5.2: Phase success rates.

indications. Of these 216 projects, 28 were reported as having been discontinued or suspended because of negative trial results, insufficient efficacy gains (including projects deemed unsuccessful) or adverse effects; six were reported to be strategic or prioritisation decisions by the sponsor, 15 were due to the sponsor ceasing operations, six were superseded by other products, and 161 did not have a reason for discontinuation or suspension (see Figure 11).

Figure 11. Reasons for discontinuation or suspension of development (IMS R&D lifecycle plus additional information from sponsors)

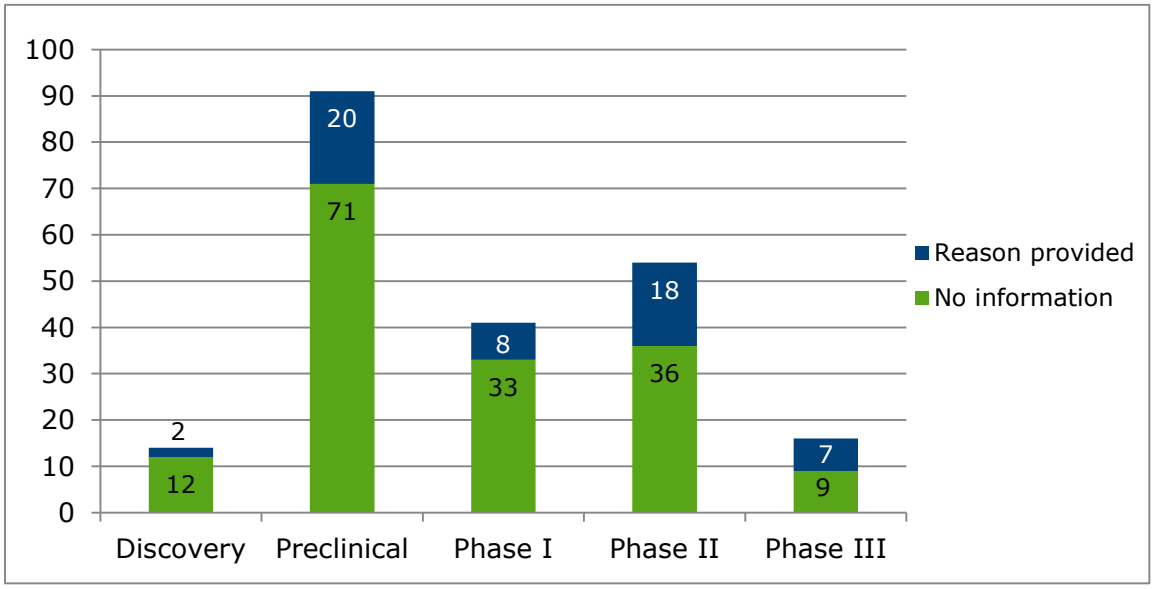


Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014) and additional information from sponsors

Of the total 216 discontinued or suspended projects, 41 were discontinued or suspended at phase I, 54 at phase II, and 16 at phase III. Fourteen were discontinued or suspended at the discovery phase, and 91 at the preclinical stage. Only 27 of the 216 have been suspended or discontinued post 2010. Figure 12 shows the phase at discontinuation, and Figure 13 shows the year of discontinuation. These figures also show the split of projects in each phase/year that did/did not have a reason for termination (i.e. the figures show how the 74% of projects with no information in Figure 11 is split across phase and year of discontinuation). Projects discontinued at phase III were much more likely to have a reason provided (only 56% had no information compared to 74% overall) than trials discontinued at other phases; trials discontinued in the periods 2001-05, 2006-10, and 2011-2015 were much more likely to report a reason

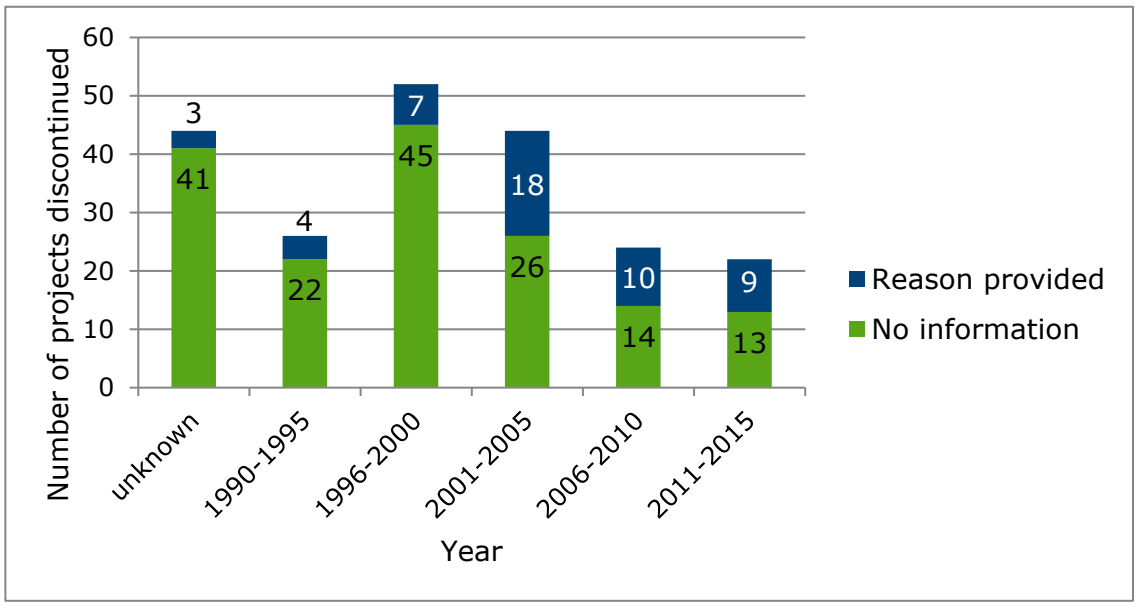
than trials discontinued in earlier years (59%, 58%, and 59% had no information compared to 74% overall).

Figure 12. Phase before discontinuation (IMS R&D lifecycle plus additional information from sponsors)



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014) and additional information from sponsors

Figure 13. Year of discontinuation



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014)

4.5 Combined analysis: IMS lifecycle & trial databases

Of the 17 projects marketed for dementia indications in IMS lifecycle (Table 5), nine have corresponding phase III trials in the combined trial database. An additional two projects are listed as registered in IMS Lifecycle; both of these have corresponding phase three trials in the combined trial database.

Table 5. Marketed and registered projects (IMS Lifecycle)

Intervention	Marketed indication	Category*	Year first marketed/ registered†	Number of corresponding phase III trials±
Marketed				
Ademetionine	Cognitive defect	Other/diagnostic	1975	0
Memantine	AD, cognitive defect	Symptom modifying	1982	15
Acetyl-L-carnitine	AD	Other/diagnostic	1985	0
Bifemelane	Cognitive defect	Symptom modifying	1987	0
Idebenone	Cognitive defect	Disease modifying	1987	0
Oxiracetam	Cognitive defect	Symptom modifying	1987	0
Choline alphoscerate	Cognitive defect	Symptom modifying	1989	1
Aniracetam	Cognitive defect, stroke	Symptom modifying	1993	0
Tacrine	AD	Symptom modifying	1993	0
Donepezil	AD	Symptom modifying	1997	18
Galantamine	AD	Symptom modifying	1997	23
Rivastigmine	AD, Dementia	Symptom modifying	1997	15
Huperzine A	AD	Symptom modifying	1999	1

123I-ioflupane	Diagnosis	Other/diagnostic	2000	3
Ipidacrine	AD	Symptom modifying	2003	0
Florbetapir (18F)	Diagnosis	Other/diagnostic	2012	5
Dextromethorphan + quinidine	Neurological	Symptom modifying	Not reported	3
Registered				
Florbetaben (18F)	Diagnosis	Other/diagnostic	2014	2
Flutemetamol 18F	Diagnosis	Other/diagnostic	2013	12

*Disease modifying, symptom modifying, target ID/validation, other/diagnostic, early genetic validation, or undeterminable.

†In some cases the year marketed varies by country/region. This column shows the year the drug was first marketed in any country

±This refers to corresponding phase III trials in the OHE combined trial database only

Table 5 shows that seven out of the eight products with no corresponding trials were marketed before the clinical trial databases were in use (the two trial databases were established in 2000 and 2004, see methods section for further details). However, the 8th product with no corresponding trials, ipidacrine, was first marketed in 2003, after the databases were set up. Upon closer inspection, the IMS Lifecycle database reveals that the phase III trials for this product were conducted in Japan in 1989, therefore once again it is clear why these do not feature in our trial database. This supports our analysis, showing consistency across the databases for these products.

However, this does not explain why some of the drugs marketed before 2000/04 *do* have associated phase III trials, for example memantine, which has 15. Looking closer at the trials for memantine, all have been conducted since 2003, more than 20 years after the drug was first marketed for AD, and thus they feature in the trial databases. The trials generally relate to variations of the marketed indication and/or intervention,[11] which may explain why they have been carried out post-marketing.

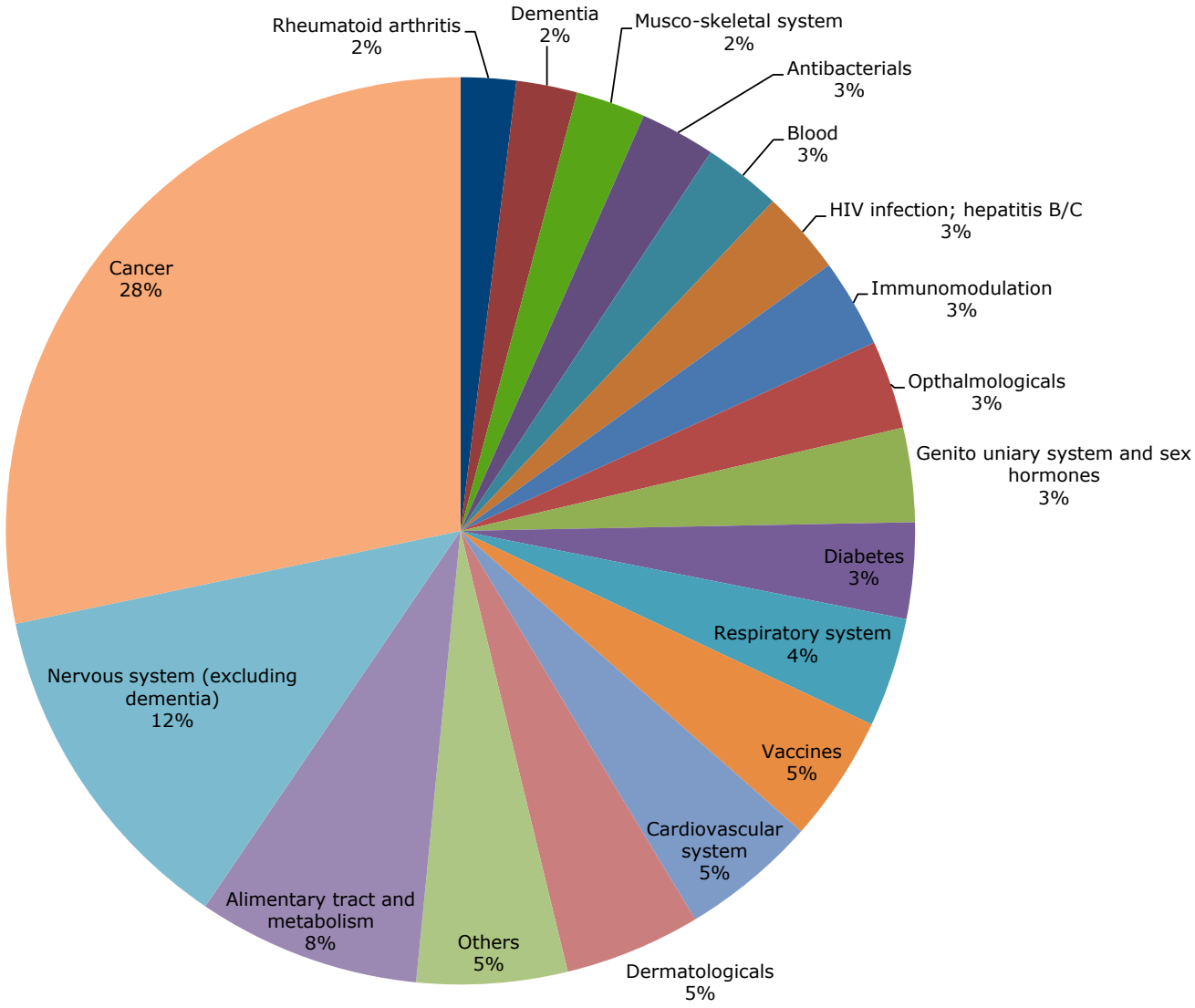
[11] Specifically, four of these trials relate to dementias other than AD; six focus specifically on a moderate to severe AD population; two were trials of combination therapy (memantine with vitamins); one looked specifically at institutionalised patients; one looked specifically at the effect of memantine on imaging measures, and the final study was to validate a new AD scale.

5. DEMENTIA & OTHER THERAPY AREAS

5.1 Numbers of treatments in the pipeline

According to the IMS LifeCycle R&D Focus database, there were 2,952 drugs in active development in phases I-III for all therapy areas; 64 (2%) of these were for dementia. Figure 14 shows the proportions of all drugs in active phase I-III development by therapy area. Project for cancer represent the largest share (28%), followed by nervous system excluding dementia (12%).

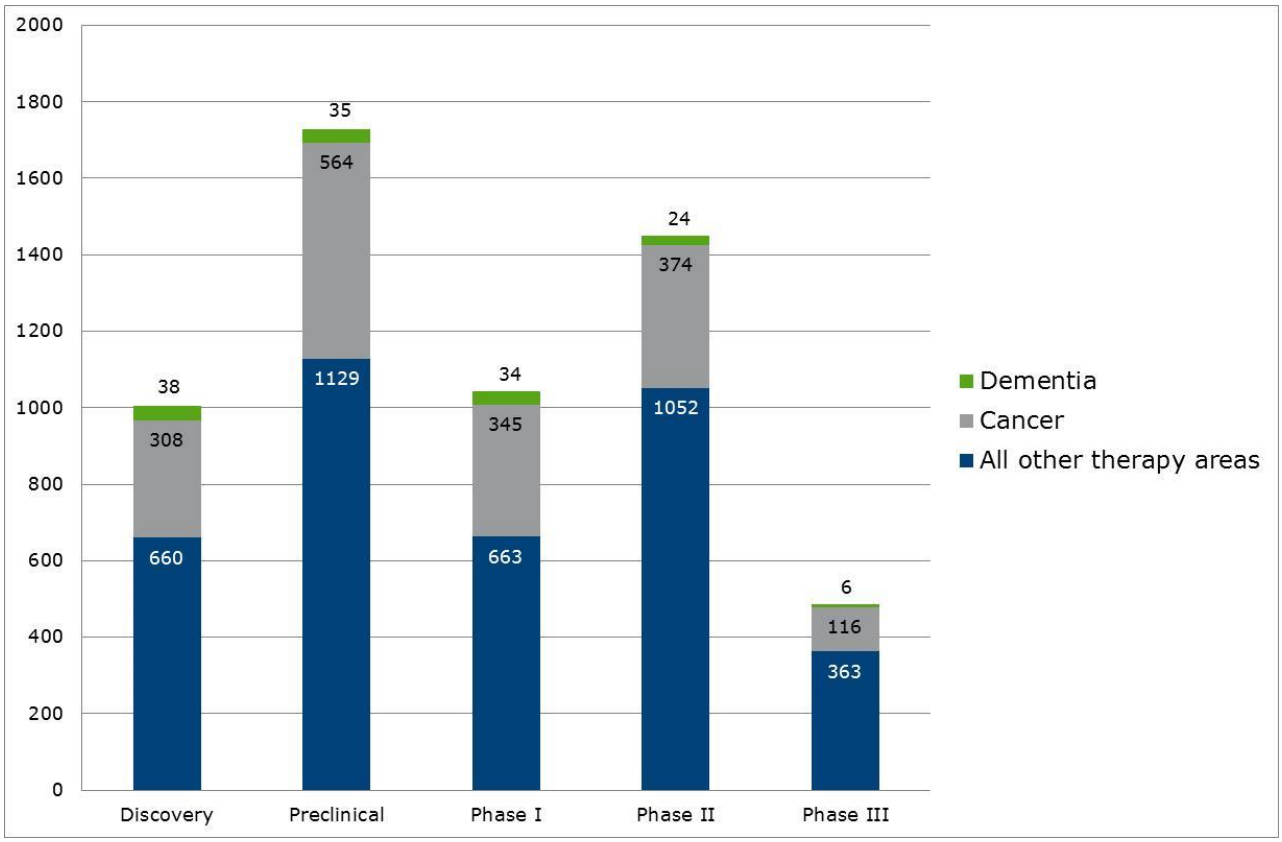
Figure 14. Drugs in active phase I-III development by lead indication therapy area



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014 and February 2015)

Figure 15 shows how active products for all therapy areas are distributed across the development stages; products with dementia as the lead indication are highlighted in green; products with cancer as the lead indication are shown in grey for comparison. The figure shows that 38 out of 1,006 products (3.8%) in discovery have dementia as the lead indication, but only 6 of 485 treatments (1.2%) in phase III have dementia as the lead indication. The equivalent figures for cancer are 308 (31% of the total 1,006) in discovery, and 116 (24% of the total 485) in phase III. The analysis also revealed that only four of 835 marketed products (0.5%) list dementia as the lead indication.

Figure 15. Drugs in active development by phase (dementia compared to all other therapy areas)



Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014 and February 2015)

5.2 Phase success rates

Results of the phase success calculations are shown in Table 6. LOA was calculated to be 7.27% (n = 342) from phase I. Maximum and minimum phase success probability calculations are shown in Table 7. Maximum LOA from phase I was calculated to be 17.22% (n=429), and minimum 3.36% (n=429).

Table 6: Phase success probabilities for IMS database

Phase	Number of projects in each phase†	$drug_{NXT}$	$drug_{DIS}$†	n	Phase success
Marketed	17				
Phase III	17	17	19	36	47.2%
Phase II	67	34	86	120	28.3%
Phase I	81	101	85	186	54.3%
Preclinical	312	182	351	533	34.1%

†Taken from IMS results and additional information from companies

Key: $drug_{NXT}$ = number of drugs which moved to phase X+1 (e.g. $drug_{NXT}$ for Phase I = 67+17+17 = 101 [= drugs thst moved to phase II, phase III and Marketed); $drug_{DIS}$ represent the number of drugs which were suspended, discontinued, or became non-active at phase X; n = $drug_{NXT}$ + $drug_{DIS}$; Phase success = $drug_{NXT}$/n

Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014)

Table 7: Phase success probabilities for IMS database – maximum and minimum values

Phase	Number of projects in each phase†	$drug_{NXT}$	$drug_{DIS}$	n	Phase success
Maximum					
Marketed	17				
Phase III	17	31	19	50	62.0%
Phase II	67	70	86	156	44.9%
Phase I	81	138	85	223	61.9%
Preclinical	312	234	351	585	40.0%
Minimum					
Marketed	17				
Phase III	17	17	33	50	34.0%
Phase II	67	34	122	156	21.8%
Phase I	81	101	122	223	45.3%
Preclinical	312	182	403	585	31.1%

Key: drugNXT = number of drugs which moved to phase X+1 (for maximum this is calculated as in Table 6 plus all active projects; for minimum calculated as inTable 6); drugDIS represent the number of drugs which were suspended, discontinued, or became non-active at phase X (for maximum this is calculated as in Table 6; for minimum this is calculated as in Table 6 plus all active projects); n = drugNXT + drugDIS; Phase success = drugNXT/n

Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014) and additional information from companies

The phase success probabilities from Hay et al. (2014) and DiMasi et al. (2010) are provided in Table 8 for comparison. The table includes the results for all diseases, neurology (as this includes dementia), and oncology (provided for comparison as this has the lowest success probabilities of all categories calculated by Hay et al.). The results are also shown graphically in Figure 16.

Note that the phase success probabilities cannot be directly compared to the number of suspended/withdrawn/discontinued trials discussed in Section 4.3 and Figure 4. The phase success probabilities relate to products successfully completing each stage of development, and a failed trial does not necessarily indicate that a product will cease development.

Table 8: Phase success probabilities and LOA from phase 1

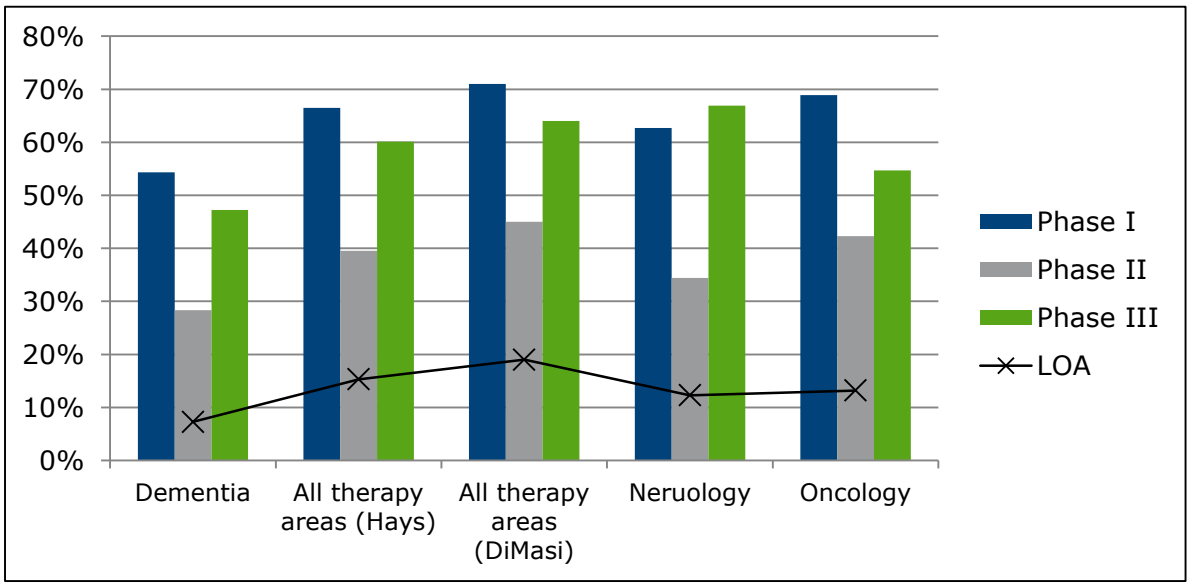
	OHE: Dementia	Hay et al: All	DiMasi et al: All	Hay et al: Neurology	Hay et al: Oncology
Phase success probabilities					
Phase III†	47.2%	60.1%	64%	66.9%	54.7%
Phase II	28.3%	39.5%	45%	34.4%	42.3%
Phase I	54.3%	66.5%	71%	62.7%	68.9%
Preclinical	34.1%	-	-	-	-
LOA					
From phase I	7.27%	15.3%	19%	12.3%	13.2%

†Note this is transisition from phase 3 to the phase of "new drug application/biologic license applications" rather than "marketed" as in our study.

Key: LOA = likelihood of approval. This is calculated as the product of the phase success probabilities leading to approval

Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014) and additional information from companies; Kay et al. (2014); DiMasi et al. (2010)

Figure 16: Phase success probabilities and LOA



Note: LOA is from phase I.

Source: OHE from IMS LifeCycle R&D Focus database (October/November 2014) and additional information from companies; Kay et al. (2014); DiMasi et al. (2010)

It is clear from Table 8 and Figure 16 that the phase success probabilities for dementia are consistently lower than those for all therapy areas, and also for Neurology and Oncology. Success rates from phase II are particularly low compared to other therapy areas; LOA is also very low, a result of the consistently small phase success probabilities. The maximum values calculated for Dementia, which assume that all current projects will progress to the next phase of development, are still generally lower than the published estimates for all therapy areas, and for Neurology (with the exceptions of Hay et al.'s estimates for phase II and phase III for all therapy areas). The maximum phase I success probability for dementia is also lower than the phase I success probability for Oncology, the lowest of the phase I estimates produced by Hay et al.

However, there are limitations to this comparison – the Dementia figures are taken from a different database to the others and thus the information recorded may be different. There may also be differences in how non-active treatments have been included in the calculations, as these have not been formally suspended or discontinued by the company, but have been assumed suspended in our analysis. In addition, the data in Table 8 is based on the lead indications (the primary or most advanced indication) for the therapies in question, whereas the dementia data is based on dementia related indications only. As some of the drugs included in our analysis have non-dementia indications which have progressed further through the drug development process (for example 24 drugs in our dataset have been marketed, but only 17 have been marketed

for dementia indications), our results are biased downwards compared to those for lead indications. Including lead indications would therefore increase the phase success probabilities and LOA. These non-dementia lead indications have not been included in our main analysis, as the focus in on dementia, but have been included in a sensitivity analysis. Using lead indications, rather than only dementia indications, does increase our phase success probabilities as expected (phase I 58%, phase II 30%, phase III 57%; LOA 10%), yet they remain lower than the published estimates in Table 8.

6. SUMMARY & REMARKS

The following is a summary of the main findings of the analysis.

The results of the literature review indicated that R&D costs are higher for neurology and AD (as well as respiratory and oncology) than other therapy areas due to lower success rates and longer development times. Such commercial considerations have been increasingly important causes for discontinuation of development in recent years, with economic considerations becoming more prevalent over time. Therefore, the higher R&D costs for dementia could partly explain why there are fewer effective treatments in this area. The review found that a key challenge for R&D in the area of dementia is the recruitment of trial participants, but problems also extend to a lack of efficacy and safety, inappropriate trial designs, and an absence of a decline in the placebo arm.

The analysis of the trial databases found approximately 2,000 relevant trials for dementia indications. Of these, 127 were imaging agents and a further 64 were dietary supplements. The majority of trials (57%) included AD as an indication (82% of commercially sponsored trials, compared to 42% of non-commercially sponsored trials), which most likely reflects the larger population size (and associated larger returns to R&D) of people with AD compared to other dementias. One-hundred and ten of the trials had been terminated early, but the reason for this was only reported in 45% of cases. Note that this means that no information on the reason for termination was provided for 55% of trials which were ended prematurely. This is a substantial percentage which drastically impedes our analysis of the reasons for failures. Of the 45% which did provide a reason, the most commonly quoted explanation was recruitment problems (17%), which echoes the findings of the literature review. The analysis also found that commercial sponsors were more likely to provide a reason for termination than non-commercial sponsors.

From the IMS database, 900 different products for dementia indications were identified. Only 197 of the 900 were in "active" development for dementia indications. In terms of mechanism of action, the majority of the projects in active development were classified as disease modifying (66%) rather than symptom modifying (31%). Unfortunately this split did not carry through to the marketed treatments, where only one of the 17 marketed products were classed as disease modifying.

The analysis of the 216 projects that had been suspended or discontinued showed that the most commonly reported reason was clinical evidence (lack of efficacy/safety). However, 74% did not report a reason. This is a major finding in itself, as it suggests that a wealth of information on the reasons for failure of drugs in this challenging disease area is lost. Three companies were able to provide further information on the

reason for discontinuation/suspension (where this was not provided in the database), but ten were not. Perhaps unsurprisingly, projects in phase III, or projects discontinued/suspended post 2000, were more likely to report reasons for discontinuation/suspension than older drugs and drugs at earlier stages of development.

We are aware of other privately-owned R&D databases that might provide information on attrition. These are: (1) Adis "R&D Insight" database (http://www.springer.com/gp/adis/products-services/adisinsight-databases/r-d-insight); (2) "Benchmarking" databases, based on confidential information provided by companies (as KMR Group (https://kmrgroup.com/), CMR International (http://cmr.thomsonreuters.com/) and Tufts CSDD (http://csdd.tufts.edu/)). OHE did not have access to such databases, and it is not clear whether these databases would provide more information on reasons for project discontinuation in dementia.

The comparison with other therapy areas showed that 2% of pipeline drugs in phases I-III (active development) across all therapy areas have dementia listed as the lead indication. This proportion starts off at 4% at the discovery phase, then reduces to 1% at phase III, and 0.5% marketed. 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). The finding that the phase success rates are lower than other therapy areas fits with the previous result (from the comparison of total numbers against other therapy areas) that the proportion of dementia drugs declines as the phase of development advances.

OHE was not able to compare the current R&D landscape for dementia with the landscape of five or ten years ago. This is because the databases we consulted are "live" and hence historic versions of them are not available. We believe this comparison might provide an interesting analysis of how the R&D pipeline for dementia has changed over time. However, it will require a considerable amount of effort because there is a need to analyse each project/compound and extract dates of all clinical trials/milestones to ascertain the development status of such projects/compounds in 2000 and 2005.A discussion by CTEG of the implied knowledge gaps and reasons behind the difficulties that have been highlighted in this report is available elsewhere.

APPENDIX A: CTEG MEMBERS

Prof Lefkos T Middleton, Imperial College London (chair)

Prof Serge Gauthier, Mc Gill, Montreal (vice-chair)

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Prof Nick Fox, University College London

Prof Michel Goedert, Cambridge University

Dr Jorge Mestre-Ferrandiz, Office of Health Economics

APPENDIX B: TABLES

Table A1: Imaging agents (combined trials register)

Intervention	Latest phase
[11C]BU99008	Phase 0
[11C]MeS-IMPY	Phase I
[11C]PIB†	Phase III
[11C]RO6924963†	Phase I
[11C]RO6931643†	Phase I
[123I]AV 39†	Phase I
[123I]AV94	Phase I
[123I]CLINDE	Phase I
[123I]-IBVM	Phase III
[123I]IMPY	Phase I
[123I]ioflupane†	Phase IV
[123I]MNI-308	Phase I
[18F]AV-45 †	Phase II
[18F]AZD4694†	Phase I
[18F]CFPyPB	Phase I
[18F]DPA-714	Phase I
[18F]-FEPPA	Phase I
[18F]-FMH3	Phase 0
[18F]MK-3328†	Phase I
[18F]MNI-558	Phase 0
[18F]MNI-777	Phase I
[18F]PBR06	Phase I
[18F]PBR111	Phase I
[18F]RO6958948†	Phase I
[F18] T807†	Phase I
[F18] T808†	Phase 0
[F-18]FDDNP	Phase 0
[F-18]W372†	Phase 0
123] 5-I-A-85380	NR
123-I MNI-340	Phase 1
18F-AV-133†	Phase II
18F-AV-1451†	Phase II
2-[18F]Fluoro-3-(2(S)-azetidinylmethoxy)pyridine	Phase II
F-18 DPA-714 (BAY85-8102) †	Phase I
F-18 FDG	Phase II
F-18 FEDAA1106 (BAY85-8101) †	Phase I
Florbetaben†	Phase III
Florbetapir †	Phase IV
Flutemetamol†	Phase III
Gadobutrol	Phase IV
MNI-330	Phase I
MNI-513-01	Phase 0
MT-4666	Phase II
R)-[N-metil-11C]-PK11195 (PK	Phase III

Note: in some cases there were multiple trials per intervention; some interventions may be listed under multiple names.
†Interventions investigated in industry trials

Table A2: Dietary supplements (combined trials register)

Intervention	Latest phase

3APS†	NR
Alpha-lactalbumin	NR
Alzhemed (Tramiprosate) †	Phase III
Anatabloc†	Phase II
Avocado or chickpeas/potatoes	Phase II
Blueberry powder	NR
Brazil nut	NR
Caprylidene (Axona®, AC-1202)	Phase IV
Cavinton Forte†	Phase IV
Cerebrolysin†	Phase IV
Chlorella	Phase III
Choline alfoscerate†	Phase III
Circadin (Melatonin)	Phase II
Copper	Phase II
Curcumin	Phase II
Curcumin + bioperine	NR
D-ribose	Phase II
EGb 761® 240 mg SF†	Phase IV
Epigallocatechin-Gallate	Phase III
Fish oil	Phase II
Fish Oil and Lipoic acid	Phase II
FloraGlo lutein†	NR
Folate	Phase IV
Freeze-dried blueberries	Phase II
Genistein	NR
Glucose	NR
Grape Powder	NR
Green tea powder	NR
High Protein. T-Diet plus Range†	NR
InflanNox	Phase III
Isomaltulose	NR
Lithia water	Phase II
Longevinex brand resveratrol supplement	Phase III
Lutein/zeaxanthin	Phase II
Magtein	NR
N-(5-chloro-2-hydroxy-3-methoxy-benzylidene)-huperzine A ZT-1†	Phase II
N-3 enriched nutrition	Phase IV
Neptune Krill Oil†	Phase IV
Nutriceutical formulation	Phase II
Omega-3 fatty acid	Phase III
Oxaloacetate (OAA)	NR
Resveratrol with Glucose, and Malate	Phase III
Rokan(r) novo 120mg†	Phase II
Sage leaf	Phase IV
Sarcosine	NR
Secoisolariciresinol diglucoside	Phase II
Selenium	NR
Sucrose	NR
Supressi. T-Diet plus Range†	NR
Tocotrienol	Phase IV
Ubiquinol	NR
Vegetable/fruit juice	Phase IV
Vegetation Protein Powder	Phase III
Vitamin B12	Phase IV

Vitamin D3	NR
Vitamin E	Phase IV
Walnuts	NR
ZT-1†	Phase II

Note: in some cases there were multiple trials per intervention; some interventions may be listed under multiple names.
†Interventions investigated in industry trials

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